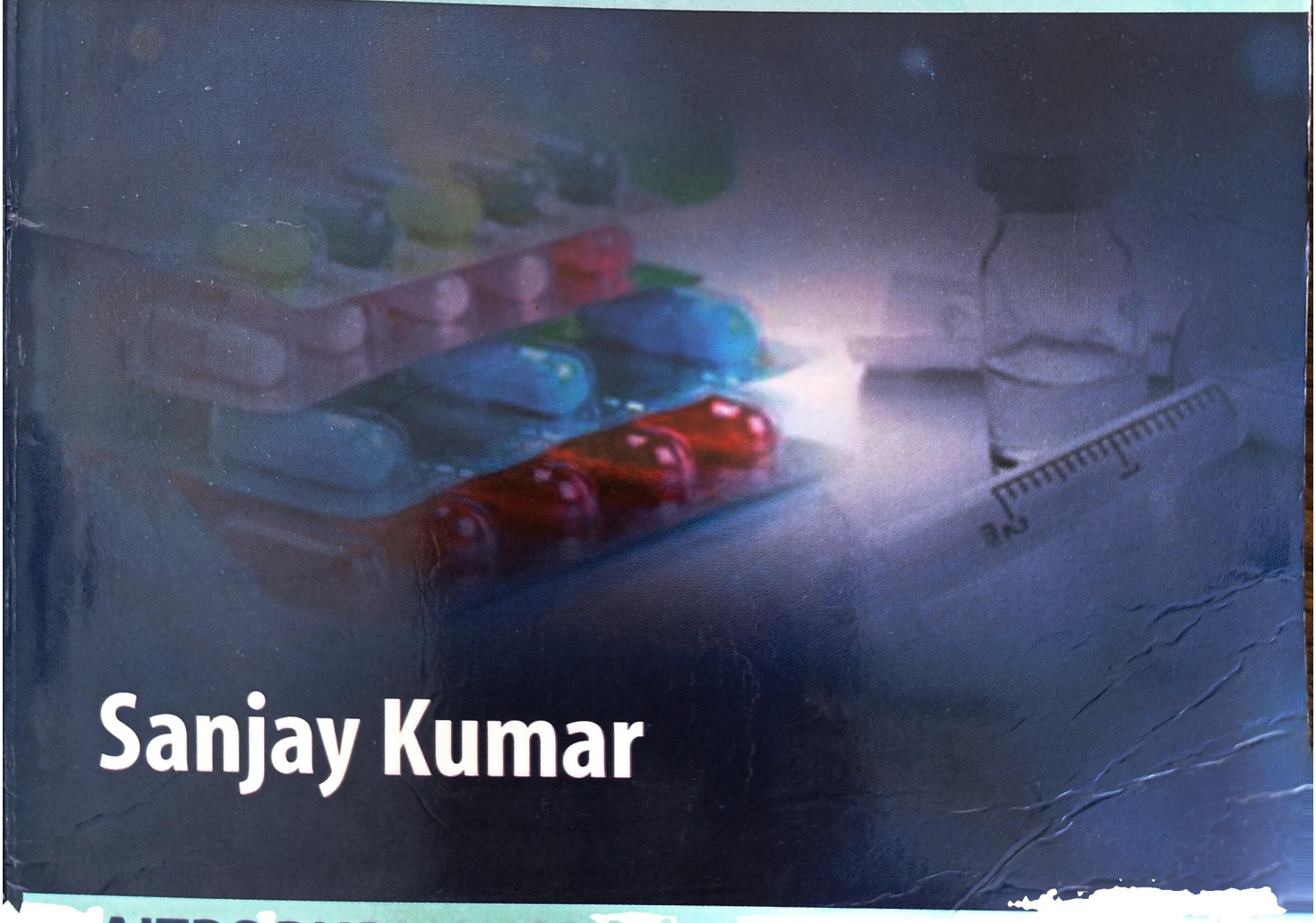
AITBS
PHARMACY BOOKS

PHARMACEUTICS
FOR DIPLOMA IN PHARMACY

Exclusively Prepared for D.Pharm 1st Year Students
(PCI ER 2020)



Sanjay Kumar

AITBS PUBLISHERS, INDIA

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FOR DIPLOMA IN PHARMACY

Exclusively Prepared for D. Pharm First year Students (PCI ER 2020)

Sanjay Kumar

U.B.S. College of Pharmacy,
Maharashtra

With compliments from A.I.T.B.S.
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RECOMMENDATION TO
STUDENTS
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AITBS EDUCATIONAL BOOKS ®
A. I. T. B. S.

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Preface

It gives me immense pleasure to present first edition of book entitled **"Pharmaceutics for Diploma in Pharmacy".** The book is designed to impart basic knowledge and skills on the art and science of formulating and dispensing different pharmaceutical dosage forms.

The book has been prepared for Diploma students as per the syllabus prescribed by Pharmacy Council of India (PCI ER 2020).

To get acquainted with the recent trends, the curriculum of Diploma has been upgraded by PCI. Thus, the aim of this book is to make students understand the concepts of this subject.

This book is a genuine effort to clarify the basics of Pharmaceutics and provide information in lucid way in the form of pictographic, flow charts and existing marketed preparations.

All efforts have been made to present the subject in student friendly manner.

However, any suggestions and constructive comments would be highly appreciated and incorporated in the future edition.

I am also thankful to Virender Kumar Arya at AITBS Publishers, India, for untiring efforts in direction of bringing out this book on time.

Author

SYLLABUS

PHARMACEUTICS (D. Pharm)

Course Code: ER20-11T **75 hours (3 Hours/Week)**

1. • History of the profession of Pharmacy in India in relation to Pharmacy education, industry, pharmacy practice and various professional associations.
   • Pharmacy as a career.
   • Pharmacopoeia: Introduction to IP, BP, USP, NF and Extra Pharmacopoeia. Salient features of Indian Pharmacopoeia.
2. **Packaging materials:** Types, selection criteria, advantages and disadvantages of glass, plastic, metal, rubber as packaging materials.
3. **Pharmaceutical aids:** Organoleptic (Colouring, flavouring and sweetening) agents.

   Preservatives: Definition, types with examples and uses.
4. **Unit operations:** Definition, objectives/applications, principles, construction and workings of:

   Size reduction: Hammer mill and ball mill Size separation: Classification of powders according to IP, Cyclone separator, Sieves and standards of sieves.

   Mixing: Double cone blender, Turbine mixer, Triple roller mill and Silverson mixer homogenizer.

   Filtration: Theory of filtration, membrane filter and sintered glass filter.

   Drying: Working of fluidized bed dryer and process of freeze drying.

   Extraction: Definition, Classification, method and Applications.
5. **Tablets** – Coated and uncoated, various modified tablets (sustained release, extended–release, fast dissolving, multilayered, etc.).

   Capsules – Hard and soft gelatine capsules.

Liquid oral preparations – Solution, syrup, elixir, emulsion, suspension, dry powder for reconstitution.

Topical preparations – Ointments, creams, pastes, gels, liniments and lotions, suppositories and pessaries.

Nasal preparations, Ear preparations.

Powders and granules – Insufflations, dusting powders, effervescent powders and effervescent granules.

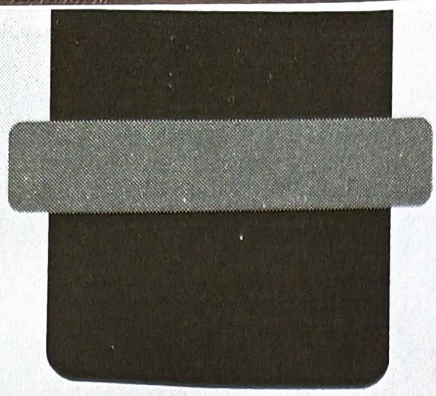
Sterile formulations – Injectables, eye drops and eye ointments.

Immunological products: Sera, vaccines, toxoids and their manufacturing methods.

6. **Basic structure, layout, sections and activities of pharmaceutical manufacturing plants**

   Quality control and quality assurance: Definition and concepts of quality control and quality assurance, Current Good Manufacturing Practice (CGMP), Introduction to the concept of calibration and validation.

7. **Novel drug delivery systems:** Introduction, Classification with examples, advantages and challenges.



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CHAPTER

1

Pharmacy Profession and Pharmacopoeia

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HISTORY OF PHARMACY PROFESSION IN INDIA

1. Before Independence

The western or the so-called Allopathic system came into India with the British traders who later become the rulers. Under British rule this system got state patronage. At that time it was meant for the ruling race only. Later it descended to the people and become popular by the close of 19th Century.

A. Before 1940: Initially, the drugs were being imported from Europe. Later, some drugs began to be manufactured in India.

- **1901:** The Bengal Chemical and Pharmaceutical Works in Calcutta, was established by Acharya P.C. Ray.



- **1903:** A small factory at Parel (Bombay) was established by Prof. T.K. Gujjar.
- **1907:** Alembic Chemical Works at Baroda by Prof. T.K. Gujjar.



Packing of B.P. Chemicals and Ayurvedic Preparations

Drugs used to be exported in crude form and imported in finished form. During 1914-1920, at time of First World War, the import of finished drugs was stopped and it was resumed after the war. Since there were no restrictions or guidelines on the quality of imported drugs, manufacturers started taking advantage and resulted in following consequences:

(i) Inferior quality medicines and adulterated drugs were being dumped by foreign manufacturers.

(ii) Unqualified men started selling useless drugs.

- A committee was set-up by the Government of India under the Chairmanship of Late Col. R.N. Chopra on 11th August, 1930. The purpose of committee was to look into the problems of pharmacy in India and recommending measures to improve it. The report was published in 1931 that stated that there was no recognized specialized profession of pharmacy. A set of people known as compounders were filling the gap.

Years	Steps taken after the report submitted by the Committee
1931	• Proff ML Schroff initiated pharmaceutical education at university level in BHU.
1935	• United Province Pharmaceutical Association was established which later converted into Indian Pharmaceutical Association.
1937	• Proff M.L. Schroff started Indian Journal of Pharmacy. • 'Import of drugs bill' was presented by government, which was later withdrawn.
1940	• All India Pharmaceutical Congress Association was established. • 'Drugs Bill' was brought by Govt. to regulate the import, manufacture, sale and distribution of drugs in British India. This Bill was finally adopted as 'Drugs Act of 1940'.
1941	• The first Drugs Technical Advisory Board (D.T.A.B.) under this act was constituted. • Central Drugs Laboratory (CDL) was established in Calcutta.
1945	• Drugs Rule under the Drugs Act of 1940' was established. • Pharmacy Bill was presented by Govt. to standardize the Pharmacy Education in India.
1946	• The Indian Pharmacopoeia List was published under the chairmanship of late Col. R.N. Chopra. It contains lists of drugs in use in India at that time which was not included in British Pharmacopoeia.

Formal Pharmaceutical Education at Banaras Hindu University: In 1937, Mahadeva Lal Schroff, father of pharmacy in India, started formal pharmacy education in BHU in 1937 as a three-year Bachelor of Pharmacy degree. The curriculum was based on pharmaceutical society of Great Britain.



Mahadeva Lal Schroff
1902-1971

2. After Independence

In 1947, India inherited a system for the pharmacy profession from the British rulers that was unorganized and there was no legal restriction on the practice of pharmacy. The concept of pharmacy practice was not realized until after independence was gained.

In 1948, the Pharmacy Act, 1948 was enacted as the Nation's first minimum standard of educational qualification for pharmacy practice to regulate the practice, education and profession of pharmacy.

1948	• Pharmacy Act, 1948 established. • Indian Pharmacopoeial committee was constituted under chairmanship of late Dr. B.N. Ghosh.
1949	• Pharmacy Council of India (PCI) established under Pharmacy Act, 1948.
1954	• Education Regulation have come in force in some states but other states lagged behind. • Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954 was passed to stop misleading advertisements (e.g., Cure all pills).
1955	• Medicinal and Toilet Preparations (Excise Duties) Act, 1955 was introduced to enforce uniform duty for all states for alcohol products. • First Edition of Indian Pharmacopoeia was published.
1985	• Narcotic and Psychotropic Substances Act has been enacted to protect society from the dangers of addictive drugs.

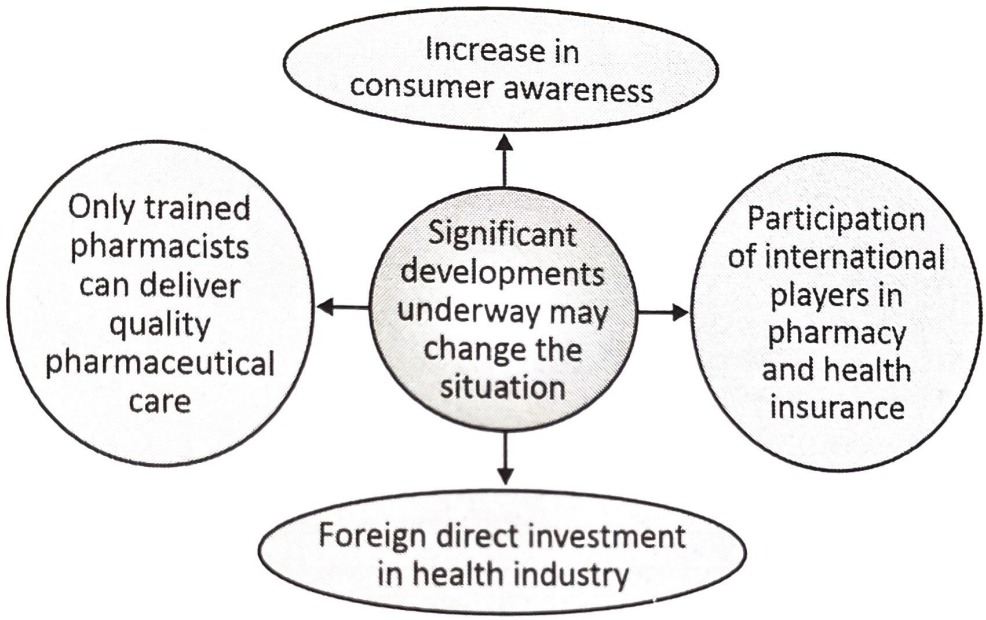
Currently, one needs at least a diploma in pharmacy to practice as a pharmacist. Provisions of the Act are implemented through the Pharmacy Council of India. The Act requires individual states to establish state pharmacy councils that are responsible for controlling and registering pharmacists in their respective states.

He revolutionized pharmacy in India by making the course available throughout the country for all students. Thus, aiding newer discoveries in the field.

3. Current Status of Pharmacy Profession in India

Pharmacy education in our country has witnessed tremendous expansion in last two decade. However, the standards in education have been eroded by rising tides of mediocrity. There is an urgent need to initiate an academic exercise aimed at attaining revamping of curriculum, keeping in pace with current and emerging trends in the field of pharmacy.

Today more than 5.5 lacs pharmacists in the India, of which 5 lacs are in community pharmacy. Diploma holders largely handle the pharmacy profession and the providing of quality pharmaceutical care is still a dream.



PHARMACY PRACTICE

The primary mission of the pharmacy profession is to have a positive impact on the provision of public health service by ensuring the safe and effective use of medications. There are various facets to this mission, including the preparation and distribution of medications, as well as contact with patients and other members of the healthcare team.

Practice of Pharmacy

According to the National Association of Boards of Pharmacy (NABP), the practice of pharmacy involves the:

Administration of medicines

Proper storage of medicines and medical devices

Proper labelling of medicines and medical devices

Dispensing of prescribed drugs

Maintenance of medical records

Providing counselling to patients

Do proper research on drugs and related topics



Labeling of the Pharmaceutical Products

Pharmacists play a key role in the provision of effective health care by managing the medication therapy for patients to ensure medications are used in an appropriate manner to achieve health goals more effectively and with minimization of costs.

Issues in the Pharmacy Practice Profession

A substantial challenge in the pharmacy practice profession is the rational use of medicine.

Patients should:

- Receive appropriate medicines.
- Get medicines at affordable cost.
- Be given appropriate doses of medicines.

But in current system, patients face issues of incorrectly prescribed medicines and issue of patients non-adherence.

Another growing concern in pharmacy practice is the antibiotic resistance. WHO reported that about 90 percent are resistant to first line antibiotics and 70 percent are resistant to other common antibiotics.

We need to take appropriate steps to review this problem.

According to WHO "Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause."

1. Only use antibiotics when prescribed by a certified health professional.
2. Always take the full prescription, even if you feel better.
3. Never use leftover antibiotics.
4. Never share antibiotics with others.
5. Prevent infections by regularly washing your hands, avoiding contact with sick people and keeping your vaccinations up to date.

LIST OF PHARMACY ASSOCIATIONS

Detail of international/multinational organisations for professionals involved in the practice of pharmacy profession are as follows:

- American Chinese Pharmaceutical Association (ACPA)
- European Association of Hospital Pharmacists (EAHP)
- European Pharmaceutical Student's Association (EPSA)
- European Pharmaceutical Union (EPU)
- European Society of Clinical Pharmacy (ESCP)
- International Pharmaceutical Federation (FIP)
- International Pharmaceutical Students' Federation (IPSF)
- International Society for the History of Pharmacy (ISHP)
- Pharmaceutical Group of the European Union (PGEU)

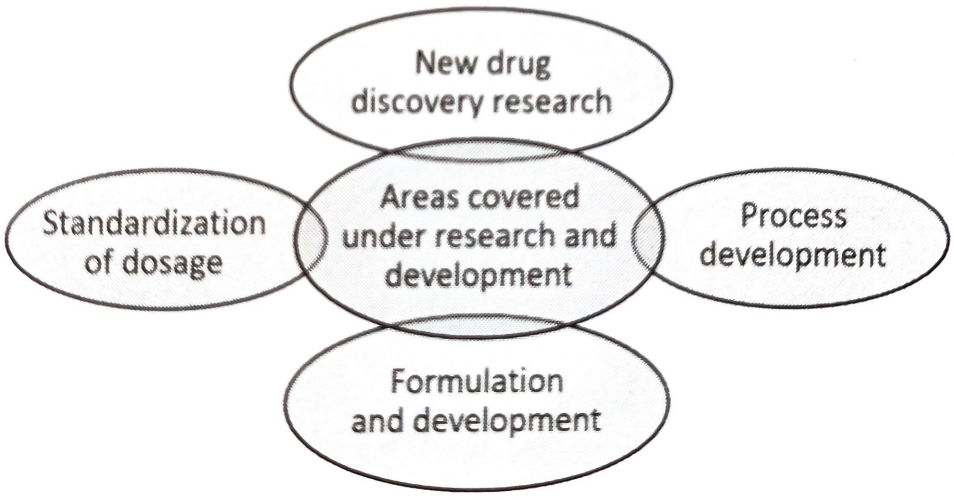
PHARMACY AS A CAREER

Pharmacy as a career option, which has always been in the forefront. Today sky is the limit for a pharma graduate. Depending on the qualification, talent and experience, there are numerous avenues for pharma professionals.

1. **Academics:** Teaching is one of the good option to pursue for those aspirants who are good in academics. The minimum qualification to be a lecturer is M Pharma as per the guidelines of AICTE. Teaching profession is considered a noble profession.
2. **Analytical Chemist:** Analytical chemists can be recruited in labs that are involved in testing of pharma and related products.
3. **Clinical Research:** With many CRO's operations in India, clinical research is an industry itself. India is becoming a hub for clinical research; the demand for professionals in this field is growing rapidly. Clinical research business in India will be worth $1 billion by 2010. Thus, there will soon be a massive demand for clinical research professionals, making it an interesting career option with massive growth potential.
4. **Drug Inspectors:** State Government recruit drug inspectors to look after day-to-day affairs of pharma business. The job of a drug inspector includes the inspection of establishment where drugs, cosmetics, and medical devices are manufactured, handled, stored or sold to enforce legal standards of purity and grading.
5. **Drug Regulatory:** With the Indian companies going globally the role of drug regulatory department is increasing day-by-day. The job involves the preparation of drug dossier and its registration in other countries. Further knowledge of exports and imports also becomes handy in such cases. The job also involves travelling abroad for licensing and alliances.
6. **Hospital Pharmacist:** Hospitals have a pharmacy department which are controlled and managed by a pharmacist. They

undertake responsibility for stock control, storage, placing orders, labeling and financial budgeting and account-keeping for the dispensary.

7. **Retail Pharmacist:** The concept of pharma retailing is rapidly capturing the A and B class cities in India. These are organized retail chains under one banner and thus these calls for a good number of pharmacists to handle the entire show.
8. **Manufacturing Chemist:** With a tremendous growth in the number of manufacturing units the demand for pharmacists is right on the top. Apart from the pharmaceutical units manufacturing chemists are also employed by allied industries such as nutraceuticals, food, cosmetics etc. The job involves to preparation of a pilot sample and see that production of a particular formulation line is right from the raw material to the end of packaging.
9. **Medical Representatives:** These are sales people who are brand ambassador for their respective companies (both National and Multinational Companies).
10. **Research and Development:** Research and development always attracts the pharma professionals. The area of research includes:



11. **Product Management:** Managing a brand is the responsibility of product management department. Pharma professionals enjoy an added advantage over scores others in terms of suitability for this job.

12. **Medical Transcription:** Medical transcription could be one of the speedy growing IT-enabled service in India also, with the rapid change in the outlook, of Indian healthcare and privatization of the insurance sector.
13. **Pharma Publishing:** This is becoming new entrepreneurship business for pharma professionals. This involves publishing of pharma magazine/Newsletters related to pharmacy topics.

PHARMACOPOEIA

Introduction

The term pharmacopoeia first used in 1580 in a book on drug standards printed in Bergamo, Italy. The word derives from the ancient Greek word *pharmakon* means "drug" and *poeia* "to make", and the combination means any recipe or formula or other standard required to make or prepare a drug.

It is a legally binding collection, prepared by a national or regional authority and contains list of medicinal substances, crude drug and formulas for making preparation from them.

The first Pharmacopoeia started in the year 1944 under the chairmanship of Col. R.N. Chopra. In 1948 Government of India appointed an Indian Pharmacopeia committee for preparing 'Pharmacopeia of India'. In 1955, 1st edition of Indian Pharmacopeia was published in the official gazette. The first edition of the British Pharmacopeia was published in 1864 and was one of the first attempts to harmonize pharmaceutical standards.

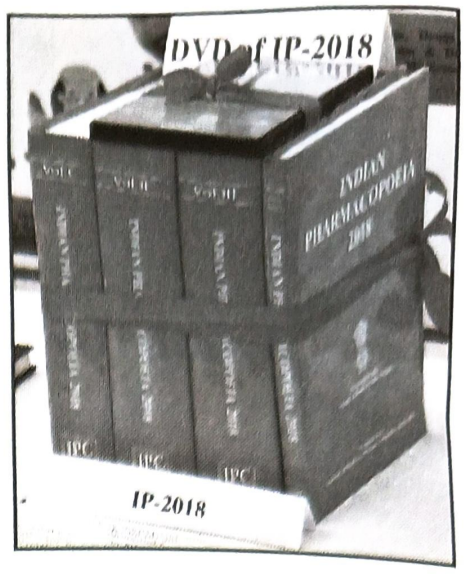
The pharmacopoeia contains:

- Actions
- Description
- Doses
- Formulas for preparation
- List of drug and other related substances
- Sources
- Storage conditions
- Tests
- Uses

Indian Pharmacopoeia

Indian Pharmacopoeia Commission (IPC) is an autonomous institution of the Ministry of Health and Family Welfare which sets standards for all drugs that are manufactured, sold and consumed in India.

The set of standards are published under the title Indian Pharmacopoeia (IP).



History of Indian Pharmacopoeia

1944	• Publishing of first pharmacopoeia began under the Chairmanship of Col. R.N. Chopra.
1946	• Indian pharmacopoeia list was published by Govt. of India, as a supplement to British Pharmacopoeia. • List contain about 180 monographs and a number of appendices prepared on the lines of British Pharmacopoeia. • Approximately 100 monographs were on vegetable drugs growing in India and on their Galenical's.
1947	• The pharmaceuticals and drug research committee of the council of scientific and industrial research decided in February 1947 to compile a "brochure" to Highlight the information and clinical uses of important indigenous drugs of India.
1948	• Government of India appointed an Indian Pharmacopoeia committee for preparing 'Pharmacopoeia of India'.
1953	• The first Indian pharmaceutical codex was published in 1953. The codex consist of two parts. The first part carried about 190 general monographs on natural products and drugs of vegetable and animal origin and a few chemicals.

the British National Formulary (BNF), the BP Vet and the European pharmacopoeia standards.

The BP is prepared by the Pharmacopoeial Secretariat, working in collaboration with the British Pharmacopoeia Laboratory, the British Pharmacopoeial Commission (BPC), and its Expert Advisory Groups (EAG) and Advisory Panels.

Editions of British Pharmacopoeia (BP):

- First edition of BP was published in 1864 that contained two sections.

  Part I: Materia Medica.

  Part II: Preparation & compounds.
- Second edition of BP was published in 1867.
- Third edition of BP was published in 1898.
- Fourth edition of BP was published in 1914.
- Fifth edition of BP was published in 1932. In this edition titles of drugs & preparations were in English instead of Latin and metric system. It has been published annually.
- In British Pharmacopoeia 2007 monographs has introduced for material specifically used in preparation of Traditional Chinese medicines.
- Term "Prolonged release" has been replaced the term "retard" and the term "Gastro-resistant" has been replaced the term "Enteric coated" in number of monographs.
- British Pharmacopoeia 2008 contains approximately 3100 monographs for substances, preparations and articles in practice. It has been made effective from 1st January 2008.
- British Pharmacopoeia 2007-2009 were published in six Volumes, i.e. Volume I to Volume VI.
  - Volumes I & I contains medicinal substances.
  - Volume II contains formulated preparations, herbal products, immunological products, radiopharmaceutical preparations, surgical materials &

the *British National Formulary* (BNF), the BP defines the UK's pharmaceutical standards.

The BP is prepared by the Pharmacopoeial Secretariat, working in collaboration with the British Pharmacopoeia Laboratory, the British Pharmacopoeia Commission (BPC), and its Expert Advisory Groups (EAG) and Advisory Panels.

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- British Pharmacopoeia 2007-2009 were given in Six Volumes, i.e., Volume I to Volume VI.
  - Volumes I & II contains medicinal substances.
  - Volume III contains formulated preparations, blood related products, immunological products, radiopharmaceutical preparations, surgical materials & homoeopathic preparations.

- Volume IV contains supplementary chapters, IR spectra etc.
- Volume V contains veterinary.
- Volume VI contains CD ROM version.

United State Pharmacopoeia (USP)

- 1st edition USP was published in 15th December 1820 in both Latin and English.
- From 1820 to 1942 it was published at Ten years intervals.
- From 1942 to 2000 it was published at Five years intervals.
- From 2002 it was published annually.
- First National Formulary of the united state appeared in 1888.
- USP21-NF16 have eight supplements.
- First appeared in January 1985 and last in November 1988.
- USP22-NF17, 1990 is the third revision that consolidates USP & NF into a single volume.
- Electronic version of USP-NF on floppy disks was introduced in 1992.
- USP23-NF18, was published in Mumbai as an Asian edition at the end of 1994.
- USP23 has ten supplements.
- First supplement was published in January 1995 & Last in May 1999.
- USP24-NF19, appeared from first January 2000.
- USP30-NF25, appeared from May 2007.
- It contains Scientific standards for drugs, dietary substances, biological products and Excipients used in dosage forms.

Highlights of United States Pharmacopoeia 30 – National Formulary 25 include:

- New heavier paper stock

- Complete table of contents and index in each volume
- Special 'Using the New USP-NF Print' tutorial CD
- Convenient slipcase for easy access and storage (English edition only).

Highlights of United States Pharmacopoeia 31 – National Formulary 26 include:

The USP-NF is a single-volume combination of two official compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). Monographs for drug substances and preparations are featured in the USP, with monographs for dietary supplements and ingredients appearing in a separate section of the USP. Excipient monographs are included in the NF.

Highlights of United States Pharmacopoeia 32 – National Formulary 27 contains:

4200 monographs

200 general chapters

Guides and charts present to get focus specific information

Information on science and medicine present

Creates in house standards for operating procedures and specifications

Highlights of United States Pharmacopoeia 33 – National Formulary 28 contains:

- More than 4,400 monographs
- Over 200 general chapters covering general tests and assays
- A new, easy-to-read format and monograph layout
- Helpful guides and charts that make it easy to find focus-specific information
- Ensures compliance with official standards

- Establishes in-house standard operating procedures and specifications
- Facilitates new product development and approval.

SALIENT FEATURES OF INDIAN PHARMACOPEIA

First Edition of Indian Pharmacopoeia:

- It is written in English and official titles of monographs given in Latin.
- It covers 986 monographs.
- Supplement of first edition was released in 1960.
- It contains both western and traditional system drugs commonly used in India.

Second Edition of Indian Pharmacopoeia:

- Second edition of IP was published in 1966 under the Chairmanship of Dr. B. Mukkerji.
- Supplement of this edition was released in 1975.
- It contains both western and traditional system drugs commonly used in India.
- Official titles of monographs given in English.
- Dose were expressed in Metric system.
- For tablets and injections "USUAL STRENGTH" have been given.
- Formulations of the drugs were given immediately after the monograph of drugs.
- 274 monographs from IP 55 & their supplement were deleted.
- 93 new monographs were added.
- 126 new monographs have been included & 250 monographs have been amended.
- Cholera vaccine has been deleted.

Third Edition of Indian Pharmacopoeia:

- Third edition of IP was published in 1985 with two volumes & nine appendices.
- Addendum I to IP was published in 1989 were 46 new monographs added and 126 amended.
- Addendum II was published in 1991 were 62 new monographs added and 110 amended.
- 261 new monographs have been added.
- 450 monographs were deleted.
- In this pharmacopoeia inclusion of traditional system of drugs was limited. However, most of the new drugs manufactured and/or marketed were included while only those herbal drugs which had definite quality control standards had got place in it.

Forth Edition of Indian Pharmacopoeia:

- Fourth edition of IP was published in 1996 under the Chairmanship of Dr. Nityanand.
- Addendum I has been made effective from 31st December 2000 were 42 new monographs have been added.
- Addendum II has been made effective from 30th June 2003 were 19 new monographs have been added.
- It has been made effective from 1st December 1996.
- It covered 1149 monographs and 123 appendices.
- It includes 294 new monographs & 110 monographs have been deleted.
- The veterinary supplement to IP 1996 contains 208 monographs and four appendices.
- In this pharmacopoeia inclusion of a large number of antiretroviral drugs, and raw plants commonly used in making medicinal products not covered by any other Pharmacopoeias and attracted much global attention. The Indian Pharmacopoeia Committee decide to delete the

obsolete or less used product monographs and added monographs based on the therapeutic merit, medicinal need and extent of use of such articles in the country.

Fifth Edition of Indian Pharmacopoeia:

- Fifth edition of IP was published in 2007 and addendum to this edition was published in 2008.
- IP 2007 is presented in three volumes.
- Volume one contains general notices and general chapters.
- Volume two and three contains general monographs on drug substances, dosage forms and Pharmaceutical aids.
- It focuses on those drugs and formulations that cover the National health care programmes and the national essential medicines. It contained monographs on antiretroviral, anticancer, anti-tubercular and herbal drugs. It further emphasized on biological monographs such as vaccines, immunosera for human use, blood products, biotechnological and veterinary (biological and non-biological) preparations.

Sixth Edition of Indian Pharmacopoeia:

- Total monographs ~2000
- New monographs – 287
- Updated monographs >600
- Special emphasis on Herbals, Biological and Veterinary products.
- It comprises of three volumes. each volume has got different features.
- Volume I comprises notices, preface, about Indian Pharmacopoeia commission, acknowledgements, introduction, general chapters and reference data.
- Volume II contains general notices, dosage forms (general monographs), drug substances, dosage forms and pharmaceutical aids (A to M).

- Volume III contains general notices, drug substances, dosage forms and pharmaceutical aids (N to Z), vaccines and immunosera for human use, herbs and herbal products, blood and blood related products, biotechnology products, veterinary products and index.
- The scope of the Pharmacopoeia has been extended to include products of biotechnology, indigenous herbs and herbal products, veterinary vaccines and additional antiretroviral drugs and formulations, inclusive of commonly used fixed-dose combinations. Standards for new drugs and drugs used under National Health Programmes are added and the drugs as-well-as their formulations not in use now-a-day are omitted from this edition.
- The number of monographs of Excipients, Anticancer drugs, Herbal products and antiretroviral drugs has been increased in this edition.
- Monographs of Vaccines and Immunosera are also upgraded in view of development of latest technology in the field.
- A new chapter on Liposomal products and a monograph of Liposomal Amphotericin B injection is an added advantage in view of latest technology adopted for drug delivery.
- A chapter on NMR is incorporated in Appendices.
- The chapter on microbial contamination is also updated to a great extent to harmonise with prevailing international requirements.

Seventh Edition of Indian Pharmacopoeia:

- A list of 577 New Monographs not included in IP-2010 and its Addendum-2012 but added in this edition containing 313 New Monographs on drug substances, Dosage forms & Pharmaceutical aids (A to Z), 43 New Drugs Substances Monographs, 10 Antibiotic Monographs, 31 Herbal Monographs, 05 Vaccines & immunosera for human use, 06 Insulin Products, 07 Biotechnology Products etc., along with the 19 new General Chapters.

- 19 New Radiopharmaceutical Monographs & 1 General chapter is first time being included in this edition.
- This edition of Indian Pharmacopoeia-2014 is now under printing and will be available to stakeholders probably in Sept. 2013, before three months of its effective date, i.e., 1st Jan. 2014.
- This pharmacopoeia presented in four volumes. Included products of biotechnology, indigenous herbs and herbal products, veterinary vaccines and additional antiretroviral drugs and formulations, inclusive of commonly used fixed-dose combinations. Standards for new drugs and drugs used under National Health Programmes are added and the drugs as-well-as their formulations which are not in use now-a-days are deleted from this edition. The seventh edition of IP incorporates 2548 monographs of drugs among this 577 are new monographs co sisting of APIs, excipients, dosage forms, antibiotic monographs, insulin products and herbal products etc.

Eighth Edition of Indian Pharmacopoeia:

Keeping in view the essential requirement for harmonization of analytical methods with those accepted internationally, steps have been taken for monitoring drug standards.

- Identification of an article was done with infrared, ultraviolet spectrophotometer instead of thin layer chromatography.
- Chromatographic method has been used to assess nature of impurities in products and ingredients.
- Most of the existing Assays and Related Substances Test methods have been upgraded by liquid chromatography to harmonize with other International Pharmacopoeias.
- Bacterial endotoxin test used instead of pyrogen test to prepare parenteral and other monographs.
- Index has been added in volume I along with the one in volume IV of IP to make pharmacopeia more user friendly.

- 53 New Fixed Dose Combination (FDCs) monographs have been included, out of which 25 FDC monographs are not available in any Pharmacopoeia.
- General Chapters on Volumetric Glassware, Conductivity, Dissolution test, Disintegration test, Dimensions of Hard Gelatin Capsule Shells etc., have been revised.
- For Controlling the Microbial quality of the entire medicinal range, a general chapter on Maintenance, Identification, Preservation and Disposal of Microorganism has been revised.



CHAPTER

2

Packaging Material

PACKAGING

Packaging means wrapping individual or several items in a box or container for shipment or delivery. It may be done by machines or manually.

PHARMACEUTICAL PACKAGING

Pharmaceutical packaging means to pack or enclose products (mainly drugs related products) before expiration of the product in safe and efficacious dosage form.

Important Points to Remember for Packaging Material

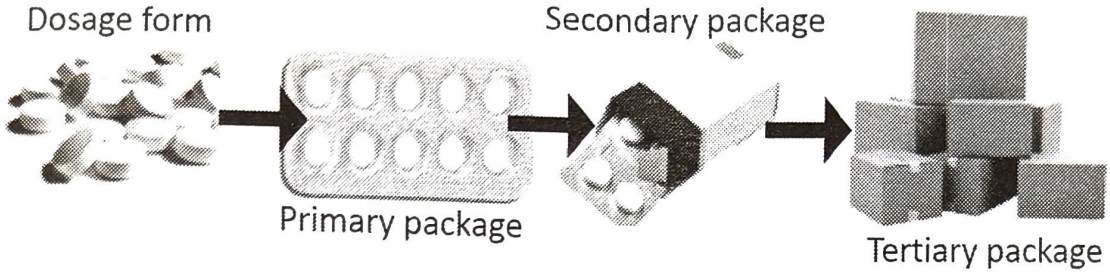
For packaging following requirements must be needed:

- Preparations should be protected from environmental conditions.
- Product should not be reactive with anything.
- Packaging material should not alter the taste or odour of the product.
- Non-toxic
- FDA approved
- Protect the dosage form from damage or breakage
- Meet tamper-resistance requirements, wherever applicable.

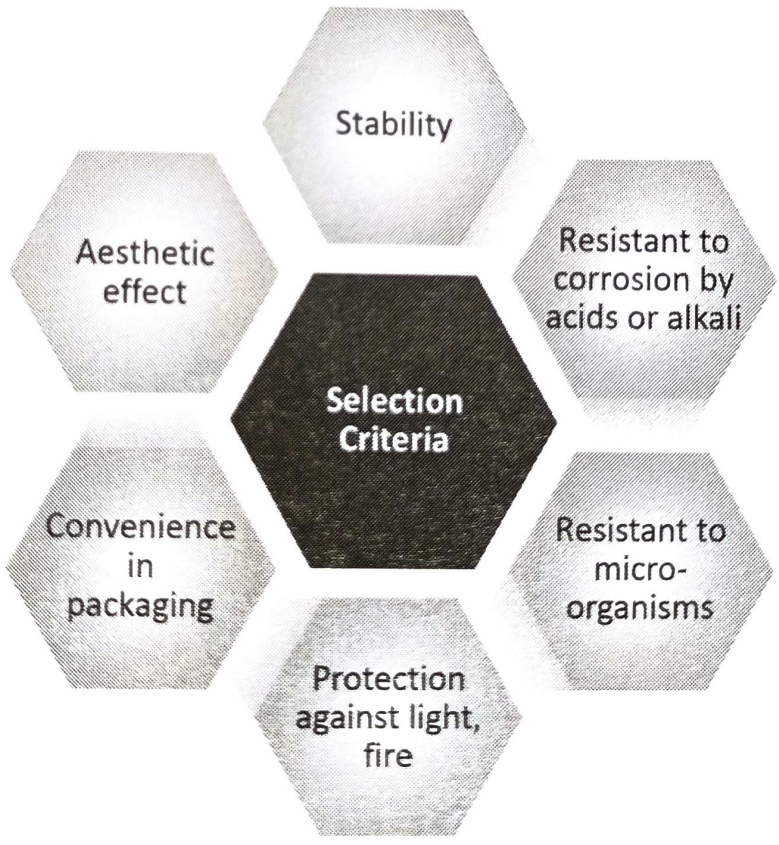
- Adaptable to commonly employed high-speed packaging equipments.

TYPES OF PACKAGING MATERIAL

1. **Primary Package Material:** Made up of those package components and subcomponents that come into direct contact with the product, or those that may have a direct effect on the product shelf life.
2. **Secondary or tertiary package system:** It includes cartons, corrugated shippers and pallets.



SELECTION CRITERIA



PACKAGING MATERIALS AND CLOSURES

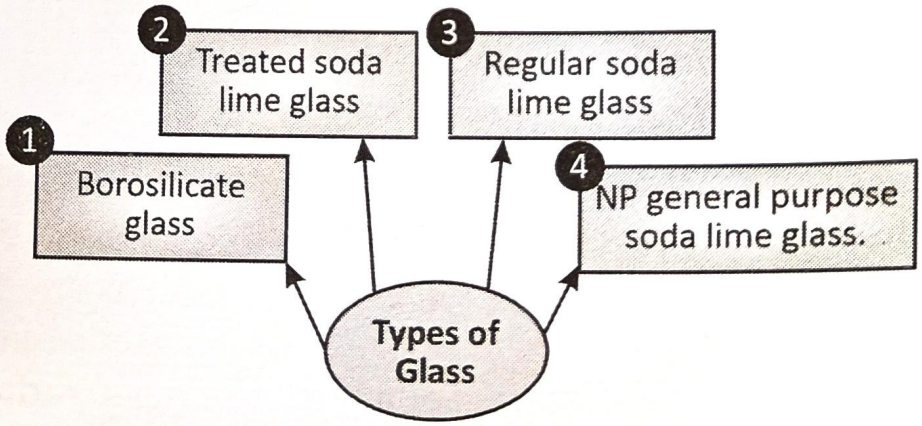
1. Glass
2. Plastic
3. Metals
4. Paper and Board
5. Rubber
6. Closures

1. Glass

Glass containers are mostly used for packaging large number of pharmaceuticals.

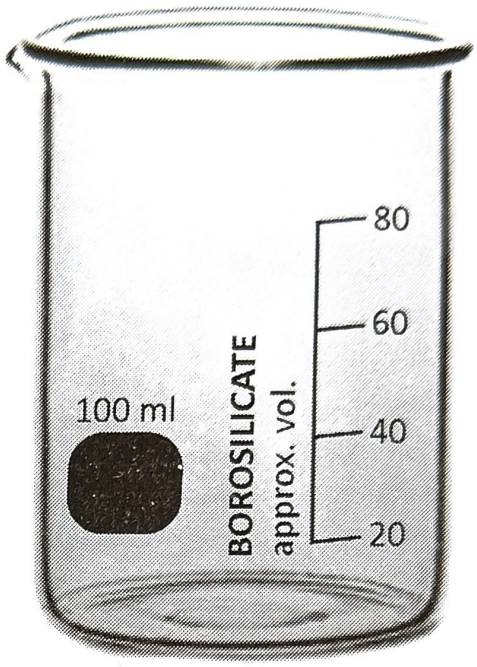


Types of Glass



Type 1: Borosilicate Glass

- *Example:* Pyrex, borosil
- ***Main constituents:***
  - Silicon dioxide (SiO_2) – 80%
  - Aluminium oxide (Al_2O_3) – 2%
  - Sodium Oxide (Na_2O)

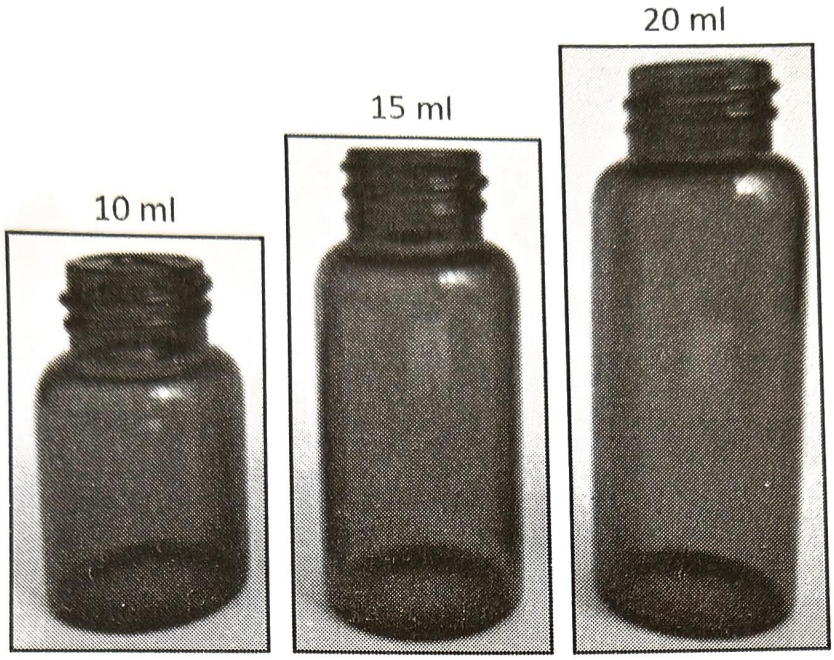


Some chemicals affect such glasses. Industrial and food acids are resistant to such glasses.

- It has very good heat shock resistance.
- A substantial part of the alkali and earth cations is replaced by boron and/or aluminium and zinc.
- It is more chemically inert than the soda-lime glass (which contains either none or an insignificant amount of these cations).
- Strong acids and alkali are stored in it.
- The addition of approx. 6% boron to form type I glass reduces the leaching action.

Type 2: Treated Soda-Lime Glass

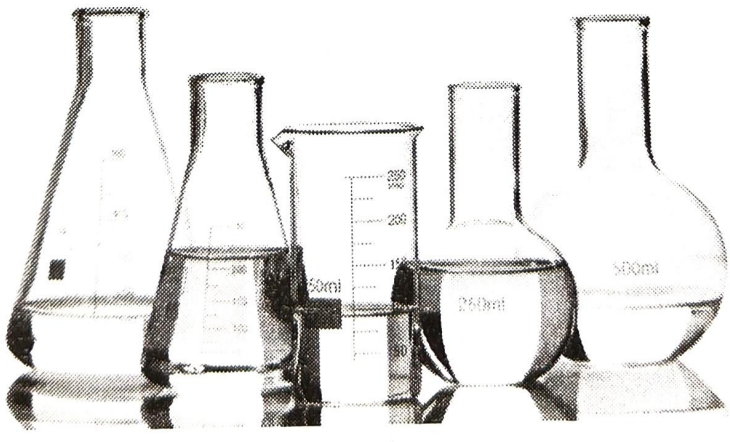
- If the glassware is stored for several months in damp atmosphere or in extreme temperatures, then the surface gets wet by condensed moisture, resulting in salt being dissolved. This is called "blooming" or "weathering" and it gives the appearance of fine crystals on the glass.
- Type II containers are made of commercial soda-lime glass that has been de-alkalized or treated to remove surface alkali
- The de-alkalizing process is known as "sulphur treatment" and virtually prevents "weathering" of empty bottles.



- In some cases, glass is being exposed to water vapour in atmosphere or acidic gases. As a result, there occurs reaction between gases and surface alkali, which is non-resistant to attack by water.
- The alkali removed from the glass appears on the surface as a sulphate bloom, which is removed when the containers are washed before filling.
- Thus, sulphur treatment neutralizes the alkaline oxides on the surface and thus, rendering the glass more chemically resistant.

Type III: Regular Soda-Lime Glass

These glasses are commercial soda-lime glass and are untreated.



Type IV: NP General Purpose Soda-Lime Glass

These are used to store non-parenteral products (oral or topical).

Package Type	Types of Formulation	Types of Glass
Ampoule	Aqueous injectables of any pH	Type I
	Aqueous injectables of pH <7	Type II
	Non-aqueous injectables	Type III
Vial	Aqueous injectables of any pH	Type I
	Aqueous injectables of pH <7	Type II
	Non-aqueous injectables	Type III
	Dry Powders for parenteral use (need to be reconstituted before use)	Type IV
Bottles and Jars	Tablets, capsules, oral solids and other solids for reconstitution	Type IV
	Oral liquids (solutions, suspensions, emulsions)	Type IV
	Nasal and ear drops	Type IV
	Certain types of external Semisolids (rubeficients, local irritants)	Type IV
	Blood and related products	Type I
Dropper	Auxiliary packaging device with certain kind of products	Type IV
Aerosol container	Aerosol product (solution, suspension, emulsion or semisolid type)	Type I

Advantages of Glass

Transparent

Can be easily labelled

Have good protection power

Economical and readily available

Chemically inert

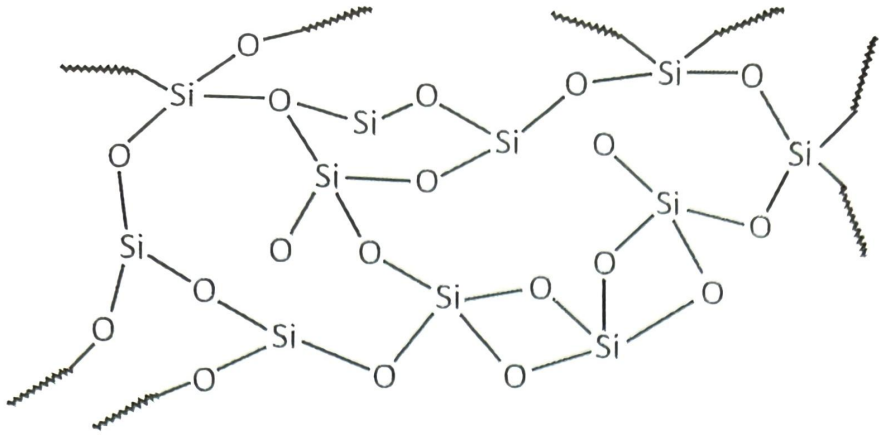
Impermeable to moisture and atmospheric gases

Disadvantages of Glass

1. **Fragility:** Its containers are easily broken when dropped or knocked.
2. **Heavy weight,** which increases the cost of its transportation from one place to another.
3. They may release alkali to aqueous preparations.

Preparation of Glass

1. **Composition of Glass:**
   - Sand
   - Soda ash
   - Lime stone
   - Cullet
2. **Pure silica Glass:**
   - Consist of three dimensional network of silicon atoms.
   - Tetrahedral arrangement surrounded by four oxygen atoms.
3. **Cullet Glass:** Broken glass that is mixed with batch and act as fusion agent for entire mixture.



Properties of Glass

1. It is very hard
2. Chemically resistant
3. Structure is less rigid so low m.p.
4. Glass made of pure silica

2. Plastic

Plastic in packaging have proved useful for a number of reasons, including the ease with which they can be formed, their high quality and the freedom of design to which they can be changed.



Advantages

- Light in weight
- Resistant to breakage
- Has sufficient mechanical strength
- Can be moulded in various shapes
- Available in different quality.

Disadvantages

1. They are not as chemically inert as Type I glass.
2. Some plastics undergo stress cracking and distortion from contact with some chemicals.
3. Some plastics are very heat sensitive.
4. They are not as impermeable to gas and vapour as glass.
3. They may possess an electrostatic charge which will attract particles.

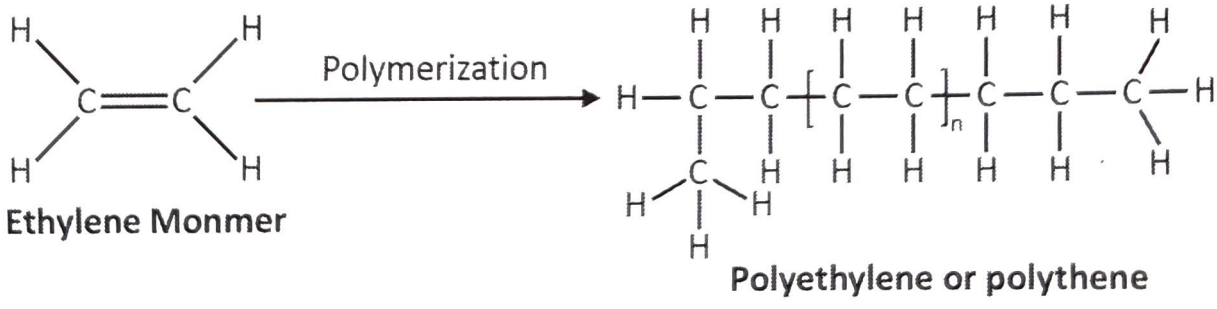
Composition of Plastic

Plastic is synthetic polymer of high molecular weight.

Polymers Used for the Production of Plastics

1. Polyethylene

- Flexible
- Very light
- Density is between 0.91 to 0.96.
- Impermeable to water vapour.
- Does not deteriorate with age.
- Used for preparing disposable syringes.

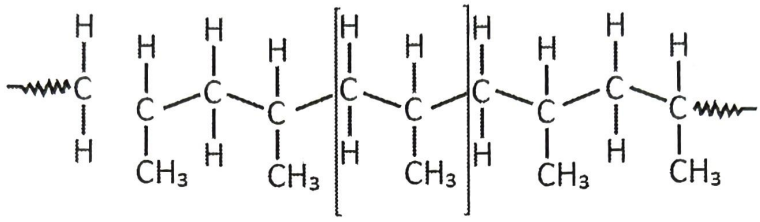


Ethylene Monmer

Polyethylene or polythene

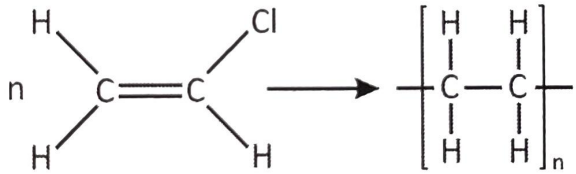
2. Polypropylene (PP):

- Same as high density polyethylene.
- Does not crack.
- It has very high melting point (170 degree), thus can be used for boilable packages and sterilisable products.
- Superior to low density polythene.



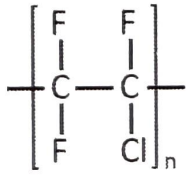
3. Poly-Vinyl Chloride (PVC):

- Inexpensive
- Tough and clear
- Provide good oxygen barrier
- Not affected by acids or alkali except oxidizing acids.
- Impermeable to moisture and gas
- Used for preparing eye ointment tubes.



4. Polymonochloro-Trifluoroethylene (PCTFE):

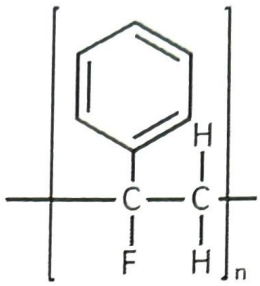
- Trade name is Aclar
- Most inert plastic
- Most expensive plastic, thus, used for blister packing.
- Has low permeability to moisture.



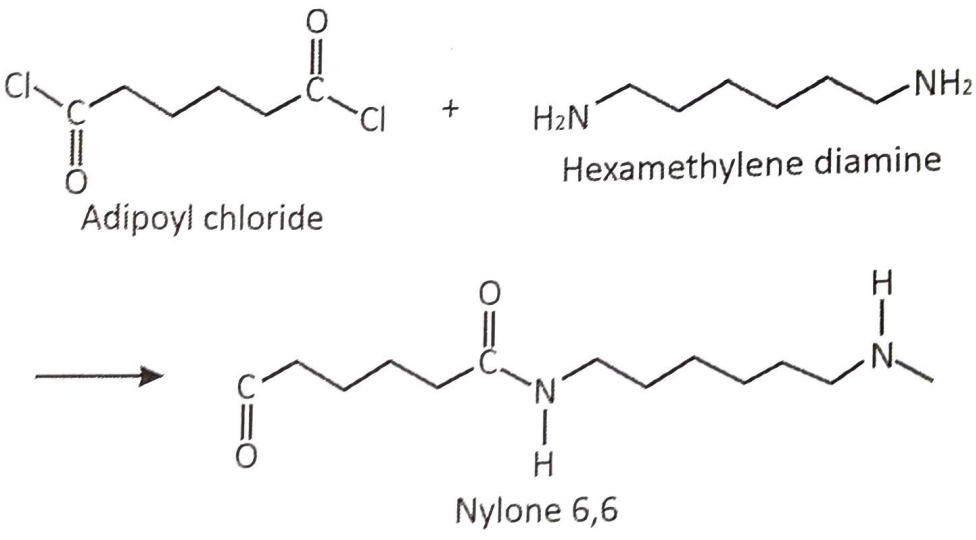
5. Polystyrene:

- Rigid
- Crystal clear

- Low cost
- Easily mouldable
- Resistant to acids except oxidizing acids or alkali
- Used for preparing bottles, tubes, syringes.



6. **Nylon (Polyamide):**
   - Extremely strong
   - Can't be destroyed by mechanical means
   - Made of dibasic acid combined with diamine
   - Impermeable to oxygen.



7. **Polycarbonate:**
   - High impact strength
   - Very good heat resistance.
   - It can be made into a clear transparent container.
   - Used in the preparation of surgical equipments.

8. **Acrylic Multipolymers (Nitrile Polymers):**
   - Represent the acrylonitrile of methacrylonitrile monomer.
   - Medium cost material produces a fairly clear container.

9. Acetal Polyxymethylene (POM):

- Prepared by polymerization of formaldehyde.
- Density is approx. 1.41
- Used in devices, aerosol valves, engineering components.

10. Polymethyl Methoacrylate (PMMA):

- Strong, hard and transparent plastic.
- Used for preparing bottles and tubes.

11. Polyethylene Terephthalate (PET):

- Used as a packaging film
- Its growth has recently escalated with its use in the fabrication of plastic bottles for the carbonated beverage industry.

12. Polytetra Fluoroethylene (PTFE):

- Opaque, translucent and possesses high resistance to solvents and chemicals.
- Unchanged even at a temperature of 250°C.

13. Amino Formaldehydes Polyamides

Dosage Form – Plastic Interactions/Limitations of Plastic Materials:

1. Permeation
2. Leaching
3. Sorption
4. Chemical modification
5. Alteration on the properties of plastics or product

1. Permeation:

- The transmission of gases, vapours or liquids from the surrounding environment into the plastic container is known as "Permeation".
- Permeation of water vapor and oxygen through the plastic wall into the dosage form can be problematic if the drug is sensitive to hydrolysis and/or oxidation.

- An increase in temperature, increases permeability of gases.
- An increase in crystallinity of the material decreases permeability.
- Hydrophilic plastic materials such as nylon are poor barriers to water vapour, while hydrophobic materials like polyethylene are better barriers.
- The concentration of drugs in formulations containing volatile ingredients might change when stored in plastic containers because of the permeation of one or more volatile ingredients through the walls of the plastic containers.
- Plastic containers also affect the physical properties of the product. For example, when water-in-oil emulsion is stored in a hydrophobic plastic bottle, there is a tendency for the oil phase to migrate and diffuse into the plastic.
- Permeation may also affect the shelf-life of a drug.

2. Leaching:

- Release of a constituent from the plastic material of the container into the formulation is known as "leaching".
- For example, particular dyes which are used as colouring agents may migrate into a product, contaminates the product and may cause a toxic effect.

3. Sorption:

- The Process of extraction/removal of one or more of the constituents from the formulation by the packaging material are referred to as "Sorption".
- Becomes a serious problem particularly for dosage forms that contain drug and/or other important ingredients in the solution form.
- May significantly affect the therapeutic efficacy of the formulation containing highly potent drug.

4. Chemical Reactivity:

- Certain ingredients used in plastic container manufacturing may chemically react with one or more components of a drug product.
- These chemically incompatible substances may also alter the appearance of the plastic or formulation.

5. **Modification:**

- The physical or chemical alteration of the packaging material by the drug product is called "modification".
- The content may extract the plasticizer, antioxidant or stabilizer, thus changing the flexibility of the container.
- Permeation, sorption or leaching may also alter the properties of the plastic container. For example:
  (a) Oils have a softening effect on polyethylene;
  (b) Fluorinated hydrocarbons attack polyethylene and PVC.

3. Metal

- Aluminium and stainless steel are the metals of choice for both primary and secondary pharmaceutical packaging.
- Metals are used for the construction of excellent tamper-evident containers.
- Metals are strong, impermeable to gases and shatter proof, so they are ideal packaging material for pressurized containers.
- It is resistant to high and low temperatures.
- They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders.

Package Type	Formulation	Remarks
Strip, blister	Tablets, capsules	Polymer coated aluminium with various thickness are available to improve the saleability of the pack and stability of the product.
Collapsible tubes	Ointments, creams, gels and other semisolids	The tubes with internal protective coating of polymers with spike and without spike are available.
Cans	Aerosols, inhalers, sprays etc.	Pressure resistant and internal polymer coated aluminium containers are available.

Advantages of Metal

1. Metal containers are strong, relatively unbreakable opaque.
2. Resistance to chemical attack.
3. Impervious to water vapour, bacteria.
4. Readily coats a number of metals.
5. They are light in weight as compared to glass containers.

Disadvantages of Metal

1. Expensive metals.
2. Still eye ointments are packed in pure tin tubes.

4. Paper and Board

They are used in various forms for packaging of pharmaceutical products. They are used to prepare outer containers like boxes, drums, envelops and cartons to provide additional protection to other containers, for example, capsules, pessaries, strip and blister packs of tablets, suppositories.

5. Rubber

Excellent material for forming seals, used to form closures such as bungs for vials or in similar applications such as gaskets in aerosol cans.

Mostly used to make stoppers and bulbs for dropper assemblies.

Examples of rubber for pharmaceutical products include:

1. Natural rubber
2. Neoprene rubber
3. Nitrile rubber
4. Butyl rubber
5. Chlorobutyl rubber
6. Bromobutyl rubber
7. Silicone rubber

6. Closures

Closure is required in every bottle to seal the contents. It protects the content. Material does not get spilled or volatilise. It prevents contamination of product from insects or dust.



Closures



CHAPTER

3

Pharmaceutical Aids

Some inorganic and organic chemicals don't have any therapeutic value. These chemicals are used in manufacturing various pharmaceuticals. These are called pharmaceutical acids.

These may be required for such purposes as preservations, stabilization, acidification, alkalization, suspending, excipient, adsorption, absorption, filtration, prevention of oxidation, stabilization, complexation etc.

CLASSIFICATION

Pharmaceutical Aids can be classified into:

- Absorbents and adsorbents
- Acidifiers and alkalisers
- Antioxidants
- Binders
- Buffers
- Buffering agent
- Colouring agents
- Disintegrating agents
- Diluents

- Desiccants
- Emulsifying agents
- Flavouring agents
- Humectants
- Lubricants
- Ointment bases
- Preservatives
- Sweetening agents
- Texturing agents
- Solvents
- Suspending agents
- Tonicity modifiers
- Vehicles

ORGANOLEPTIC PHARMACEUTICAL AIDS

Organoleptic substances promote appearance and palatability of pharmaceutical dosage form and contribute to the acceptance of the pharmaceutical products.

The colouring, flavouring and sweetening are grouped together as organoleptic aids.

Bitter and arid taste drugs are avoided by patients through oral route because of unpleasant taste and odour as-well-as collour. Thus, organoleptic aids are incorporated to improve their colour, flavour, and taste, mainly for products prescribed for geriatric and pediatric patients.

Colouring Agents or Colourants

Colouring agents provide distinctive colour to pharmaceutical dosage forms. These are used to enhance aesthetic appearance of dosage forms. These are used in tablets, gelatine capsules, topical creams, toothpastes. These coloured products appeal children and they can take medicines easily when prescribed.

All colouring agents used in pharmaceutical formulations must be approved and certified by FDA as per D&C Act, 1940.

Pharmaceutical preparations are coloured mainly for following reasons:

- **Increases acceptability:** Colorants can make unattractive medicines acceptable to patients.

  Colorants can make preparations more uniform.
- **For identification:** It helps to identify a product in its manufacturing and distribution stages.
- **Standard preparations:** Natural calamine is not used in pharmaceutical purposes as it does not have constant colour. Thus, it has been replaced with artificial material tinted with a kind of ferric oxide. Tint of green soft soap may vary due to different quality of oils used while preparing. Such differences may be masked by a suitable dye. When lactose is used as the diluent for powdered opium it should be coloured with Caramel to give a uniform appearance to the product.
- **Stability purpose:** Some of the insoluble colours or pigments that are used in tablets or gelatine shells can provide opacity to tem, thus, providing additional benefit by contributing to stability of light sensitive active materials in tablet formulations. Pigments such as the iron oxides, titanium dioxide, and some of the aluminum lakes are especially useful for this purpose.

Types of Colouring Agents

A. **Natural Colours:** They are obtained from animals, plants and minerals.

   1. **Animal Colours:** These are obtained from animal sources:
      - ***Tyrian Blue:*** This is obtained from oxidizing of a colourless secretion from the gland of snails.

- ***Cochineal:*** This is obtained from an insect coccus cactus and has a brilliant red colour (Carminic Acid).

2. **Plant:** These are obtained through extraction.
   - ***Indigo:*** This is obtained from plant Indigofera TYinctoria. The colour wavelength is in between blue and violet and the colour spectrum is 420-450 nm.
   - ***B-Carotene (Carotenoid):*** It is a natural pigments found in broccoli, carrots and spinach. The orange colour is masked by green colour of chlorophyll. It is a source of Vitamin A, can protect body against oxidative damage and can protect the product from UV light.
3. **Minerals:** These are pigments used in cosmetics, lotions.

B. **Synthetic Colours:** These enhance the appearance of pharmaceutical products without being toxic.

1. **Coal tar dyes:** These are obtained from petrochemicals and coal. These are used in medicated shampoo, soap and ointment, etc.
2. **Caramel (Burnt Sugar):** Caramelization process involves heating sugar slowly at 170°Celsius, resulting in breaking down of molecules that reform into compounds with characteristic colour and flavour.



3. **Lake dyes:** These are calcium salts or aluminium of any water soluble colour. A lake pigment is manufactured by precipitating a dye with metallic salt.

Ideal Properties of a Colourant

- Non-toxic and free from impurities.
- Composition is definite, thus making it reliable.
- High colouring power which can impart colour when even used in low quantity.
- Unaffected by light, tropical temperatures, hydrolysis and microorganisms and therefore, be stable on storage.
- Unaffected by oxidizing or reducing agents and pH changes.
- Compatible with medicaments and not interfere with them.
- Readily soluble in water. But it causes difficulty in oil-soluble and spirit soluble components.
- Does not interfere with the tests and assays to which the preparations containing it are subject. Should not be appreciably adsorbed on to suspended matter.
- Free from objectionable taste and odour.
- Readily available and inexpensive.

Flavouring Agents

Flavouring agents refers to mixed sensation of taste, touch, smell, sight and sound which involve a combination of physio-chemical and physiological actions that influence the perception of substances. Flavouring agent is required in order to increase the patient acceptance.

Many artificial flavours have been created with expansion of technology. Cough syrups, laxatives, sedatives antihistamines, antibiotics, vitamins and pediatric and geriatric formulations now are available in a variety of flavours which successfully mask unpleasant tastes without affecting physical and chemical stability.

Flavour acceptance is also affected by age. In general, children like sweet candy like preparations with fruit flavour but adults may prefer less sweet, a more acid taste, while many old people find mint or wine flavours more agreeable. Response to the flavour may not be the same in health and disease while a flavour acceptable for a short time may become objectionable if the treatment prolonged.

The chewable or effervescent tablets need flavours as-well-as sweetening agents to improve patient acceptance.

Drug	Preferred flavour
Antibiotics	Cherry, maple, pineapple, orange, raspberry, banana-vanilla, butterscotch, coconut-custard, fruit-cinnamon, strawberry, vanilla
Antihistamines	Apricot, cherry, cinnamon, grape, honey, lime, peach-orange, peachrum, raspberry, wild cherry.
Barbiturates	Banana-pineapple, banana-vanilla, cinnamon-peppermint, orange, peach-orange, grenadine-strawberry.
Decongestants and Expectorants	Anise, apricot, butterscotch, chery, coconut-custard, custard-mintstrawberry, grenadine-peach, strawberry-lemon, gooseberry, orangelemon, coriander, pineapple, raspberry.
Electrolyte-solutions geriatrics	Cherry, grape, lemon-lime, raspberry, wild cherry syrup, grenadinestrawberry, lime, portwine, cherrywine, wild-strawberry.

The types of flavouring agent used in the preparation are:

1. **Sweetening Agents:** These include sucrose, invert syrup, treacle (used in chlorodyne, i.e., chloroform and morphine tincture BPC), sorbitol, saccharine sodium etc.
2. **Flavoured Syrup:** These include fruit flavoured syrup, syrups with weak therapeutic activity for example the pleasantly aromatic odour and pungent taste of Ginger syrup make it a satisfactory flavour for laxative mixtures containing rhubarb while its carminative action (ability in relieve flatulence) is helpful in this type of preparation, and cocoa syrup.
3. **Aromatic Oils:** Like caraway, clove, dill, lemon, orange, pepper-mint etc.

4. **Synthetic Flavours:** These include synthetic sweeteners, chloroform, vanillin, benzaldehyde etc., and variety of organic compounds like alcohols, aldehydes, esters, ketones, fatty acids and lectones are used alone or combined with essential oils.

Sweetening Agent

Sweetening agents are used to impart sweet taste to the bitter pharmaceutical formulation.

Two types of sweeteners are available:

1. Natural sweeteners of plant origin sweeteners
2. Artificial or synthetic sweeteners.

Natural sweetening agents are preferred over synthetic sweetening agents because

- These do not cause adverse impact on health.
- These have low calories, non-toxic and super sweet.
- These are sugar substitutes for diabetic patients.

The active sweet principles stored in plants can be grouped under: terpenoids, steroidal saponins, dihydroiso-coumarins, dihydrochalcones, proteins, polyols, volatile oils, etc., in nature.

Ideal Properties of Sweetening Agents

Sweetening agents should have the following ideal properties:

- Effective when used in small concentration.
- Must be stable at wide range of temperatures.
- Carcinogenic effects should not be produced if used for prolong period.
- They should have very low or non-calorific value.
- They should be compatible with other ingredients in formulations.
- They should not show batch to batch variations.

Uses of Natural Sweetening Agents

A. Pharmaceutical uses:

1. In pharmaceutical industries these are used in liquid, oral preparations, lozenges, pills and tablets.
2. In liquid orals sugar is used to prepare syrup base, to maintain the consistency and viscosity of the preparation and to mask the bitter taste of the drug.
3. Sugar is also employed in the coating of pills and tablets
4. Honey plays an important role in Ayurvedic system of medicine. It is used as an important vehicle for many preparations

B. Food Industry: Sweetening agents are used to prepare jams, chocolates, sweets, ice-creams, cakes, candies, juices, soft-drinks, beverages, chewing gums and many other food items.

Classification of Natural Sweetening Agents

1. Natural Sweetening Agents:

A. Saccharides Sweetening Agents, e.g., sucrose, liquid glucose, honey etc.

B. Non-saccharides Sweetening Agents:

(a) Terpenoids
(b) Steroidal saponins
(c) Proteins
(d) Dihydrochalcones
(e) Dihydro isocoumarins
(f) Volatile oils
(g) Polyols

2. Synthetic Sweetening Agents

PRESERVATIVES

Preservatives are substances that are commonly added to various foods and pharmaceutical products in order to prolong their shelf

[illegible] by microbial growth or by undesirable

[illegible] preservatives to such products, especially to [illegible] water content, is essential for avoiding [illegible] contamination by microorganisms during storage. [illegible] are put in foods to inhibit growth of bacteria, yeasts, [illegible] that can cause disease.

[illegible] preservations slow down the spoiling process caused by microorganisms. Frozen and canned foods are preserved after heating the food items to kill microorganisms. Processed foods are foods that are put through a process to kill harmful bacteria that may exist in the food. These processes are supposed to be helpful to the products, but they can also add harmful substances.

Need for Preservatives

- To protect our drug from microbial attack
- To stabilize our product
- To enhance activity and efficacy of drug
- To increase shelf life of our product

Ideal Properties of Preservatives

- It should be non-irritant, non-toxic and physio-chemically stable.
- It should be compatible with other ingredients used in formulation.
- It should be act as antimicrobial agent and exert wide spectrum of activity.
- It should be potent and act effectively in small concentrations.
- It should maintain activity throughout product manufacturing, shelf life and usage.

life, to prevent decomposition by microbial growth or by undesirable chemical changes.

The addition of preservatives to such products, especially to those that have higher water content, is essential for avoiding alteration and degradation by microorganisms during storage. Preservatives are put in foods to inhibit growth of bacteria, yeasts, or molds that can cause disease.

Chemical preservations slow down the spoiling process caused by microorganisms. Frozen and canned foods are preserved after heating the food items to kill microorganisms. Processed foods are foods that are put through a process to kill harmful bacteria that may form in the food. These processes are supposed to be helpful to the products, but they can also add harmful substances.

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- It should maintain activity throughout product manufacturing, shelf life and usage.

Classification of Preservatives

Preservatives are classified on variety of the basis and some of these are as follows:

A. Based on Mechanism of Action:

1. **Antioxidants:** The agent which prevent oxidation of Active pharmaceutical ingredient which otherwise undergo degradation due to oxidation as they are sensitive to oxygen.

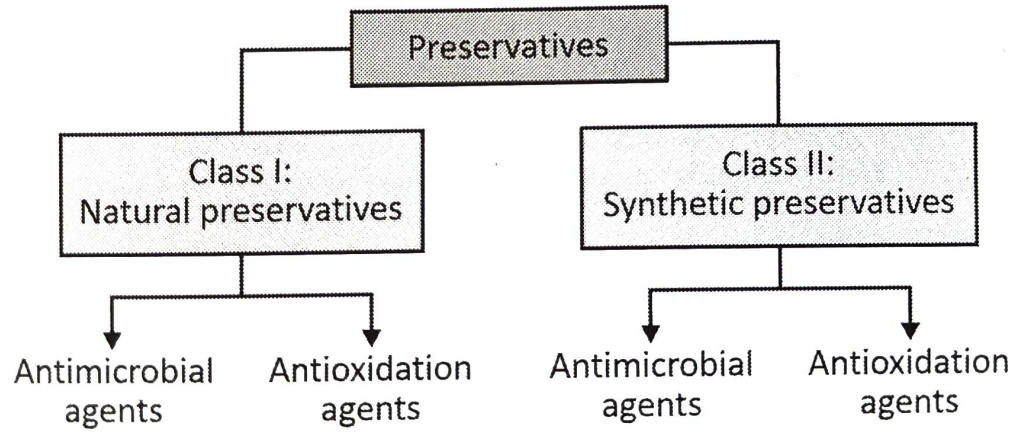
   For example, Vitamin E, Vitamin C, Butylatedhydroxyanisole (BHA), Butylatedhydroxytoluene (BHT).

2. **Antimicrobial Agents:** The agent which active against gram positive and gram negative microorganism which causes degradation of pharmaceutical preparation. Which are active in small inclusion level.

   For example, Benzoates, Sodium benzoate, Sorbates.

3. **Chelating Agents:** The agents which form the complex with pharmaceutical ingredient and prevent the degradation of pharmaceutical formulation.

   For example, Disodium ethylenediamine tetra acetic acid (EDTA), Polyphosphates, Citric acid.



B. Based on Source:

1. **Natural Preservatives:** These drugs are obtained by natural sources that is plant, mineral sources, animal etc.

   For example, Neem Oil, Salt (sodium chloride), Lemon, Honey etc.

2. **Artificial Preservatives:** These preservatives are man made by chemical synthesis active against by various micro-organisms in small concentration.

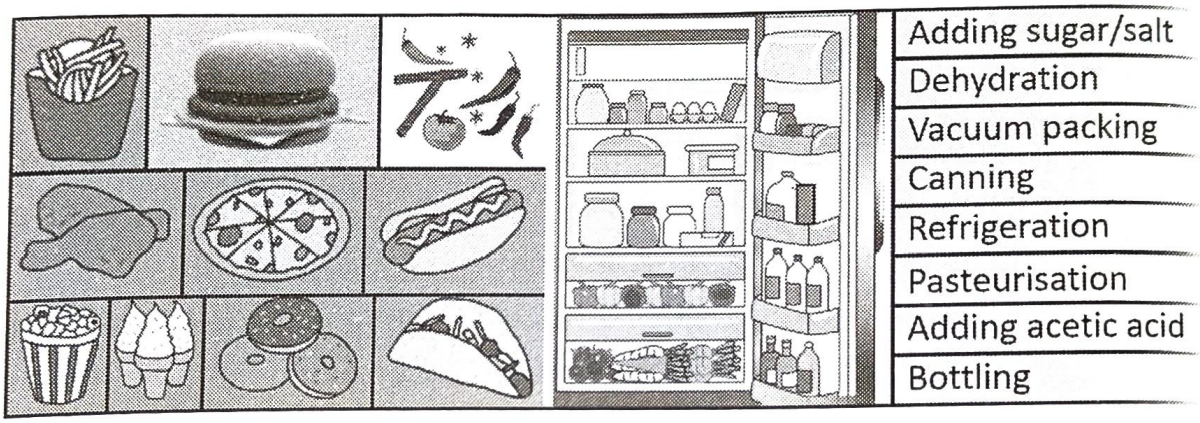
   For example, Benzoates, Sodium benzoate Sorbates, propionets, nitrites etc.

Uses and Benefits Preservatives

1. **Preservatives in Food:** preservatives prevent the bacteria, fungus, yeast and mould to grow and multiply in food and spoiling it.

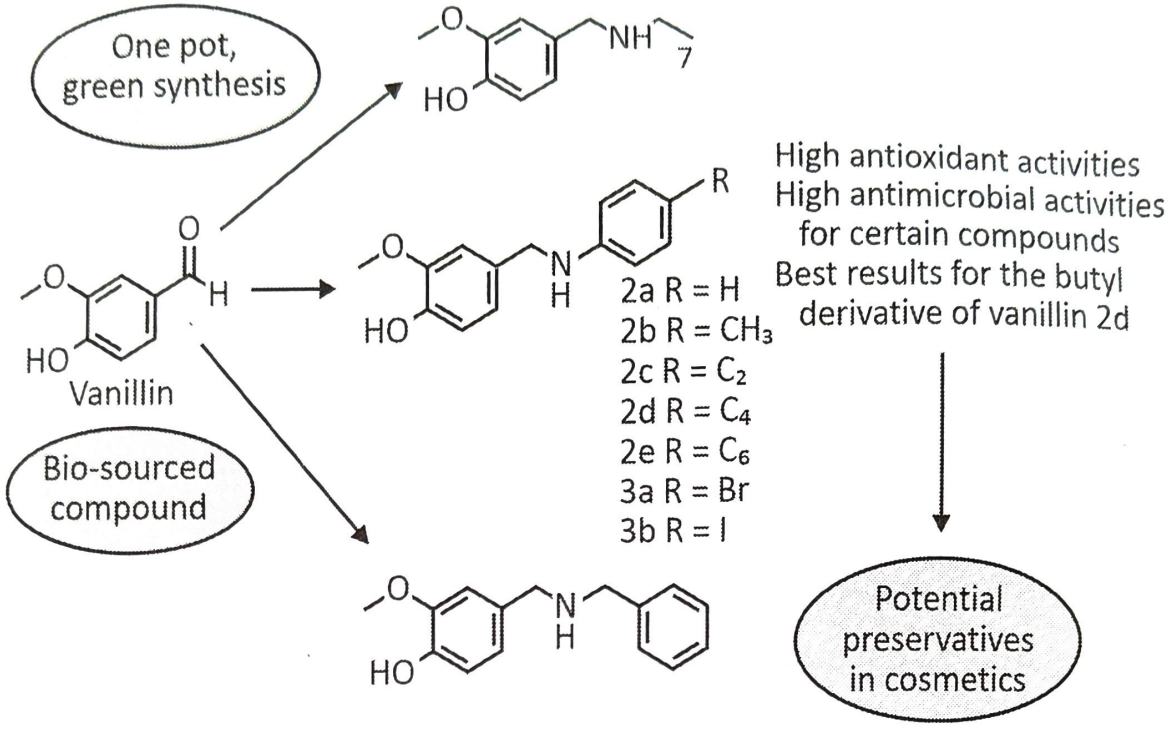
   Preservatives also increase the shelf life of food.

   Preservatives also slow down the process of rancidity of food.



2. **Preservatives in Medicine and Pharmaceuticals:** Some preservatives are used to prevent the microbial contamination of some medicines like acetaminophen, insulin and cough syrup. Preservatives mainly prevent growth of microorganisms causing disease.
3. **Preservatives in Cosmetics and Personal Care Products:** Preservatives are added in cosmetics like sunscreens, lotions, shampoos, cleansers, toothpaste and makeup to prevent growth of harmful bacteria.
4. **Antimicrobial preservatives** in cosmetics and personal care products help prevent the growth of moulds, yeasts and bacteria, guarding against contamination that can cause irritation or infections. Some ingredients in the cosmetics combine with oxygen in presence of heat or light and may spoil the product.

Thus, antioxidant preservatives are added in cosmetics to prevent this oxidative reaction.



5. **Preservatives in Wood:** Wood treated with preservatives can be used to build telephone poles, road signs and marine pilings as well as decks, play structures and raised garden beds.



CHAPTER

4

Unit Operations

Each chemical process frequently consists of a fewer number of distinct individual steps. Each step is called as unit operation.

Each unit operation is based on one type of scientific principle.

The following are the principles of unit operation:

1. **Size Reduction:** In this drug are reduced to smaller pieces, coarse particles or fine powder, e.g., manufacture of talcum powder and tooth powder.

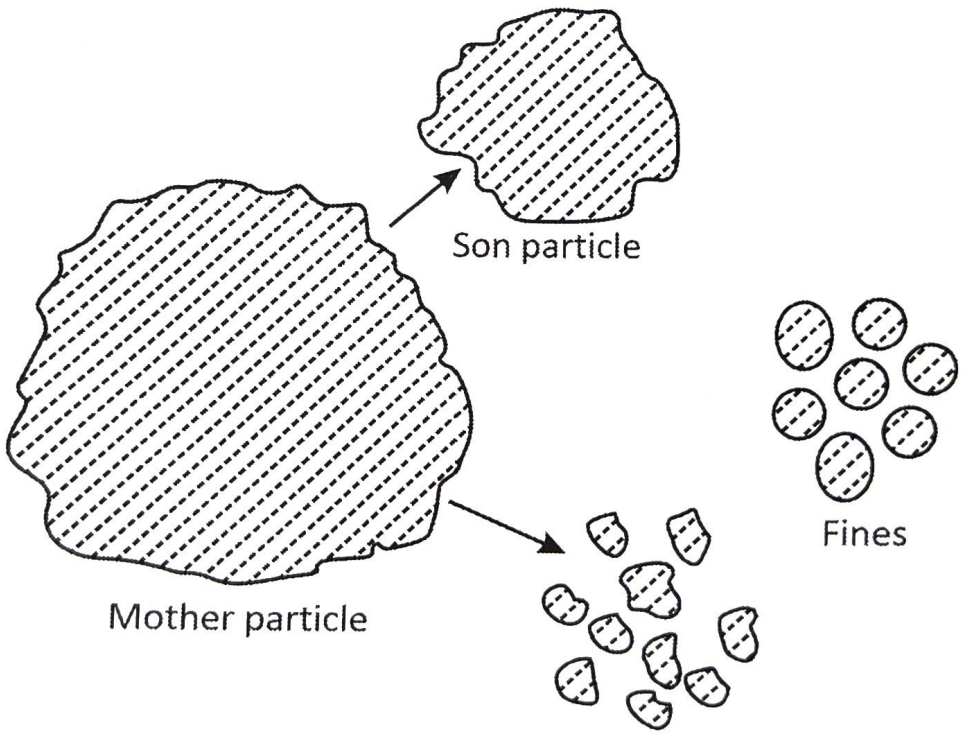


Fig. 4.1: *Size Reduction*

2. **Drying:** Solids are heated to evaporate liquid or moisture from them.
3. **Distillation:** In this process, first liquid is heated and converted to vapours and then cooled again to get back liquid, e.g., lemon grass oil.

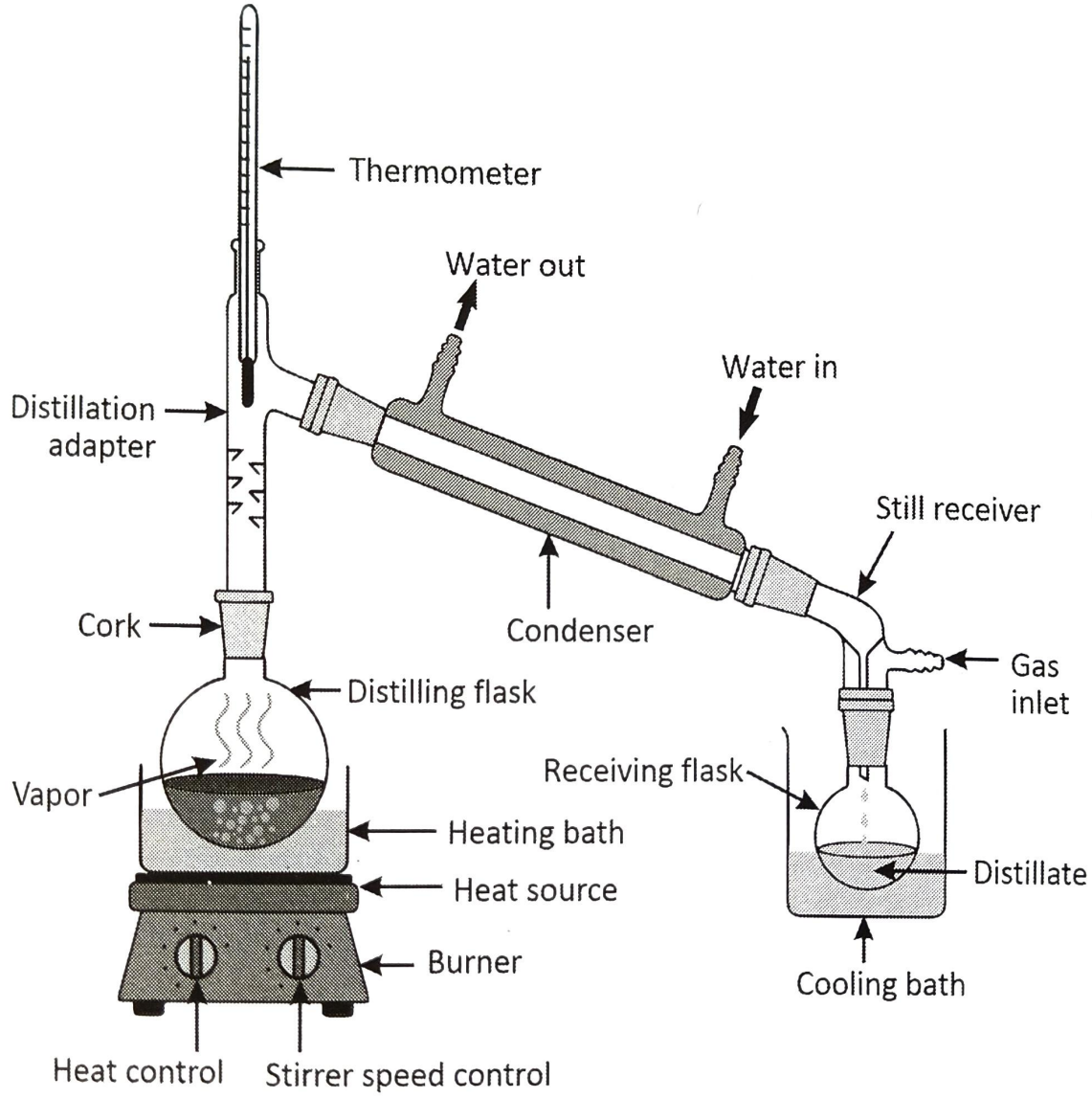


Fig. 4.2: *Distillation*

4. **Evaporation:** In this, liquid is heated below its boiling point, e.g., manufacture of sugar.

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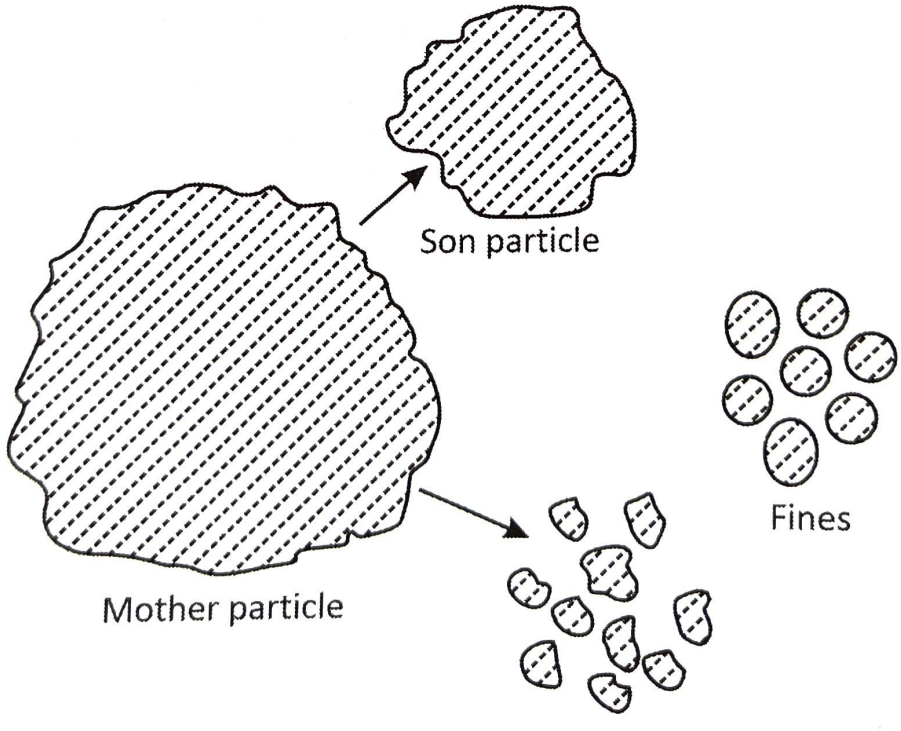


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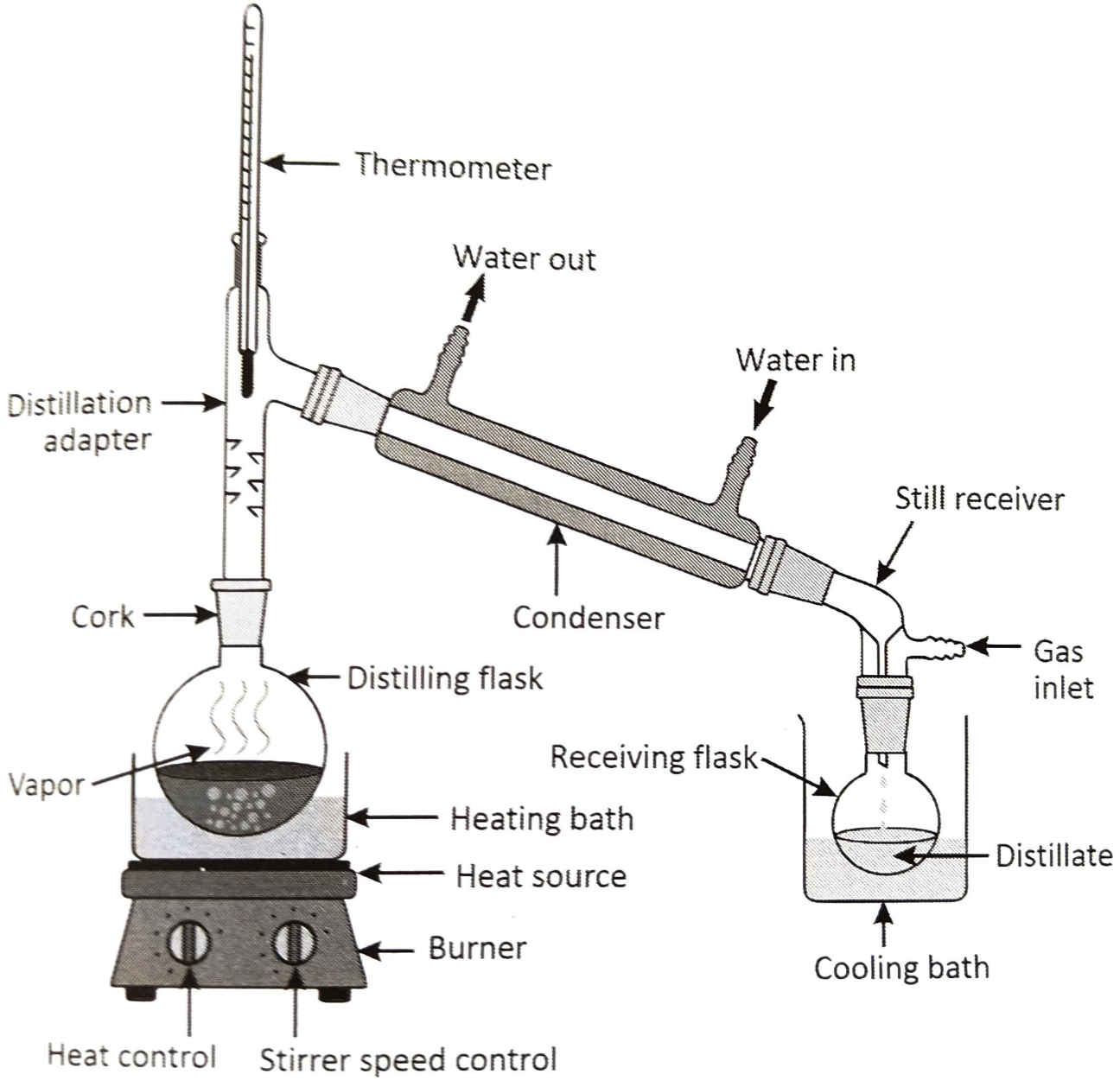


Fig. 4.2: *Distillation*

4. **Evaporation:** In this, liquid is heated below its boiling point, e.g., manufacture of sugar.

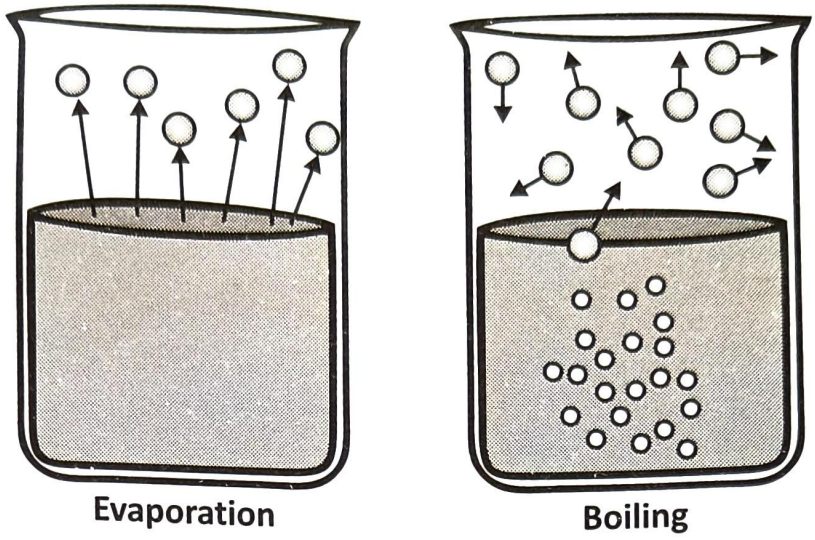


Fig. 4.3: Evaporation

SIZE REDUCTION

Definition

Size reduction is a process of reducing large solid unit masses into small masses, i.e., coarse particles or fine particles.

Size reduction is also called as comminution or diminution or pulverization.

Size Reduction Methods

It is achieved by two processes:

1. Precipitation method
2. Mechanical method

1. **Precipitation Method:** In this method, first the substance is dissolved in a particular solvent. Then a second solvent is to be added which should be miscible with first solvent added but should not dissolve the substance. For example, inorganic chemicals such as calcium carbonate, magnesium carbonate and yellow mercuric oxide.
2. **Mechanical Method:** The substance is subjected to mechanical forces using grinding equipment.

Advantages of Size Reduction

1. **Content uniformity:** The small and uniform size of particles make the mixing of different substances effective.

   The larger the number of particles better is the mixing. Thus, better content uniformity can be achieved.
2. **Uniform flow:** Smaller particle size and controlled size distribution promote the flow of powders into dies during compression of tablets.
3. **Effective extraction of drugs:** Smaller particles allow solvent to rapidly penetrate into the tissue or cells of vegetable.

4. **Effective drugs:** Drying of a granular mass can be rapid and effective, if the size of granules is small and uniform.
5. Improved physical stability.
6. **Improved dissolution rate:** Size reduction increases surface area, which facilitates intimate contact of solid particles and gastric or intestinal juices. Thus, the rate of dissolution increases.
7. **Improved rate of absorption:** The smaller the particle size, the faster is the absorption, because of enhanced dissolution.

Disadvantages of Size Reduction

1. **Drug degradation:** Increased surface area increases the chance of drug decomposition that further enhances dissolution.
2. **Poor mixing:** An increase in surface area may promote the absorption of air, which may inhibit wet ability of the drug during production. Hence optimum particle size is desirable to improve blending and to avoid poor mixing.
3. **Contamination:** During milling and grinding Surfaces of impurities in the powder wear off. Such type of mills should be avoided, when drugs of high purity are required.

Objectives of Size Reduction

1. **Size reduction leads to increase of surface area.**

   Example 1: Size reduction facilitates the dissolution of solid drug particles. Griseofulvin, an antifungal drug, when administered in its micronized form shows around five times better absorption.

   Example 2: The absorptive power of charcoal and kaolin increases after size reduction due to increase in surface area.
2. Size reduction narrows the size range resulting in easy mixing of powders.

3. Pharmaceutical suspensions require finer particle size. It reduces rate of sedimentation.
4. Pharmaceutical capsules, insufflations (i.e., powders inhaled directly into the lungs), suppositories and ointments require particles size to be below 60 m size.

HAMMER MILL

Principle

It works on the principle of impact between rapidly moving hammers mounted on a rotor and the powder material.

Construction

The construction of hammer mill is shown in Fig. 4.4. The hammer mill can be either the horizontal or vertical shaft type. Hammers are usually made up of hardened steel, stainless steel with impact surface.

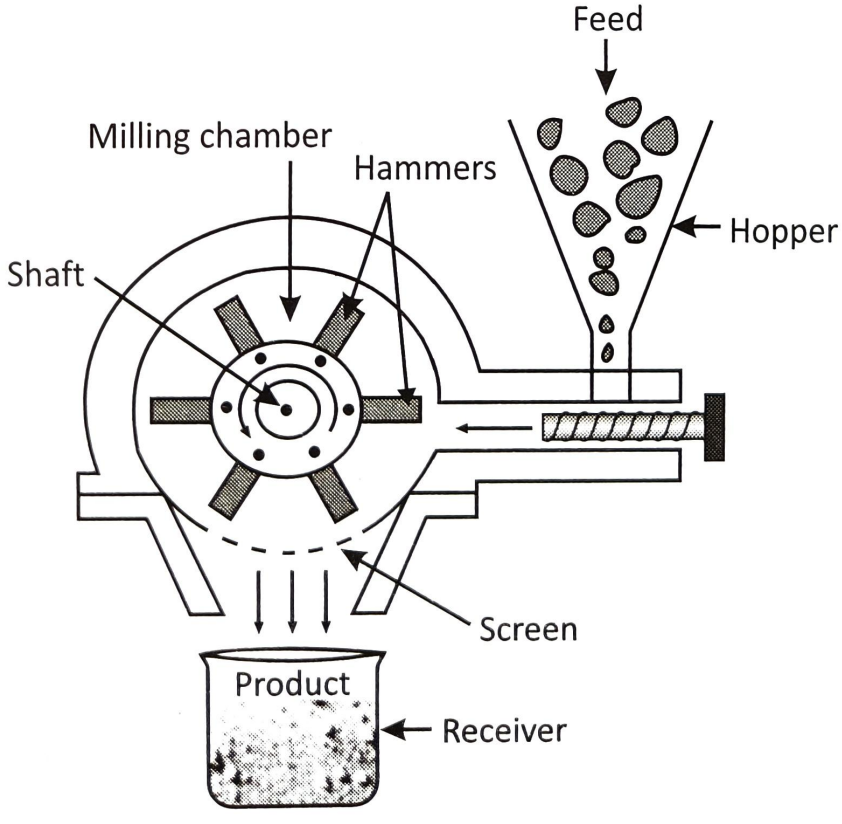


Fig. 4.4: *Hammer Mill*

Hammers may take several shapes. The shapes are stirrup ar bar. Bar shaped hammer is used extensively in tablet granulation

The hammer blades can be with flat edges or sharp edges o both on each side.

This unit is enclosed with a chamber containing a grid o removable screen through which material must pass. Screens ar prepared using metal sheets of verifying thickness.

Working

The material is put in the hopper of mill's chamber, which i connected with drum and has ganged hammers which are attached to shafts. Fast moving of hammers crush the material in powdered form of desired size.

The advantage of this mill is that the chance of jamming is less as hammers are not fixed. Thus, mill is in continuous operation.

Due to high speed of operation, the heat generated which may affect thermolabile materials. Moreover, high speed of operation also causes damage to the mill if foreign objects such as stone or metal present in the feed.

The screens are interchangeable so that any grade of fineness can be obtained.

The fineness of the product can be regulated by altering:

- Rotor speed,
- Feed rate,
- Clearance between hammers and grinding plates,
- Number and type of plates,
- Size of discharge opening

Uses

Hammer mill is used for producing intermediate grades of powder from almost all types of substance.

BALL MILL

Also known as tumbling mill or pebble mill.

Principle

- Ball mill works on the principle of impact and attrition that is size reduction is done by impact as the balls drop from near the top of the shell.
- Impact between the rapidly moving balls and the powder material.
- Attrition will be the predominant mode of action.

Construction

The construction of ball mill is shown in Fig. 4.5.

1. Ball mill consists of hollow cylinder which is made up of a metal and can be rotated on its longitudinal axis.
2. The cylinder is filled with balls that are made of stainless steel or rubber.

The cylinder contains ball that occupy 30-50% of the mill volume. The weight of ball is kept constant. The ball size depends on the size of feed and diameter of mill.

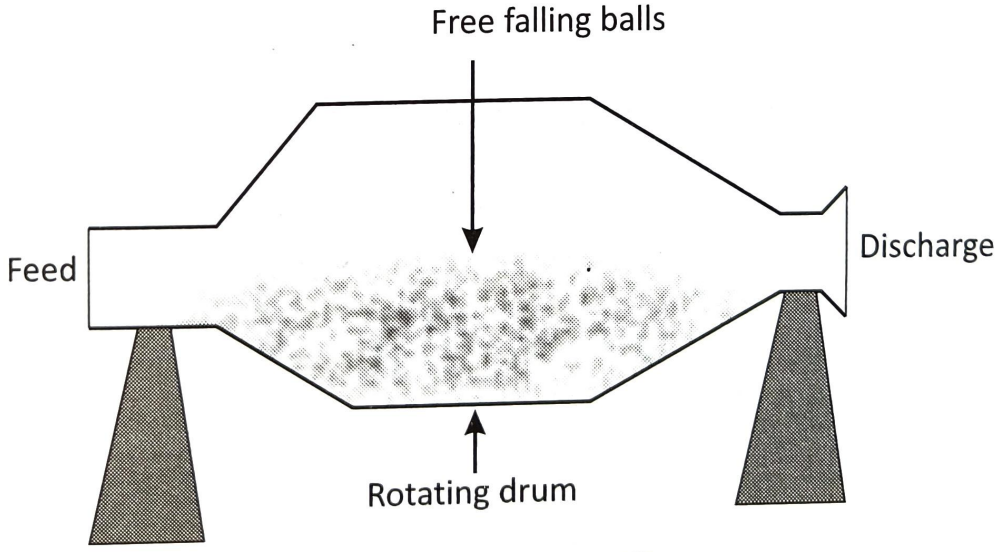


Fig. 4.5: *Ball Mill*

Working

The drug to be ground is put into the cylinder of the mill and is rotated. The speed of rotation is very important. The quantity of drug that it is filled to about 60% of the volume. A mill is allowed to rotate on its longitudinal axis.

At a low speed, the mass of balls will slide or roll over each other and only a negligible amount of size reduction will occur [Fig. 4.6 (a)].

At high speed, the balls will be thrown out of the walls by centrifugal force and no grinding will occur [Fig. 4.6 (b)].

At correct speed, i.e., at 2/3rd of the speed, the centrifugal force just occurs with the result that the balls are carried almost to the top of the mill and then fall in by this way the maximum size reduction is affected by the impact of particles between the balls and attrition between balls [Fig. 4.6 (c)].

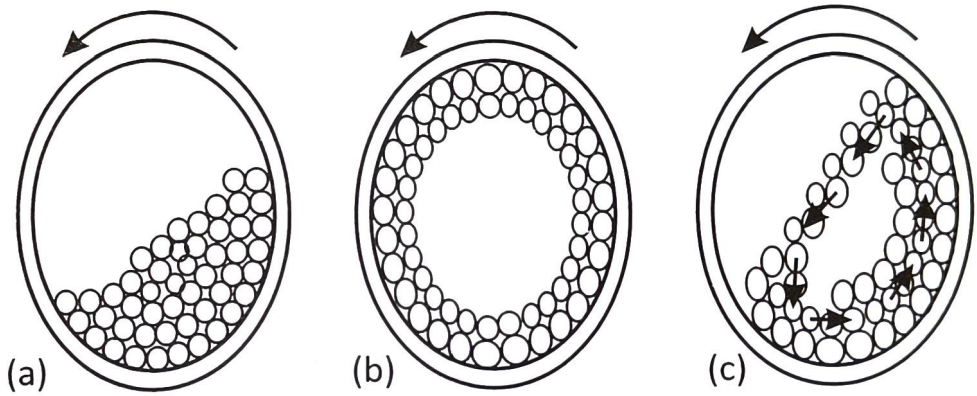


Fig. 4.6: *Correct cascade of action of a ball mill in operation*

Uses

1. The mill is used to grind brittle drugs to fine powder.
2. Fine grinding with a particle size of 100 to 5 mm or less can be obtained, particularly for hard and abrasive materials.
3. Ball mill at low speed is used for milling dyes, pigments and insecticides.

Advantages

1. It can Produces fine powder.

2. It can be used for continues operation, if sieve or classifier is attached to the mill.
3. Ball mill is suitable for both wet and dry grinding process.
4. It is suitable for milling toxic materials since cylinder is in completely closed form.
5. It is used in milling highly abrasive materials.

Disadvantages

1. Machine produces large noise.
2. Wear and tear of balls may result in contamination of product.
3. Soft, tacky, fibrous material cannot be milled by ball mill.

SIZE SEPARATION

Size separation is a unit operation that involves the separation of a mixture of various sizes of particles into two or more portions by means of screening surfaces.

Size separation is also known as sieving, sifting, classifying or screening. Size separation is based on physical differences between the particles such as size, shape and density.

During the process of size reduction, it is not possible to obtain the particles of uniform size. Hence, a special technique is used to separate particles of specialized size which is known as size separation.

Screening is method of separating particles according to size alone. The material that remains on the given screening surface is known as oversize or plus material. The material passing through the screening surface is known as undersize or minus material.

Applications of Size Separation

1. Useful in production of tablets and capsules.
2. As a quality control tool for the analysis of raw material such as Griseofulvin and aspirin.
3. To test the efficiency of size reduction equipment or process.
4. To optimize agitation, screening, feed rate during production.
5. To separate undesirable particles.
6. To prevent environmental pollution.

Objectives of Size Separation

1. After size reduction, particles of solid materials are of varying sizes. The size-reduced particles are then passed through sieves to get fractions of narrow size range.
2. During tablet granulation the granules should be within narrow size range, otherwise, weight variation will take place during tablet punching.

CLASSIFICATION OF POWDER ACCORDING TO IP/OFFICIAL STANDARDS FOR POWDER

1. Coarse powder
2. Moderately coarse powder
3. Moderately fine powder
4. Fine powder
5. Very fine powder

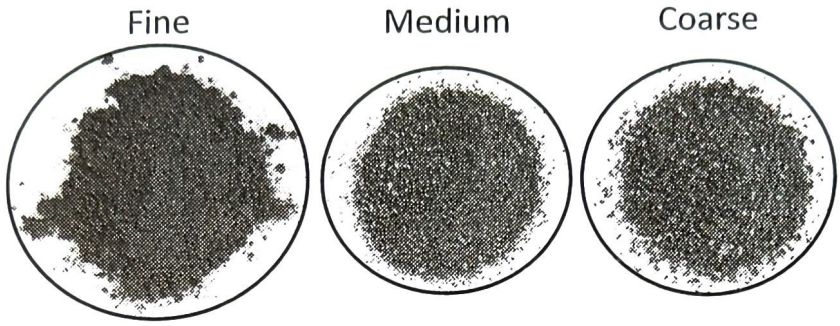


Fig. 4.7

1. **Coarse powder:** A powder of which all the particles pass through a sieve with nominal aperture of 1.70 mm (No. 10 sieve) and not more than 40.0 percent through a sieve with nominal mesh aperture of 355 μm (No. 44 sieve) is called coarse powder.
2. **Moderately coarse powder:** A powder of which all the particles pass through a sieve with nominal mesh aperture of 710 μm (No. 22 sieve) and not more than 40.0 percent through a sieve with nominal mesh aperture of 250 μm (No. 60 sieve) is called as moderately coarse powder.
3. **Moderately fine powder:** If all the particles of powder pass through a sieve with nominal mesh aperture of 355 μm (No. 44 sieve) and not more than 40.0 percent through a sieve with nominal mesh aperture of 180 μm (No. 85 sieve) is called as moderately fine powder.
4. **Fine powder:** In case all particles pass through a sieve with a nominal mesh aperture of 180 μm (No. 85 sieve) is called as fine powder.
5. **Very fine powder:** If all particles of the powder pass through a sieve with a nominal mesh aperture of 125 μm (No. 120 sieve) it is said to be very fine powder.

Table 4.1: Official standards of powder according to IP

Grade of powder	Sieve through which all particles must pass	Nominal mesh aperture size	Sieve through which 40% of particles pass	Nominal mesh aperture size
Coarse powder	10	1.7 mm	44	355 µm
Moderately coarse powder	22	710 µm	60	250 µm
Moderately fine powder	44	355 µm	85	180 µm
Fine powder	85	180 µm	—	—
Very fine powder	120	125 µm	—	—

CYCLONE SEPARATOR

Principle

In this process solids are separated from fluids. This is based on the principles of centrifugal force. The separation process depends on particle size and particle density. It is also possible to allow fine particles to be carried with the fluid.

Construction

1. It consists of a cylindrical vessel having a cone at base.
2. Tangential inlet is fitted at upper part of vessel.
3. Solid outlet is present at the base.
4. Fluid outlet is present at the centre of top portion, which extends inwardly into separator. This prevents short circuiting of air directly from inlet to outlet of fluid.

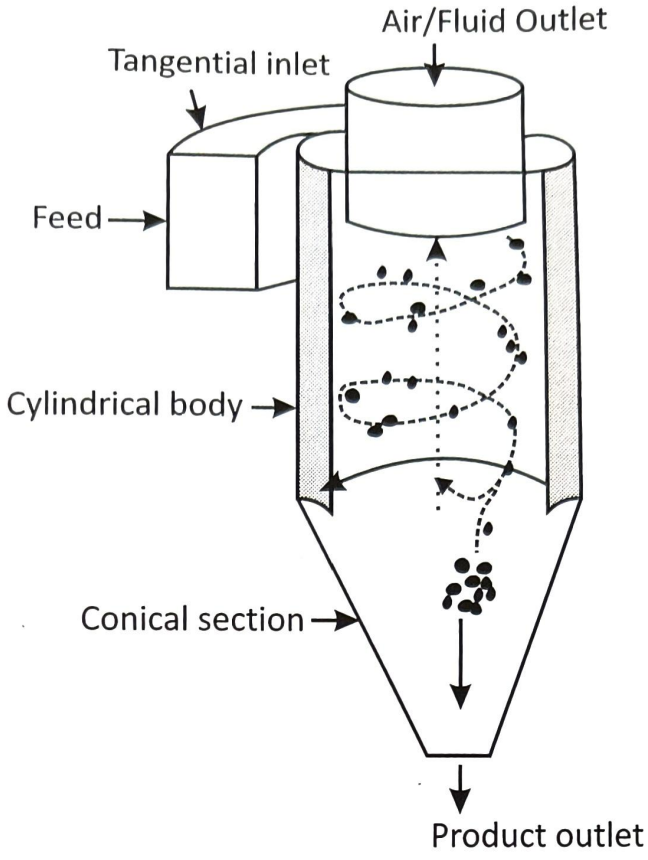


Fig. 4.8: *Cyclone Separator*

Working

Solids suspended in a stream of fluids are introduced tangentially at a very high velocity into the vessel. Rotatory movement takes place within the vessel. Centrifugal force throws the solid particles towards the wall of the vessel. With the diminishing speed, these solid particles fall at the base and are collected at the solid outlet. The fluid (air) can escape from the central outlet at the top.

SIEVES

Sieves are the simplest and sieving is the most frequently used method for size separation.

Sieves for pharmaceutical testing are woven from wires of brass, bronze, stainless steel or other suitable material. Wire should have uniform cross section. Sieves are coated with galvanizing materials to prevent corrosion.

STANDARDS OF SIEVES

1. **Number of sieves:** Sieve number indicates the number of meshes in a length of 2.54 cm in each transverse direction parallel to the wires.
2. **Nominal size of aperture:** Nominal size of aperture indicates the distance between the wires. It represents the length of the side the square aperture. The IP has given nominal mesh aperture in mm or in μm.
3. **Nominal diameter of the wire:** Wire mesh sieves are made from the wire having the specified diameter in order to give a suitable aperture size and sufficient strength to avoid distortion of the sieve.
4. **Approximate percentage sieving area:** This standard expresses the area of the meshes as percentage of the total area of the sieve. It depends on the size of the wire used for any particular sieve number. The sieving area is within the range of 35 to 40%.
5. **Aperture tolerance average size:** Some variation in the aperture size is unavoidable. This variation is expressed as a percentage and is known as aperture tolerance average.

MIXING

Definition

Mixing is defined as a process that tends to result in a randomization of dissimilar particles within a system.

In mixing two or more than two substances are combined together.

Objectives

The main objectives of mixing are:

1. Mixing is done to get uniform mixture.
2. To promote the chemical reaction to get uniform products.
3. Suspension is formed by dispersing solids in liquids.
4. Emulsion is formed by dispersing two immiscible liquids.

Types of Mixtures

Mixtures may be classified as follows:

1. Positive Mixtures
2. Negative Mixtures
3. Neutral Mixtures

1. **Positive Mixtures:** These types of mixtures are formed when two or more than two gases or miscible liquids are mixed together by means of diffusion process. In this case no energy is required provided the time allowed for solution formation is sufficient. These types of materials do not create any problem in mixing.
2. **Negative Mixtures:** These types of mixtures are formed when insoluble solids are mixed with a vehicle to form a suspension or when two immiscible liquids are mixed to form an emulsion. These mixtures are more difficult to prepare and require a higher degree of mixing with external force as there is tendency of the components of these mixtures separate out unless they are continuously stirred.

3. **Neutral Mixtures:** Many pharmaceutical products such as pastes, ointments and mixed powders are the examples of neutral mixtures. They are static in their behaviour. The components of such products do not have any tendency to mix spontaneously but once mixed, they do not separate out easily.

Factors Influencing Mixing

1. **Nature of the product:** Rough surface of one of the components does not induce proper mixing. The reason for this is that the active substance may enter into the pores of the other ingredient. A substance that can absorb on the surface can decrease aggregation, for example, addition of colloidal silica to a strongly aggregating zinc oxide can make it a fine dusting powder which can be easily mixed.
2. **Particle size:** Variation in particle size leads to separation as the small particles move downward through the spaces between the bigger particles. As the particle size increases, flow properties also increase due to the influence of gravitational force on the size. It is easier to mix two powders having approximately the same particle size.
3. **Particle shape:** For uniform mixing, the particles should be spherical in shape. The irregular shapes can become inter-locked and there are less chances of separation of particles once these are mixed together. Particle charge – Some particles exert attractive forces due to electrostatic charges on them. This results to separation or segregation.
4. **Particle size:** It is easy to mix two powders having approximately the same particle size. The variation of particle size can lead separation, the small particles move downward through the spaces between the bigger particles.
5. **Density of particle:** Demixing is accelerated when the density of the smaller particles is higher or when the mixing process stop abruptly. This is due to the fact that dense material always moves downward and settles at the bottom.

Table 4.2: Classification of mixing equipment

Sr. No.	Type of mixing	Name of the mixer	Uses
1.	Liquid-liquid mixing	Shaker mixers Propeller mixers Paddle mixers Turbine mixers Sonic and ultrasonic devices such as Rapisonic homogenizer Silverson emulsifier Colloid mill	Used in the preparation of emulsions, antacid suspensions, mixtures such as anti-diarrhoeal bismuth-kaolin mixtures etc. Rapisonic homogenizer is particularly used in the mixing of immiscible liquids, i.e., preparation of emulsions.
2.	Solid-solid mixing	Agitator mixers Tumbling mixers Double-cone mixers V-blenders	Used for the mixing of dry powders.
3.	Semi-solid mixing	Agitator mixers like sigma mixers and planetary mixers Shear mixers like colloidal mills and triple roller mills	These mixers are used for wet granulation process in the manufacture of tablets, in the production of ointments. Sigma mixers can also be used for solid-solid mixing.

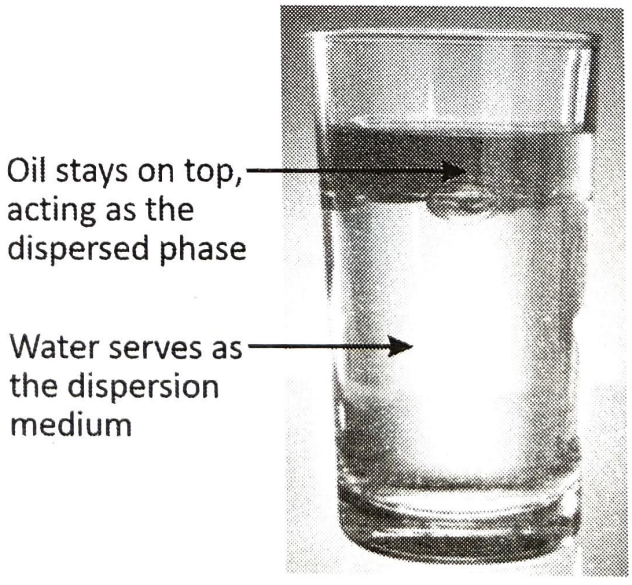


Fig. 4.9: *Liquid-liquid Mixing*

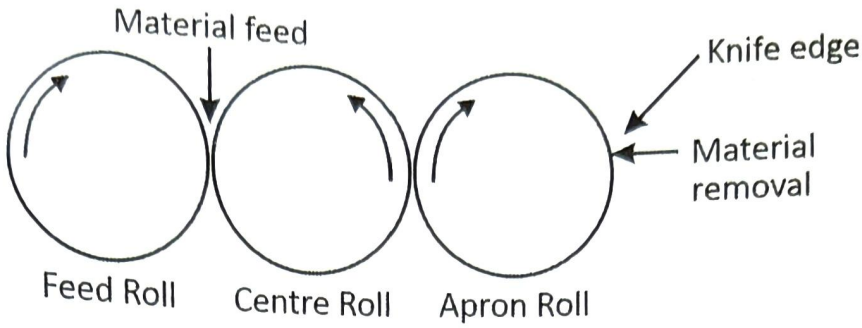


Fig. 4.10: *Semi-solid Mixing*

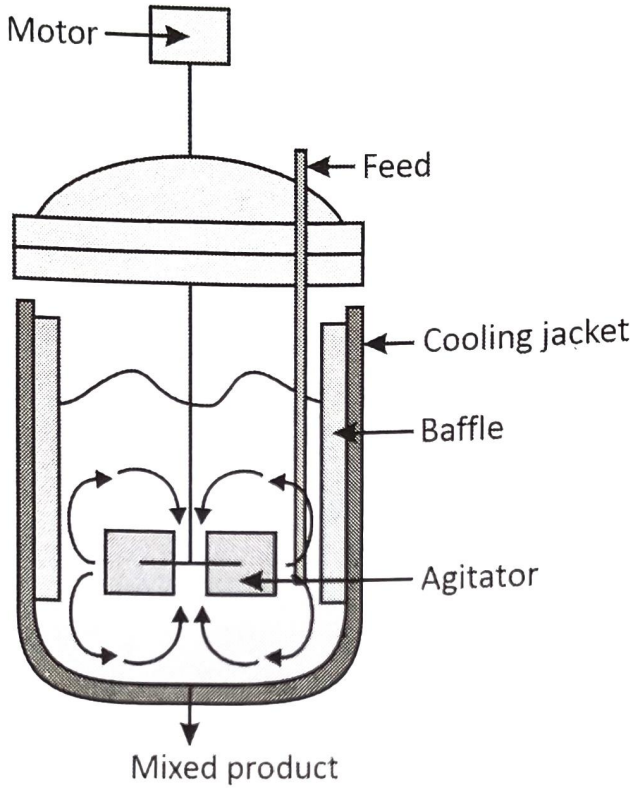


Fig. 4.11: *Solid-solid Mixing*

MIXING OF POWDER

Mechanism of Mixing

In all type of mixers, mixing is achieved by applying one or more of the following mechanisms:

(a) **Convective Mixing:** During convective mixing transfer of groups of particles in bulk take place from one part of powder bed to another. Convective mixing is referred to as macromixing.

(b) **Diffusive Mixing:** During this mixing, the materials are tilted so that the gravitational forces cause the upper layers to slip and diffusion of individual particles take place over newly developed surfaces. Diffusion is also sometimes referred to as micro-mixing.

(c) **Shear Mixing:** During shear mixing, shear forces are created within the mass of the material by using agitator arm or a blast of air.

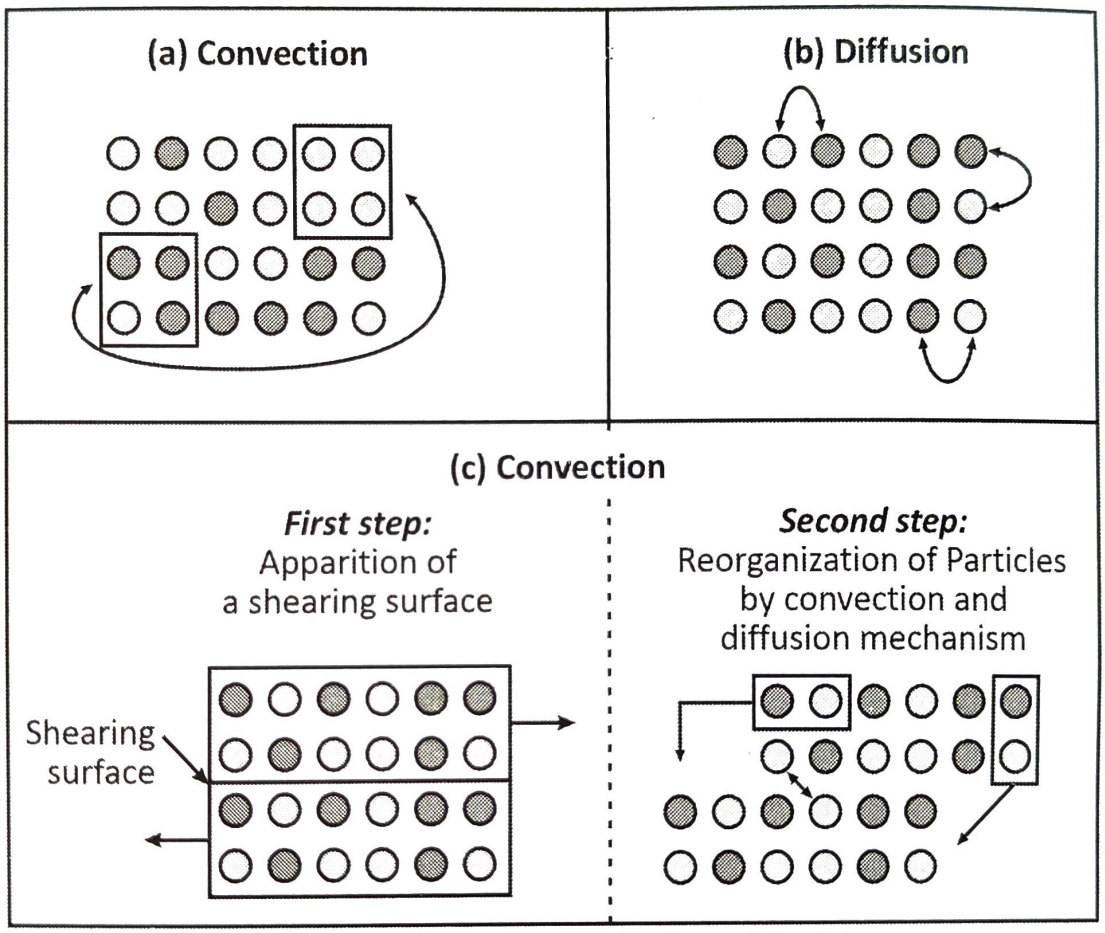


Fig. 4.12: ***Mechanism of Mixing Powder***

Equipment

Double Cone Blender

The mixing of powder in double cone blender is due to tumbling and shearing action with blade.

It is made up of stainless steel and is available in different capacity ranging from 5-200 kg or even more. The efficiency of

blender depends on the speed of rotation. The rate of rotation should be optimum which depends on the size and shape of tumbler as well as nature of material. The common range is 30-100 r.p.m.

The material to be blended is loaded approximately 50 to 60% of the total capacity of the blender. As the blender rotates the material undergoes tumbling motion and mixes the material thoroughly. Agitator blade can also be fixed in order to produce shearing action.

The double cone blender is an efficient design for mixing powders of different density and is used mainly for small quantity of powders.



Fig. 4.13: *Double cone blender*

Advantages

1. They handle large capacities.
2. Easy to clean, load and unload.
3. This equipment requires minimum maintenance.

Disadvantages

1. If powders are free flowing, serial dilution is required for the addition of low dose active ingredients.

MIXING OF LIQUIDS

Liquid mixing may be divided into following two sub-groups:

1. **Mixing of liquids and liquids:**
   (a) Mixing of two miscible liquids
   (b) Mixing of two immiscible liquids
2. **Mixing of liquids and solids:**
   (a) Mixing of liquids and soluble solids
   (b) Mixing of liquids and insoluble solids

Mechanism of Mixing

1. Bulk transport
2. Turbulent mixing
3. Laminar mixing
4. Molecular diffusion

1. **Bulk transport:** Bulk transport is the process of transfer of large portion of material from one location to other, which is achieved by mixing devise.
2. **Turbulent mixing:** Turbulent mixing is defined as mixing due to turbulent flow, which results in random fluctuation of the fluid velocity at any given point within the system.In turbulent flow, fluid velocity at a given point fluctuates continuously in three directions, x, y and z. Turbulent flow is highly effective mechanism for mixing.
3. **Laminar mixing:** Laminar mixing is the mixing of two dissimilar liquids through laminar flow, i.e., the applied shear stretches the interface between them. In this mechanism, layers fold back upon themselves. Thus, the number of layer increases. This is also suitable for liquids, which require moderate mixing.
4. **Molecular diffusion:** Molecular diffusion is the mixing at molecular level in which molecules diffuse due to thermal motion. Molecular diffusion is explained by the Fick's law

which depends on the concentration gradient at different region. When molecular diffusion and laminar flow occur simultaneously, molecular diffusion reduces the sharp discontinuities at the interface between the two layers.

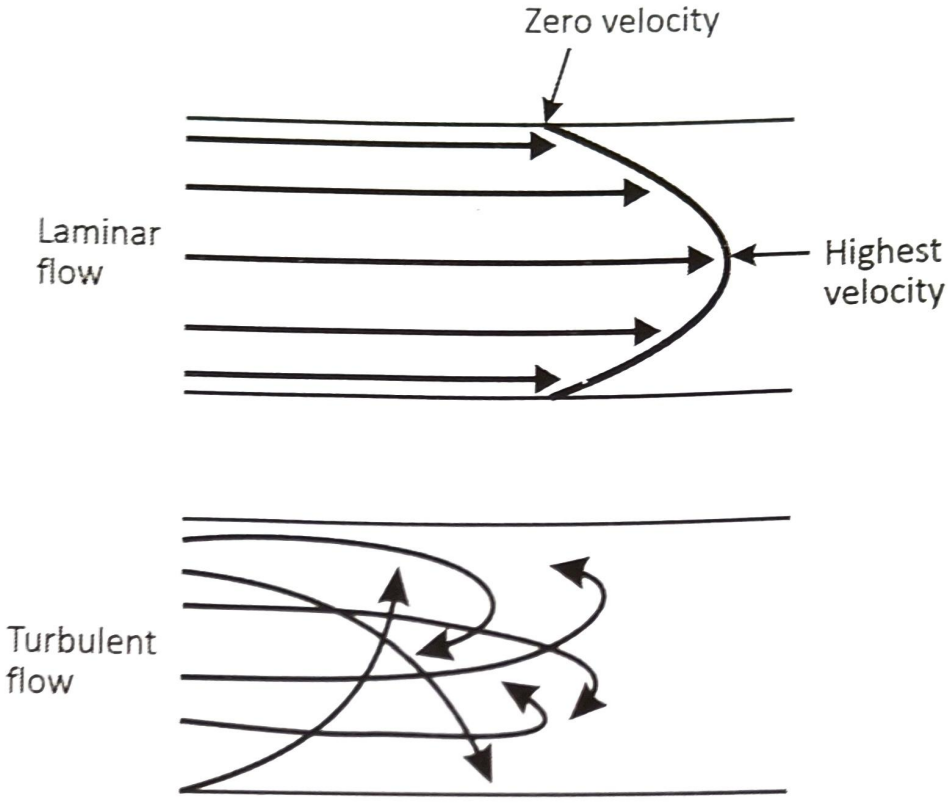


Fig. 4.14: *Mechanism of Mixing of Liquids*

Equipment

Turbine Mixer

It consists of a vessel and a circular disk impeller. A number of short, straight or curved blades are attached to it. The turbine impeller is usually rotated at somewhat lower speed than the propeller. The turbine mixer is used for mixing of more viscous liquids.

For example, syrups, liquid paraffin, glycerine etc.

Baffles are often used to prevent vortexes.

A mixing vessel is said to be baffled when four vertical strips, each having a width of 1/10 to 1/12 of the tank diameter, are attached to the internal surface of the cylindrical container

perpendicularly at 90 degrees position. If solids are present, the baffles are fixed with a gap of about 1 inch between the baffle and the vessel wall.



Fig. 4.15: *Turbine mixer*

Uses of Turbine Mixers

Turbines are effective for high viscous solutions with a wide range of viscosities up to 7, oopascal.

Advantage

Turbines give greater shearing forces than propellers and thus they are more suitable for preparation of emulsions.

MIXING OF SEMI-SOLIDS

The mixing of semi – solids is done for preparing ointments, creams, pill masses and wet mass for making granules etc.

Equipments

1. Triple Roller Mill

Construction:

The mill consists of three rollers which are made of a hard abrasion-resistant material.

These rollers are arranged in such a way that they come very close to each other.

These rollers are rotated at different rates of speed. The material coming between the rollers is crushed depending on the gap between them and the difference in rates of movement of the two surfaces.

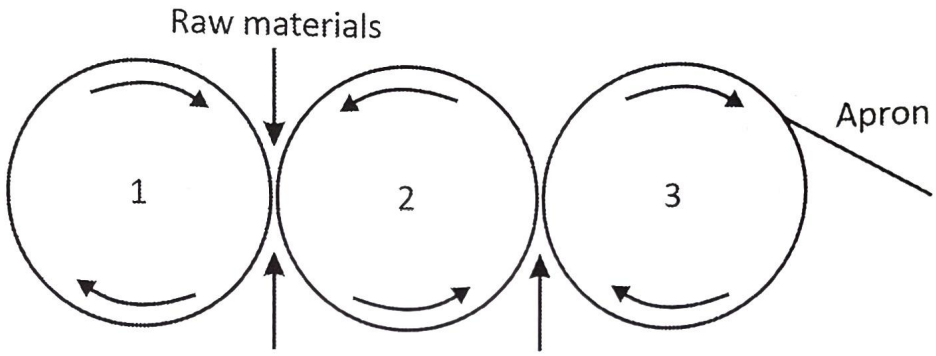


Fig. 4.16: *Triple roller mill*

Working:

The material is passed into the hopper after passing the material into hopper, comes between roller 1 and 2 and is reduced in size in the process. The gap between roller 2 and 3 is usually less than that between 1 and 2, further crushes and smooth the mixture which adheres to roller 2. A scrapper is arranged in such a way, that it can remove the mixed material from the roller no. 3 and does not allow the material which has not passed between both sets of the rollers to reach the scrapper (apron).

Uses:

The triple roller mill is very useful for the purpose of mixing of solid powder in ointment base.

Advantage:

The triple roller mill produces very uniform dispersion and is suitable for continuous processes.

2. Silverson Mixer Homogenizer

Principle:

The silverson homogenizer works on the principle that the large globules in a course emulsion are broken in to smaller globules by intensive shearing forces and turbulence by high-speed rotors.

Construction:

- It consists of emulsifier head that contains turbine blades.
- The blades are surrounded by mesh which is enclosed by cover having perforations.
- Electric motor fixed at top rotates the blades.
- Shaft is attached to motor at one end and emulsifying head at other end.

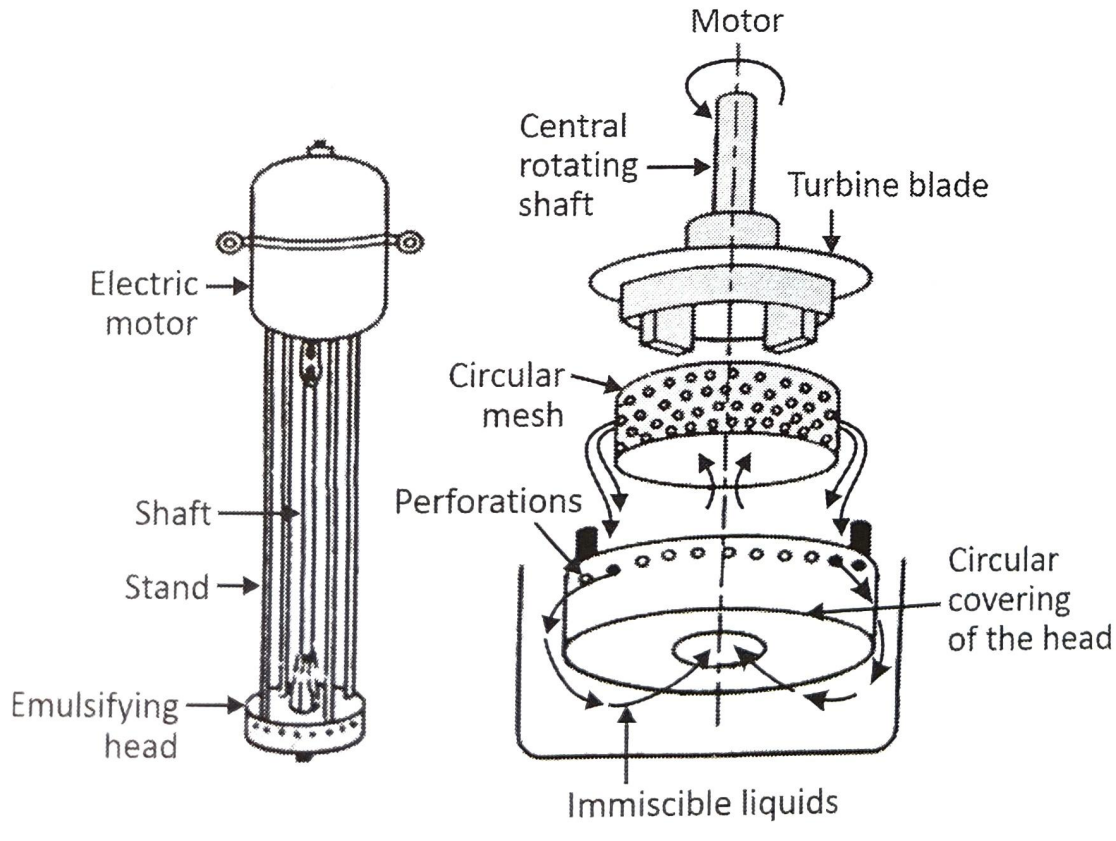


Fig. 4.17: *Silverson Mixer Emulsifier*

Working:

The emulsifier head is dipped in to the vessel containing immiscible liquids. When the motor is started, shaft rotates the head. Therefore, turbines blades also rotate at very high speed. The liquids are sucked trough the fine holes. The complex flow pattern can cause droplet break up under either laminar or turbulent conditions Centrifugal force expels the content through mesh and then to cover and subjects them to mechanical shear. This is followed by intense hydraulic shear. The oil is reduced in to globules quickly resulting in a homogenous uniform product. Then the fine emulsion emerge trough opening of cover. As a result, bigger globules rapidly break in to smaller globules.

Uses:

Used in preparation of creams, ointments, pharmaceutical suspension and emulsion of fine particle size.

Advantages:

1. Fast and efficient.
2. They are used to get a fine droplet or particle size (2-5 microns).
3. Process efficiency is good.
4. Low operating cost.

Disadvantage:

1. Chance of chocking of pores of mesh.

FILTRATION

It is the process of separating solid from liquid or gas. In this process, solution is passed through a porous medium and solid constituents are retained at top and fluid passes below.

When a solid are present in a very small portion i.e., not exceeding 1.0 percent the process of its separation from liquid is called clarification.

TERMS USED IN FILTRATION

- **Slurry:** Suspension to be filtered.
- **Filter medium:** porous medium used to retain solid.
- **Filter cake:** Accumulated solids on the filter.
- **Filtrate:** Clear liquid passing through the filter.

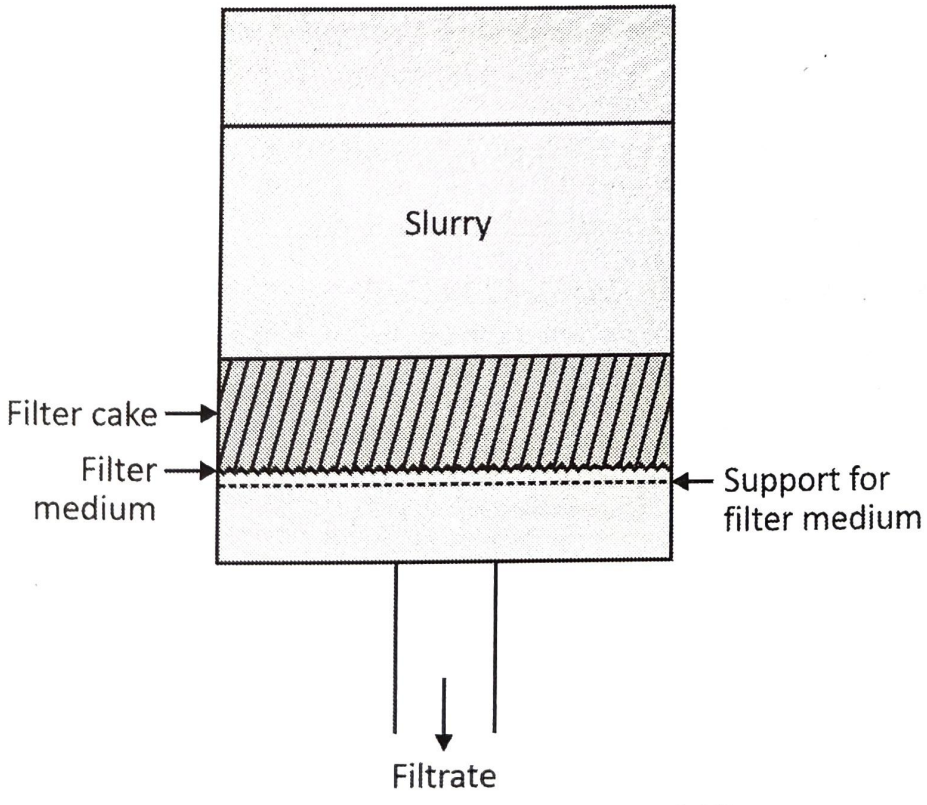


Fig. 4.18: *Silverson Mixer Emulsifier*

PROCESS OF FILTRATION

- Pores of filter paper should be smaller than the size of particles to be separated.
- Filter medium (filter paper) is placed on a support (mesh).
- Slurry is placed over the filter medium.
- Due to pressure difference across the filter, fluid flows through the filter medium
- Fluid flows below by the action of gravity.
- So, solids are trapped on the surface of the filter medium

APPLICATIONS OF FILTRATION

- Production of sterile products
- Production of bulk drugs
- Production of liquid dosage formulation
  - Dewaxing of oils
  - Removing suspended oils from aqueous solutions
  - Removing of undesirable solids
  - Clarifying the potable water
- Effluents and waste water treatment

MECHANISM OF FILTRATION

The mechanism whereby particles are retained by a filter is significant only in initial stages of filtration.

1. **Straining:** In this, pores of filter medium are larger than size of solid constituents. Due to which solid particles remain at the top.
2. **Impingement:** Solids having the momentum move along the path of streaming flow and strike (impinge) the filter medium. Thus, the solids are retained on the filter medium.

3. **Entanglement:** Particles become entwined (entangled) in the masses of fibres (of cloths with fine hairy surface or porous felt) due to smaller size of particles than the pore size. Thus, solids are retained within filter medium.
4. **Attractive forces:** There occurs attraction between the solid constituents and the filter medium, due to which solid constituents are separated from fluid.

TYPES OF FILTRATIONS

1. **Surface/screen filtration:** It is a screening action by which pores or holes of medium prevent the passage of solids.

   Mechanism involved: Straining and impingement

   For this, plates with holes or woven sieves are used.
2. **Depth filtration:** In this slurry penetrates to a point where the diameter of solid particles is greater than that of the tortuous void or channel.

   Mechanism: **Entanglement:** The solids are retained with a gradient density structure by physical restriction or by adsorption properties of medium.

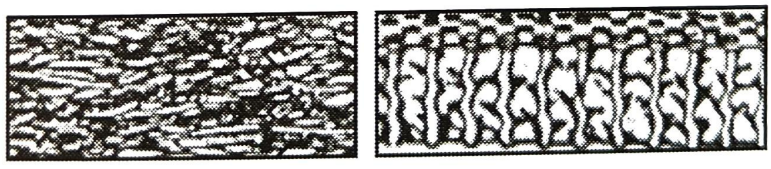


Fig. 4.19: ***Types of Filtrations***

THEORIES OF FILTRATION

- The flow of liquid through a filter follows the basic rules that govern the flow of any liquid through the medium offering resistance.
- **The rate of flow may be expressed as:**

$$\text{Rate} = \text{Driving force} \div \text{Resistance}$$

- The rate of filtration may be expressed as volume (litres) per unitn time (dv ÷ dt).
- **Driving force:**

  Pressure upstream – Pressure downstream
- Resistance is not constant.
- It increases with an increase in the deposition of solids on the filter medium.
- Therefore, filtration is not a steady state.
- The rate of flow will be greatest at the beginning of filtration process, since the resistance is minimum.
- After forming of filter cake, its surface acts as filter medium andn solids continuously deposit adding to thickness of the cake.

Resistance to movement:

$$\frac{\text{(Pressure upstream – Pressure downstream)}}{\text{Length of capillaries}}$$

1. **Poiseuille's Equation:** Poiseuille considered that filtration is similar to the streamline flow of liquid under pressure through capillaries.

   Poiseuille's Equation is:

   $$V = \pi \Delta P r4/8L\eta$$

   where, V = rate of flow

   m^3/s (l/s) ΔP = Pressure difference across the filter, Pa

   r = Radius of capillary in the filter bed, m

   L = Thickness of filter cake (capillary length), m

   5v = Viscosity of filtrate, Pa.

   If the cake is composed of bulky mass of particles and the liquid flows through the interstice, then flow of liquids through these may be expressed by this equation.
2. **Darcy's Equation:** Poiseuille's law assumes that the capillaries found in the filter are highly irregular and nonuniform.

Therefore, if the length of capillary is taken as the thickness of bed, a correction factor for radius is applied so that the rate is closely approximated and simplified.

The factors influencing the rate of filtration has been incorporated into an equation by Darcy, which is:

$$V = KA\Delta P/L\eta$$

where, K = Permeability coefficient of cake, m^2

A = Surface area of porous bed (filter medium), m^2

K depends on characteristics of cake, such as porosity, specific surface area and compressibility.

Permeability may be defined quantitatively as the flow rate of a liquid of unit viscosity across a unit area of cake having unit thickness under a pressure gradient of unity.

This equation is valid for liquids flowing through sand, glassn beds and various porous media.

This model is applied to filter beds or cakes and other types of depth filter.

This equation is further modified by including characteristics of K by Kozeny-Carman.

3. **Kozeny-Carman (K-C) equation:** Kozeny-Carman equation is widely used for filtration.

$$V = A/\eta S2 \times \Delta P/KL \times \varepsilon 3/(1 - \varepsilon)2$$

where, ε = porosity of cake (bed)

S = Specific surface area of particles comprising the cake m^2/m^3

K = Kozeny constant (usually taken as 5)

FACTORS AFFECTING THE RATE OF FILTRATION

1. **Pressure:** The rate of filtration of liquid is directly proportional to the pressure difference between the filter medium and filter cake.

2. **Viscosity:** The rate of filtration is inversely proportional to the viscosity of the liquid undergoing filtration. Liquids which are very viscous get filtered slowly in comparison to liquids with low viscosity.
3. **Surface area of the filter media:** The rate of filtration is directly proportional to the surface area of filter media. Pleating the filter paper or using a fluted funnel increases the effective surface area of filter paper for filtration.
4. **Temperature of liquid to be filtered:** Temperature plays an important role in the rate of filtration. Viscosity is reduced by rise in temperature and the filtration of viscous oils, syrup etc., is often accelerated by filtering them while they are still hot.
5. **Particle size:** The rate of filtration is directly proportional to particle size of solid to be removed.
6. **Pore size of filter media:** The rate of filtration is directly proportional to the pore size of the filter media. The liquid having coarse particles requires a coarse filtering media to remove them.

FILTRATION EQUIPMENT'S

1. Filter press
2. Meta filter
3. Filter leaf
4. Membrane filter
5. Filter candles
6. Sintered filters

Membrane Filter

Membrane filters act as a barrier to separate contaminants from water, or they remove the particles contaminating the water. Reverse osmosis, ultrafiltration, and nanofiltration all use a membrane in their different filtration processes.

Construction

Membrane filters are made of thin and flat membranes of cellulose derivatives, such as, cellulose acetate and cellulose nitrate.

- These filters are brittle when in dry condition and can be stored for an indefinite period.
- The filters are between 50 and 150 μ thick and are available in sizes upto 60 cm^2.

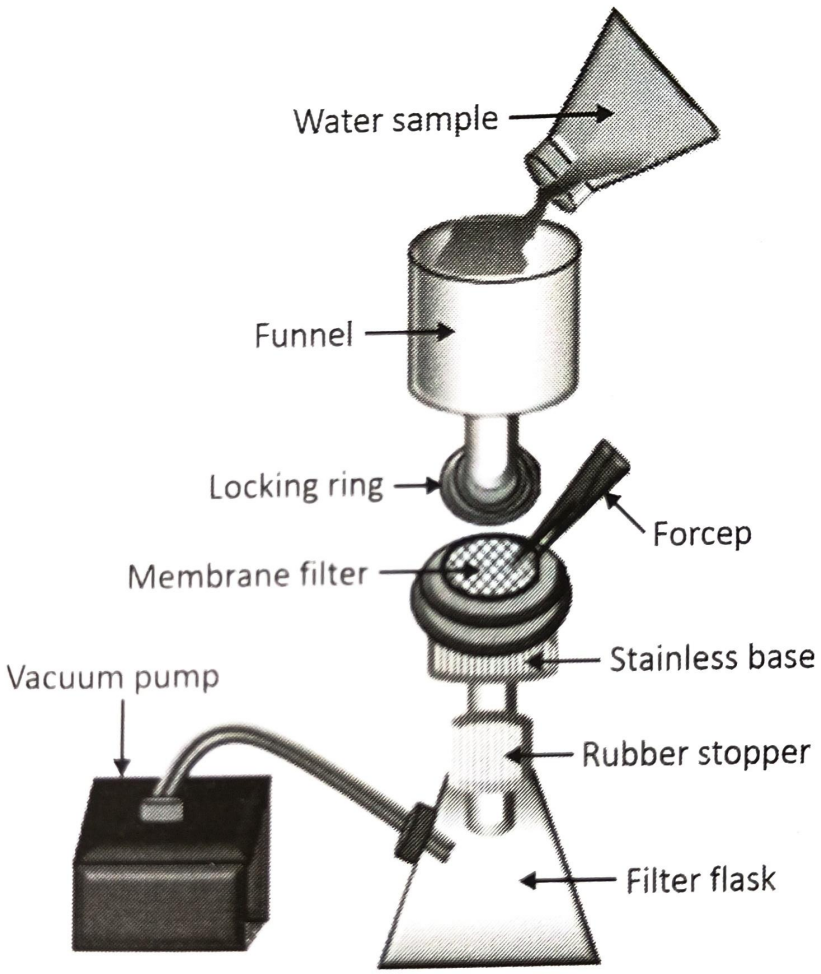


Fig. 4.20: *Membrane filter unit*

Working

- A membrane filter has 400 to 500 million pores per square centimetre of filter surface.
- The pores are absolutely uniform in size and occupy about 80% of filter volume.
- To avoid rapid clogging of a membrane, pre-filtration is often

- The selection of a membrane filter for a particular application depends on the particles to be removed.

Uses

- These filters are mainly used for sterilization of both aqueous and oily liquids.
- The membrane filters cannot be used for filtration of organic solvents, such as alcohols, ketones, esters and chloroform.

Advantages

1. No bacterial growth through the filter takes place during prolonged filtration.
2. They are disposable and hence no cross contamination takes place.
3. Adsorption is negligible they yield no fibres or alkali into the filtrate.
4. Filtration rate is rapid.

Disadvantages

1. They may clog though rarely.
2. Ordinary types are less resistant to solvents like chloroform

Sintered Filter

Construction

- These are made of borosilicate glass.
- Borosilicate glass is finely powdered, sieved, and particles of desired size are separated.
- It is then packed into a disc mould and heated to temperature at which adhesion takes place between the particles.
- The disc is then fused to a funnel of suitable shape and size.

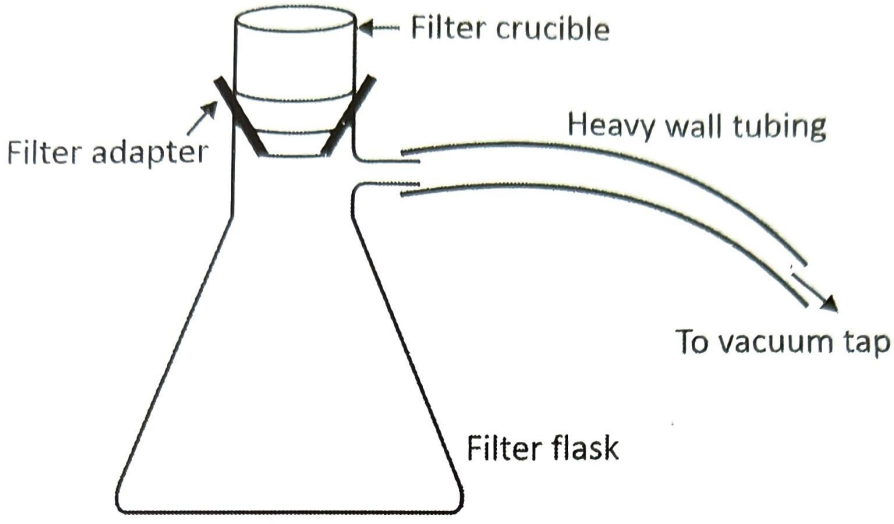


Fig. 4.21: *Sintered filter*

Working

- The sintered glass filters are available in different pore size.
- The funnel with sintered filter is numbered according to the pore size.
- The filtration is carried out under reduced pressure.
- These funnels are used for bacterial filtration.
- These are also available in stainless steel which has greater mechanical strength.

DRYING

DEFINITION

Drying is defined as removal of small amount of water or other liquid from a material by the application of heat.

Drying is important technique used in pharmaceutical industry.

Proper drying prevents deterioration of the product and it also improves the solubility of product.

Drying is a downstream operation and commonly utilized in the last stage of the process and thus has considerable importance.

APPLICATIONS OF DRYING

1. In the pharmaceutical industry it is used as a unit process in the manufacture of granules which can be dispensed in bulk or converted into tablets or capsules.
2. Drying can also be used to reduce the bulk and weight of the material, thereby lowering the cost of transportation and storage.
3. It helps in the size reduction of crude drugs. The presence of moisture in the crude drug does not allow it to get powdered easily.
4. It helps in preservation of crude drugs of plant from mould growth, which occurs due to presence of moisture.
5. Drying is also used in the processing of material e.g., the preparation of dried aluminium hydroxide, the spray drying of lactose and in preparation of solid extracts.

EQUIPMENTS USED IN DRYING PROCESS

1. Tray dryer
2. Tunnel dryer

3. Rotary dryer
4. Fluidized bed dryer
5. Vacuum dryer
6. Freeze dryer

Fluidized Bed Dryer

Principle

In fluidized bed dryer, hot air is passed at high pressure through a perforated bottom of container containing granules to be dried. The granules are lifted from the bottom and suspended in the stream of air. This condition is called as fluidized state.

Construction

Two types of fluid dryers are available, vertical fluid bed dryer and horizontal fluid bed dryer.

The construction of vertical fluidized bed dryer is shown in Fig. 4.22.

The dryer made up of stainless steel or plastic.

A detachable bowl is placed at the bottom of the dryer, which is used for charging and discharging.

The bowl has perforated bottom with a wire mesh support for placing materials to be dried.

A fan is mounted in the upper part for circulating hot air.

Fresh air inlet, prefilter and heat exchanger are connected serially to heat the required temperature.

The temperature of hot air and exit air are monitored.

Bag filters are placed above the drying bowl for recovery of fans.

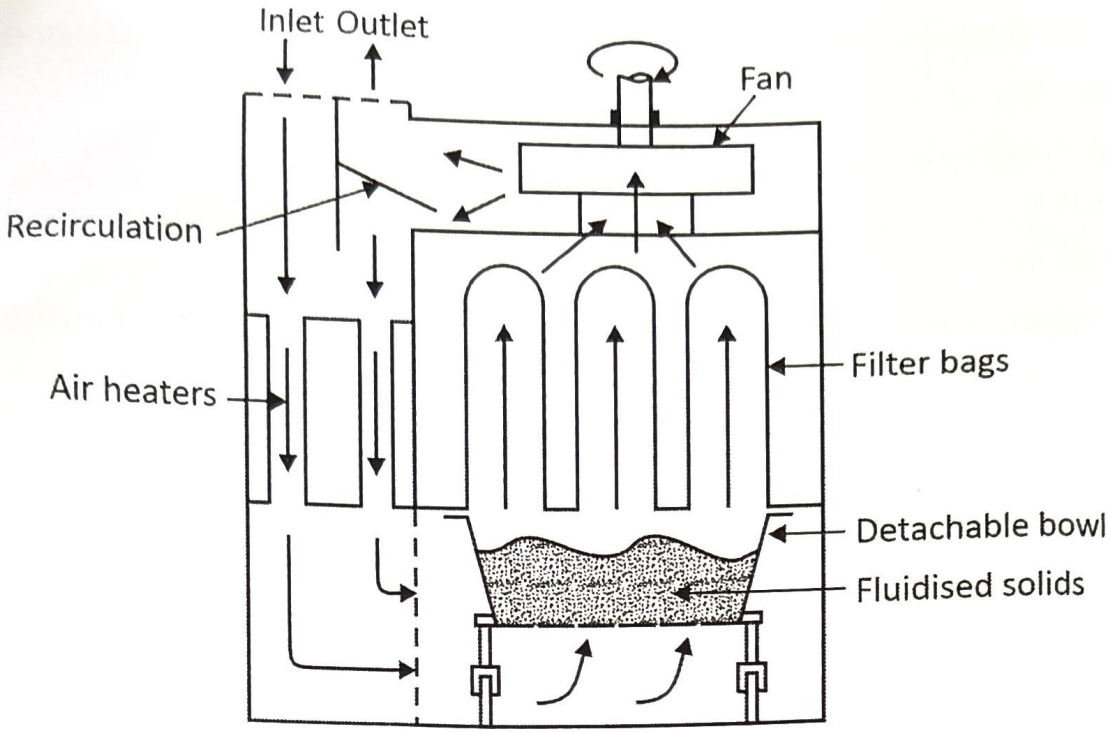


Fig. 4.22: *Fluidized bed dryer*

Working

The wet granules are placed in the detachable bowl, which is passed in the dryer.

Now fresh air is subjected from pre filter, which is heated up on reaching bottom of bowl.

Simultaneously fan is allowed to rotate.

To make the granules partially suspended in gas stream, velocity of air is kept greater than setting velocity of granules.

After some time, a point of pressure is reached at which frictional drag on the particles is equal to the force of gravity.

The granules rise in the container because of high velocity gas (1.5 to 7.5 m per minute) and later fall back in a random boiling motion.

This condition is said to be fluidized state.

The gas forms blanket around every granule to let them dry completely.

The air leaves the dryer by passing through the bag filter.

The entrained particles remain adhered to the inside surface of the bags.

Periodically the bags are shaken to remove the entrained particles.

The residence time for drying is about 40 min.

The material is left in the dryer for some time to attain ambient temperature.

The bowl is taken out for discharge.

Uses

1. Granules used in the production of tablet are dried by this process.
2. It is used for three operations such as mixing, granulation, and drying.
3. It is modified for coating of granules.

Advantages

1. It requires less time to complete drying, i.e., 20-40 min compared to 24 hr of tray dryer.
2. Drying capacity ranges from from 5 to 200 kg per hrs.
3. Mobile drying containers make the handling process simpler and labour cost effective.
4. The thermal efficiency is 2 to 6 times better than tray dryer.
5. It can be used as batch type or continuous type.
6. It has high output from a small floor space.

Disadvantages

1. The turbulence of the fluidized state of granules may cause attrition of some materials resulting in the production of fines.
2. There are chances of electrostatic build up during the drying process of many organic powders. To avoid this, there is need of fluid bed dryers with electrical earthing materials.

Freeze Dryer

Freeze drying is also known as lyophilization, i.e., system is made solvent loving for removing the same.

Principle

In freeze drying, frozen water is sublimed into vapour without attaining liquid state.

Construction

The construction of freeze dryer is shown in Fig. 4.23. It consists of:

1. Drying chamber in which trays are loaded.
2. Heat supply in the form of radiation source, heating coils.
3. Vapour condensing or adsorption system.
4. Vacuum pump or steam ejector or both.

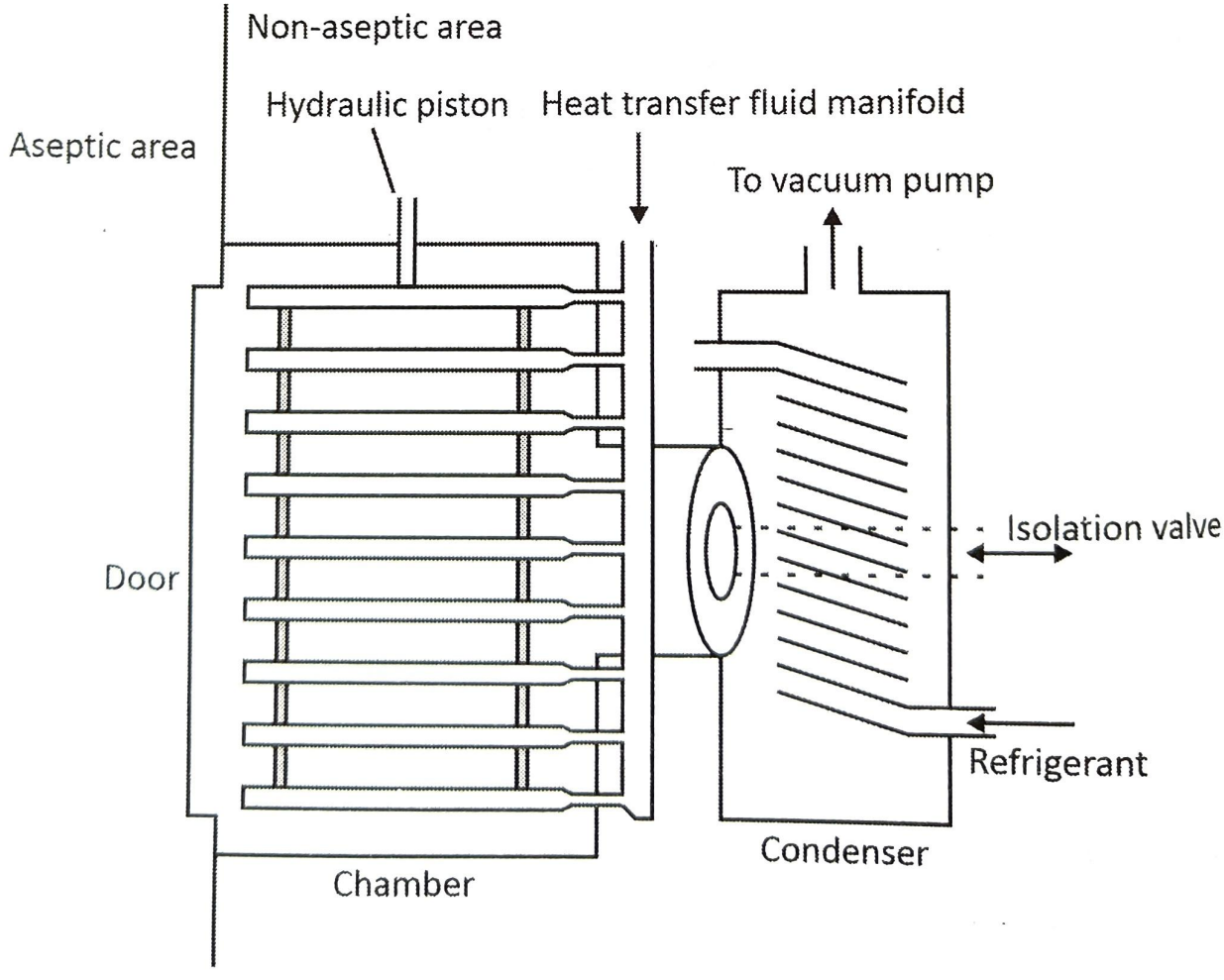


Fig. 4.23: *Freeze dryer*

The chamber for vacuum drying is generally designed for batch operation. It consists of shelves for keeping the material. The distance between the subliming surface and condenser must be less than the rate of drying. This increases the rate of drying. The condenser consists of relatively large surface cooled by solid carbon dioxide slurred with acetone or ethanol. The temperature of the condenser must be much slower than the evaporated surface of frozen substance.

Working

The working of freeze dryer consists of following steps:

1. Preparation and pretreatment
2. Prefreezing to solidify water
3. Primary drying (sublimation of ice under vacuum)
4. Secondary drying (removal of residual moisture under high vacuum)
5. Packing

1. **Preparation and pretreatment**: This step is done to decrease the volume of the solution as the container has limited capacity. The solution is pre-concentrated under normal vacuum tray drying. Sometimes solid or liquid desiccants are also used for this purpose. This reduces the actual drying by 8-10 times.
2. **Pre-freezing to solidify water:** In this process, the solution is cooled below its melting point to completely freeze it. The ampoules, vials and bottles in which aqueous solution is packed, are frozen in cold shelves at a temperature below –50°C.
3. **Primary drying:** The material to be dried is spread in order to increase the surface area for sublimation. Sublimation of water is allowed at the temperature and pressure below the triple point of water. Heat is supplied which transfers as latent heat and ice sublimes directly into vapour state which are ultimately removed.



98-99% moisture.

4. **Secondary drying:** Ordinary vacuum drying is done to remove the moisture left in the process of primary drying. This drying process is slow and done at temperature of 50-60°C.
5. **Packing:** Dried products should be sterile. Hence, freeze dried products should be stored in such a way that provides protection from moisture. The containers should be closed under controlled atmospheric condition and also observing aseptic condition. The ampoules are sealed immediately after drying, whereas the vials and bottles are closed as such or after replacement of vacuum by inert gas, if required.

Advantages:

1. The heat sensitive materials can be dried.
2. There occurs minimum loss of volatile products.
3. It is easy to maintain sterility of product.
4. The product obtained is light and porous having excellent solubility.
5. Due to very low temperature used for drying, the chances of hydrolysis are minimized.

Disadvantages:

1. The process of drying is expensive because a complicated plant is used.
2. The product obtained by freeze drying process is very hygroscopic.
3. The period of drying is quite long.
4. Equipment and running cost is high.

Uses:

Used for drying of biological products such as antibiotics, blood products, vaccines, enzyme preparations, microbiological cultures and other thermo labile pharmaceutical substances.

EXTRACTION

Extraction is a process by which active constituents are separated from solid or liquid by the solvent action.

In extraction process, desirable components are separated from unwanted components by chemical or physical process.

In physical process, extraction involves the mechanical force. Example: Extraction of juices from fruits and vegetable oil from seeds. This process is termed as expression.

In chemical process, the extraction involves the use of solvents for selectively dissolving the constituents. Example: Extraction of reserpine from rauwolfia root powder.

PURPOSE FOR EXTRACTION

- To obtain the therapeutic portion of dosage form from raw materials and to eliminate the unwanted or inert material by treatment with solvent.
- They play a decisive role in the determination of qualitative and quantitative composition of extracts.
- The extracts obtained are also utilized for the isolation and characterization of therapeutically active chemical constituents.

GENERAL TERMS

Marc: The unwanted or insoluble substances left behind after the process of extraction is called marc. These are not used for further purpose in the process of extraction.

Menstruum: The solvent used in the process of extraction is called solvent. The most commonly used menstruum is water.

Choice of Menstruum:

The menstruum should have the following properties:

1. Highly selective for the compound to be extracted

2. High capacity of extraction
3. Should not react with the extracted compound or any other compound in the raw material.
4. Should have low price and easily available
5. Should be harmless to man and environment
6. Completely volatile

EXPRESSION

The accomplishment of extraction with the help of machines or with mechanical aids is called expression.

Solvents used in Extraction

The solvents play an important role in the method of extraction.

The main solvents used in the process of extraction are:

1. Water
2. Alcohol
3. Ether
4. Chloroform
5. Light petroleum

Classification

1. Liquid – Liquid extraction
2. Acid – Base extraction
3. Solid – phase extraction
4. Supercritical extraction
5. Ultrasound assisted extraction
6. Heat reflux extraction
7. Mechanochemical assisted extraction
8. Maceration
9. Microwave-assisted extraction

10. Instant controlled pressure drop extraction
11. Perstraction

1. Liquid-liquid Extraction

Liquid–liquid Extraction (LLE), also known as solvent extraction and partitioning, is a method to separate compounds or metal complexes, based on their relative solubility in two different immiscible liquids, usually water (polar) and an organic solvent (non-polar). There is a net transfer of one or more species from one liquid into another liquid phase, generally from aqueous to organic.

LLE is also widely used in the production of fine organic compounds, the processing of perfumes, the production of vegetable oils and biodiesel, and other industries. It is among the most common initial separation techniques, though some difficulties result in extracting out closely related functional groups.

2. Acid-base Extraction

Acid-base Extraction is a process of purifying acids and bases from mixtures based on their chemical properties using sequential liquid-liquid extractions.

Acid–base extraction is routinely performed during the work-up after chemical synthesis and for the isolation of compounds and natural products like alkaloids from crude extracts. The product is largely free of neutral and acidic or basic impurities. It is not possible to separate chemically similar acids or bases using this simple method.

3. Solid-phase Extraction

Solid-Phase Extraction (SPE) is an extractive technique by which compounds that are dissolved or suspended in a liquid mixture are separated from other compounds in the mixture according to their physical and chemical properties. Analytical laboratories use solid phase extraction to concentrate and purify samples for analysis. Solid phase extraction can be used to isolate analytes of interest

from a wide variety of matrices, including urine, blood, water, beverages, soil, and animal tissue.

4. Supercritical Fluid Extraction

Supercritical Fluid Extraction (SFE) is the process of separating one component (the extractant) from another (the matrix) using supercritical fluids as the extracting solvent. Extraction is usually from a solid matrix, but can also be from liquids. SFE can be used as a sample preparation step for analytical purposes, or on a larger scale to either strip unwanted material from a product (e.g., decaffeination) or collect a desired product (e.g., essential oils). Carbon dioxide (CO_2) is the most used supercritical fluid.

Methods of Extraction

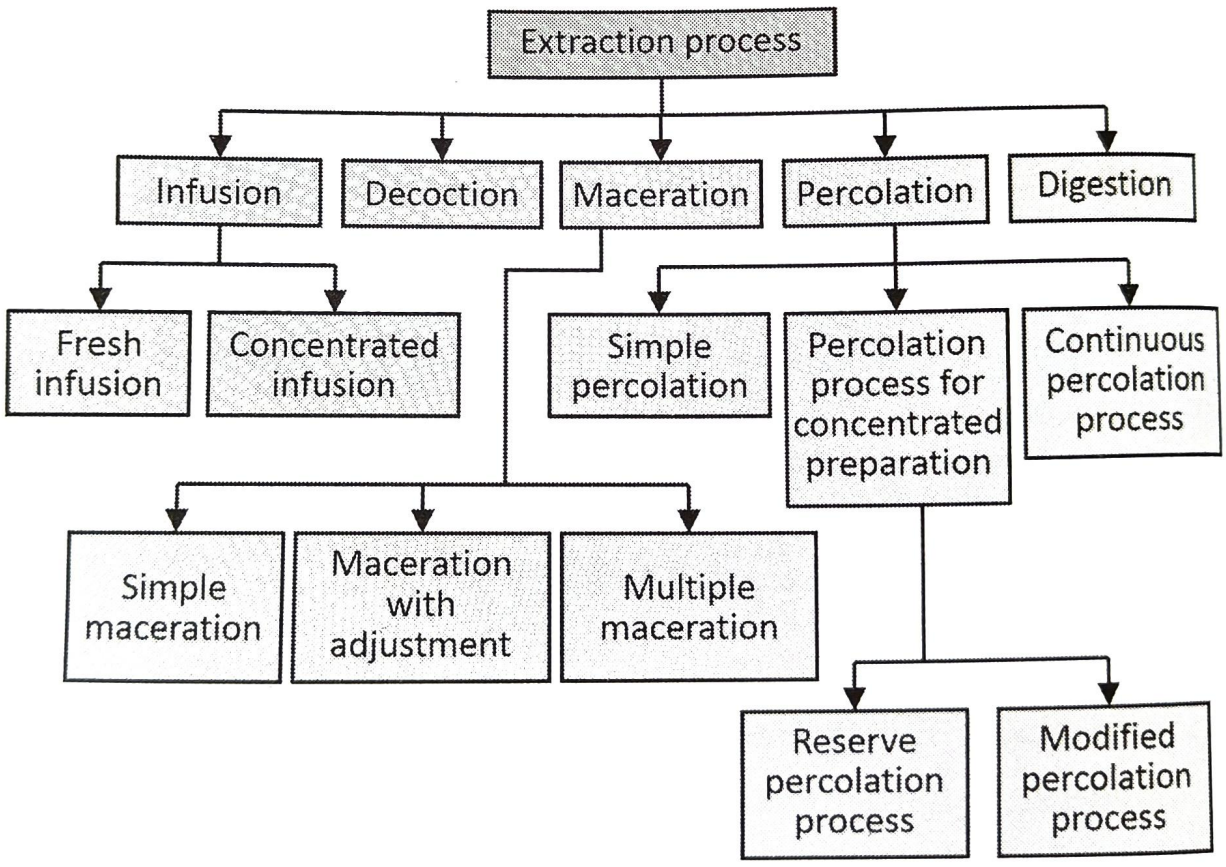


Fig. 4.24: ***Different methods of extraction process***

1. **Infusion:** This method is used for those drugs
   (a) Which are soft in nature so that water may penetrate easily to the tissues and

(b) The active constituents are water soluble.

Apparatus: Infusion is prepared using coffee or tea pot. Sometimes infusion pots are used that consists of loosely perforated shelf that rest on projection near the top of the pot.

Method: In coffee-pot or tea-pot:

(i) The drug is placed at the bottom of the pot. Water is added and it is well stirred three or four times during the period of infusion.

(ii) In an alternative method of infusion, drug is enclosed in a muslin bag and suspended below the water level in the beaker. Since water keeps circulating due to increase in specific gravity of water near the drug, thus, stirring is not needed.

In infusion pot: The drug is placed on the perforated shelf. The pot is filled with water and the perforated shelf is adjusted below the surface of water.

Final volume is not adjusted.

There are two types of infusions:

1. Fresh infusion
2. Concentrated infusion

Fresh infusion	Concentrated infusion
• Prepared by infusion process.	• Prepared by maceration or percolation process.
• Water is used as menstruum.	• Alcohol is used as menstruum.
• Infusion prepared should be used within 12 hours of preparation.	• Infusion can be used even after a long time.
• **Example:** Infusion of Quassia.	• **Example:** Infusion of chirata

2. Decoction:

➢ Decoction is the process of extracting water soluble and heat stable constituents from hard woody crude drugs.

- Small pieces of drug are boiled in water used as menstruum for about 15 minutes.
- Then the liquid is cooled and filtered.
- Required volume is obtained by adding more water.
- Freshly prepared decoction should be used within 24 hours.

3. Maceration: In this process solid ingredients are placed in a stoppered container with the whole of the solvent and allowed to stand for a period of at least 3 days (3 - 7 days) with frequent agitation, until soluble matter is dissolved. The mixture is then strained (through sieves / nets), the marc pressed and the combined liquids clarified (cleaned by filtration) or by decantation, after standing. Stoppered container is generally taken to reduce the loss of solvents by evaporation. If the volume of solvent is reduced by evaporation, then the extract may become concentrated, which may not be desired.

The drug is allowed to stand for few days.

(a) To help the solvent to penetrate the cells of the drugs,

(b) To provide the time for partitioning the active ingredient into the solvent and

(c) To transfer the drug out of the cells into the bulk of the solvent.

Frequent agitation is required to reduce the localized concentration around the cells and tissues.

As indicated in the pharmacopoeia the process consists of the following:

- Placing the solid materials with whole menstruum in the closed vessel and allowed to stand for 7 days shaking occasionally.
- Strained, pressed the marc and the liquid is obtained.
- Liquid (i.e., the extract) is clarified by subsidence or filtration.

There are three types of maceration:

A. **Simple maceration:** A process for tinctures made from organized drugs, e.g., roots, stems, leaves etc.

B. **Maceration with adjustment:** A process for tinctures made from unorganized drugs such as oleo-resins and gum resins.

C. **Multiple maceration:** A process to prepare concentrated extract. It includes 'Double maceration' and 'Triple maceration.

A. **Simple Maceration:** Organized drugs having specific cell structures like roots, stems, leaves, flowers etc., are extracted by this procedure.

Apparatus: A wide mouthed bottle or well stoppered container is used for the maceration process. concentrated alcohol is used as menstruum. Evaporation of menstruum is prevented by using closed container. Otherwise, this may lead to variation in strength as no adjustment in volume is made.

Method: Water or alcohol is used as menstruum and the drug menstruum ratio is 1: 10.

- The drug is placed with the whole of the menstruum in a closed vessel for seven days. During this period shaking is done occasionally.
- After 7 days the liquid is strained and marc is pressed.
- The expressed liquid is mixed with strained liquid.
- It is then filtered to make a clear liquid.
- The final volume is not adjusted

Explanations:

1. Shaking of the drug during maceration is essential in order to replace the saturated layers around the drug with fresh menstruum.
2. After straining, the marc is pressed in a filter press, hydraulic press or hand press etc. The marc can be squeezed out of a fine muslin piece, when the quantity

of the drug is very small. 3. The pressed liquid is mixed with the strained liquid and then filtered.

No final adjustment is made, since the volume of pressed liquid is likely to vary with the process of pressing the marc. If the final adjustment in volume is made, it will give variation in the concentration of active principle although the volume of the final preparation may be the same. 4. Filtration is necessary to remove insoluble cell contents obtained during the pressing of marc.

Examples: The tinctures made by simple maceration process are:

1. Tincture of orange
2. Tincture of lemon
3. Tincture of squill

B. Maceration with Adjustment: The process is used for unorganized drugs.

Apparatus: Same as simple maceration.

Method:

- In this process the unorganized drug is placed with 4/5th of the menstruum in a closed vessel for a period of 2-7 days. During this period, shaking is done occasionally.
- After the stated period, the liquid is filtered and the volume is made up by passing the remaining 1/5 the of the menstruum through the filter.
- The marc is not pressed.

Explanations:

1. The period of maceration is reduced from 7 to 2 days in some cases, because the unorganized drugs behave like simple chemicals that dissolve in the solvent very easily and quickly.
2. $4/5^{th}$ of the menstruum is used to keep the drug in contact with it in order to take into account the increase in volume after dissolving the soluble matter of the drug.



The volume is made up at the end with $1/5^{th}$ of the menstruum remained.

3. The marc left is a compact gummy matter. It does not retain the menstruum and hence, it is not necessary to press the marc.
4. The final volume is made up because all the active constituents of drug get dissolved in the menstruum. Marc is not pressed. hence, there is no change in the concentration of the preparation in case the final volume is made up.

Example:

1. Tincture of Tolu
2. Compound tincture of Benzoin.

C. **Multiple Maceration:** Multiple maceration process is carried out in the same way as simple maceration process, but the menstruum used is divided into two parts in double maceration process and three parts in triple maceration process

Double Maceration Process: In this process, the drug is macerated twice by using the menstruum which is divided into two parts in such a manner that the same volume is used for each maceration. The quantity of menstruum required for two macerations are calculated as follows:

Volume of menstruum required for first maceration = Total vol. of menstruum – Vol. to be retained by the drug/2 + Vol. to be retained by the drug

Volume of menstruum required for second maceration = Total vol. of menstruum – Vol. of menstruum used in first maceration

The volume of menstruum to be retained by the drug is determined by experiment, in a test batch of drug by adding a known volume of menstruum to known weight of the drug. After maceration, straining and pressing of the marc, measured volume of liquid is obtained.

Difference in the volume and the volume used represents the volume retained by the weighable quantity of the drug used.

- In double maceration process, the whole of the drug is macerated for 48 hours with the quantity of the menstruum required for first maceration.
- The liquid is strained and the marc is pressed.
- The marc is macerated again for 24 hours with the remaining menstruum required for second maceration.
- The liquid is strained and the marc is pressed.
- First and the second liquid is mixed and allowed to stand for 14 days and then filter.

Examples: The following concentrated infusions are prepared by double maceration process:

1. Concentrated infusion of orange.
2. Concentrated compound infusion of chirata.
3. Concentrated compound infusion of gentian.

Triple Maceration Process: In this maceration process, the drug is macerated thrice by using the menstruum which is divided into three parts in such a manner that the same volume for three parts in such a manner that the same volume is used for each macerate in the quantity of menstruum required for three macerations is calculate as follows: Volume of menstruum required for first maceration = Total vol. of menstruum - Vol. to be retained by the drug / 3 +Vol. to be retained by the drug

Volume of menstruum required for 2nd and 3rd maceration= Total vol. of menstruum - Vol. of menstruum used in first maceration/2

- The whole of the drug is macerated for one hour with part of menstruum required for first
- The marc is macerated again for one hour with the part of the menstruum required for 2^{nd} maceration and strained.

- The marc is macerated again for one hour with the part of the menstruum required for 3rd maceration and strained.
- The marc is pressed lightly.
- The liquid obtained from 2nd and 3rd maceration is pooled and evaporated to a specified concentration. This concentrated liquid is mixed with the liquid obtained from the 1st maceration.

Examples: The following concentrated infusions are prepared by triple maceration process:

1. Concentrated Infusion of Quassia
2. Liquid Extract of Senna

4. Percolation:

A. Simple percolation process

B. Percolation process for concentrated preparations

I. Reserved percolation

II. Modified percolation

C. Continuous hot percolation/Soxhlet Extraction/Soxhlation

A. Simple Percolation

Apparatus: Three types of apparatus are generally used,

(i) Conical percolator

(ii) Cylindrical percolator

(iii) Steam jacketed percolator [for higher temperature extraction]

(i) Conical Percolator: It is generally made of glass (or) metal usually copper which is tinned inside. It is conical in shape having the lower diameter not less than half of the upper diameter. There are less chance of choking of conical percolator in case the drug swells up, because a drug can slope against the walls of the percolator.

Disadvanges: Loss of menstruum due to evaporation because of its upper bigger diameter.

(ii) **Cylindrical Percolator:** This percolator is cylindrical in shape. It is having two diameters, i.e., upper and lower diameter. The chances of choking are very less when the drug swells up. Higher alcohol (or) any volatile solvents is used as menstruum.

(iii) **Steam Jacketed Percolator:** The percolator is subjected to high temperature in order to increase the solvent action of menstruum. The percolator is heated by steam

Stages:

1. **Size Reduction:** The drug to be extracted is subjected to suitable degree of size reduction, usually from coarse powder to fine powder, to
   (i) Increase the surface area of the drug exposed to the menstruum,
   (ii) For uniform packing of the percolator,
   (iii) To slow down the movement of the menstruum and
   (iv) To ensure complete exhaustion of the drug.
2. **Imbibition:** During imbibition the powdered drug is moistened with a suitable amount of menstruum and allowed to stand for four hours in a well closed container. During this period the drug swells up as the menstruum penetrates the cell walls. The preliminary moistening of the drug is necessary because: the dried tissue swells when it comes in contact with the menstruum but if packed in the dry condition subsequent swelling will reduce the porosity of the material and choke the percolator, the air present in the interstices is removed by menstruum, which will otherwise disturb the packing of the percolator due to which the menstruum will run through the channels results in inefficient extraction, (i) it does not allow the fine particles to be washed out of the percolator during percolation.

3. **Packing:** After imbibition the moistened drug is evenly packed into the percolator. Cotton wool or fibres of flax; previously moistened with menstrum is placed on the perforated plate of the percolator. The packing should not be too tight, it will lead to slow extraction rate. Similarly, loose packing will allow the menstrum to pass through quickly resulting in incomplete contact with the drug. The drug should occupy 2/3rd capacity of the percolator. After packing , a piece of filter paper is placed over top of the bed, on which small quantity of washed sand is placed to prevent disturbance of the packed material.
4. **Maceration:** After packing sufficient menstrum is added to saturate the material. When the liquid begins to drip from the bottom of the percolator, the tap fitted at its bottom is closed. More menstrum is added if required, so that a shallow layer of menstrum is maintained over the drug bed. The percolator is allowed to stand for 24 hours to macerate the drug.
5. **Percolation:** After 24 hours maceration, the lower tap is opened and liquid collected therein is allowed to drip slowly at a controlled rate until 3/4th volume of the finished product is obtained. Sufficient amount of menstruum is simultaneously added over the drug because at no time packed material should be allowed to become dry. After collecting 3/4th volume, the percolate is tested for complete exhaustion of the drug by various tests.

   Tests to check complete exhaustion of the drug:

   (i) Take a few ml of the last percolate and evaporate to dryness, it no residue remains – it shows that the drug is completely exhausted.

   (ii) The specific gravity of last few ml of percolate is [illegible]ecific gravity of the

fresh menstruum the exhaustion is taken to be complete.

(iii) Specific chemical tests may be performed on the percolate for the drugs containing alkaloids, glycosides, tannins, resins or bitter constituents.

B. Percolation process for concentrated preparations: The various processes used for the preparing concentrated preparations are:

(i) Reserve percolation process

(ii) Modified percolation process

(i) Reserve percolation process: In this process, a part of the percolate, generally $3/4^{th}$ the volume of the finished preparation, is reserved. Then the percolation process is continued till the drug is completely exhausted. The percolate is subjected to evaporation or distillation to convert it into a soft extract. This soft extract is dissolved in the reserve portion of percolate and then sufficient menstruum is added to produce the required volume.

The portion of the percolate which is reserved must be the first percolate because it is more concentrated. The portion of the percolate which is evaporated contained traces of active constituents of drug.

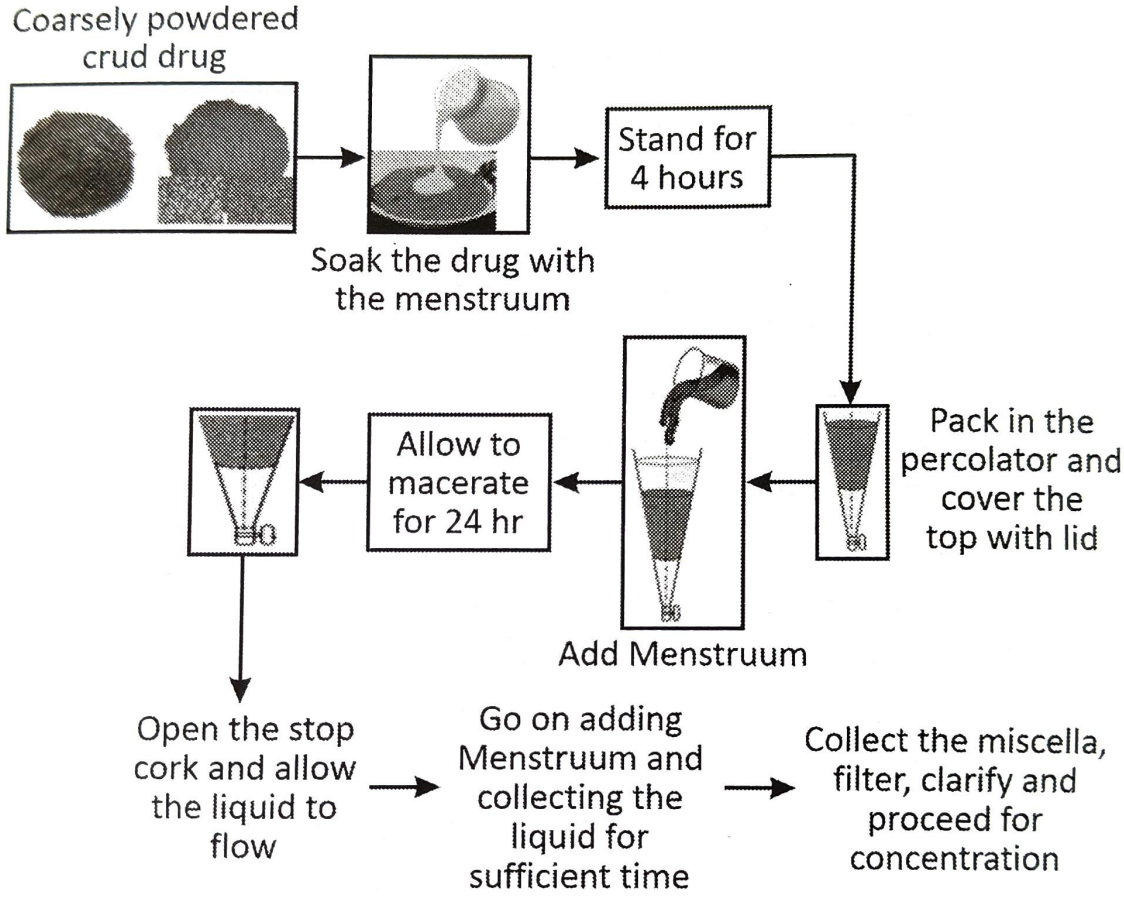
(ii) Modified percolation process: In percolation process for preparation of tinctures, the drug/percolate(d/p) ratio is about 1:4. The d/p ratio is reduced to 1: 3 by modifying the percolation process and hence there is a lot of saving in heat, time and menstruum.

Percolation is a displacement process. The strong solution of active constituents of drug formed during maceration is displaced by the fresh menstrum when percolation process is started. It is proved that stationary menstruum (menstruum remaining in contact with the drug) dissolves more menstruum is required to exhaust the drug when simple percolation is used. But if

continuous percolation stage has suitable breaks by short maceration stages, the d/p ratio can be reduced to 1:3.

Example: In simple percolation process:

Drug (200 gm) → Imbibition (for 4 hrs) → Maceration (for 24 hrs) → Percolation and collect the percolate, i.e., 3/4th of the volume of finished preparation.



C. **Continuous Hot Percolation Process/Soxhlet Extraction/ Soxhlation**: When active constituents of the drug are not freely soluble in the solvent or difficult to be displaced from the cells of the drug, then it become necessary to extract the crude drug by the action of hot menstruum for a considerable length of time.

The fixed oils from seeds and alkaloids from the drug are extracted by continuous hot percolation process using benzene, chloroform, petroleum, ether etc.

Apparatus:

(i) A flask in which the menstruum is boiled,

(ii) Soxhlet extractor in which drug to be extracted is packed. It has a side tube which carries the vapours of solvent from the flask to the condenser and a siphon tube which siphons over the extract from soxhlet extractor to the flask.

(iii) A condenser in which the vapours of the solvent are condensed again into solvent.

Procedure: The drug to be extracted is packed in a paper cylinder made from a filter paper and it is placed in the flask.

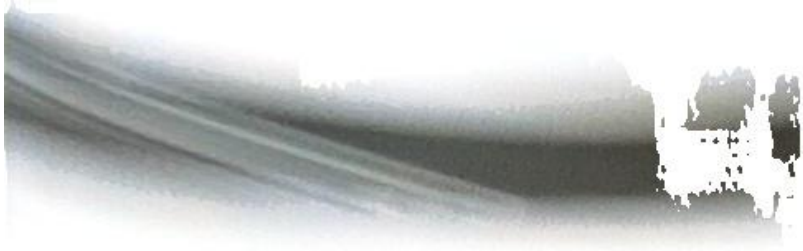
When solvent is boiled on heating the flask, it gets converted into vapours enter into the condenser through the side tube and get condensed into hot liquid which falls on the column of the drug. When the extractor gets filled with the solvent, the level of siphon tube also raises up to its top.

The solvent containing active constituents of the drug in the siphon tube siphon over bad run into the flask, thus emptying the body of extractor.

This alteration of filling and emptying the body of extractor goes on continuously. The soluble active constituent of the drug remain in the flask while the solvent is repeatedly volatilised. The process of filling and emptying of the extractor is repeated until the drug is exhausted.

6. **Digestion:** In digestion process, the drug is extracted by heating at a particular pressure. This will increase the penetration power of menstruum, so that there is complete extraction of the drug. Precautions should be taken so that the increased temperature may not harm the active constituent of the drug.

The apparatus known as digestor. It is a vessel made up of metal. The whole of the drug along with the menstruum is placed in the body of the digestor. Place the cover over it with



the help of nuts. The drug is treated with menatruum for a definite period under specified conditions of temperature and pressure.

Applications of extraction:

1. It is used in perfumes, vegetable oil, biodiesel processing, etc.
2. By this method, plutonium irradiated from nuclear fuel can be recovered and which is reused as nuclear fuel.
3. It is used to segregate hazardous contaminants from sludge and sediments.
4. It is used in the drug industry like preparation of microspheres.
5. It is used for the separation and purification of organic compounds.



CHAPTER

5

Pharmaceutical Formulations

TABLETS

Introduction

According to Indian Pharmacopeia, pharmaceutical tablets are:

1. Prepared by compressing a drug or mixture of drugs with or without diluents.
2. Present in solid, flat or biconvex shapes.
3. Present in unit dosage form.

Definition

"Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients."

They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration

Advantages

- It is easy to administer the tablets.
- Dispensing the tablets is easy.

- Tablets are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Packaging and striping of tablets is easy.
- Tablets are light, compact and cost friendly.
- Tablets possess chemical and microbial stability in all dosage forms.

Disadvantages

- Children and unconscious patients find it difficult to swallow tablets.
- Some drugs are amorphous in nature and possess lower density. Due to which it is difficult to compress these drugs into dense compacts.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- There are some drugs that are bitter in taste or possess objectionable odour. Some drugs are also sensitive to oxygen. Such drugs require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.
- Some solids like aspirin may cause irritants effects on gastrointestinal mucosa.
- Possibility of bioavailability problems resulting from slow disintegration and dissolution.

INGREDIENTS USED IN TABLET FORMULATION

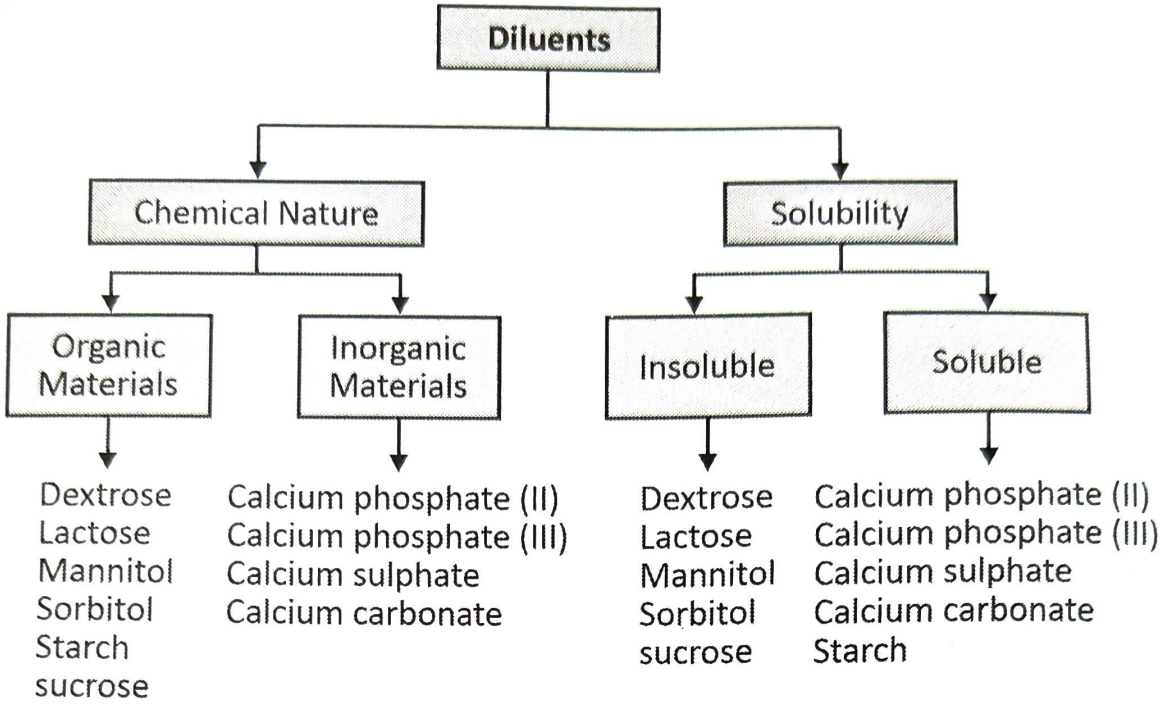
In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

Table 5.1: Ingredients and their examples

Sr. No.	Ingredients	Examples
1.	Diluents	Calcium Phosphate; Carboxymethylcellulose Calcium; Cellulose; Dextrin; Lactose; Microcrystalline Cellulose; PR gelatinized Starch; Sorbitol; Starch
2.	Binders	Acacia; Alginic Acid; Carboxymethylcellulose; Cellulose; Dextrin; Gelatin; Liquid Glucose; Magnesium Aluminum Silicate; Maltodextrin; Methylcellulose; Povidone; Sodium Alginate; Starch; Zein
3.	Lubricants	Calcium Stearate; Glyceryl Palmitostearate; Magnesium Oxide; Poloxamer; Polyvinyl Alcohol; Sodium Benzoate; Sodium Lauryl Sulfate; Sodium Stearyl Sulfate; Stearic Acid; Talc; Zinc Stearate
4.	Glidants	Magnesium Trisilicate; Cellulose; Starch; Talc; Tribasic Calcium Phosphate
5.	Anti-adherents	Corn Starch; Metallic Stearate; Talc
6.	Disintegrates	Alginic Acid; Carboxymethylcellulose; Cellulose; Colloidal Silicon Dioxide; Croscarmellose Sodium; Crospovidone; Potassium Polacrilin; Povidone
7.	Colouring agents	FD&C or D&C Dyes or Lake Pigments
8.	Flavouring agents	Ethyl Maltol; Ethyl Vanillin; Menthol; Vanillin
9.	Absorbents	Kaolin; Magnesium Aluminium Silicate; Tricalcium Phosphate

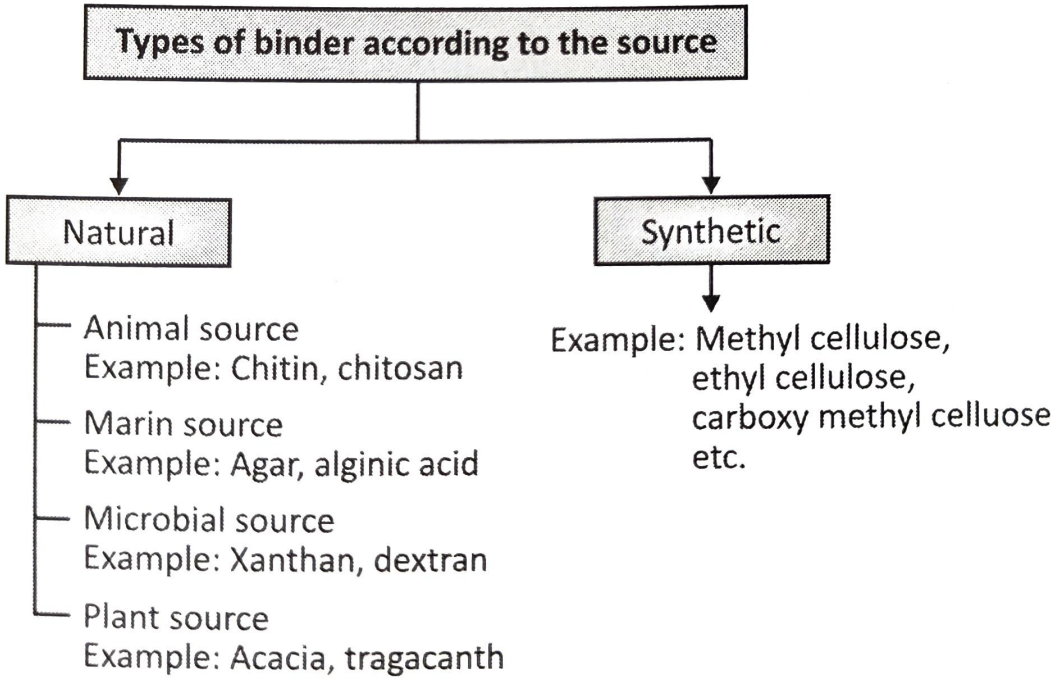
Diluents

Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. Also used to improve cohesion, to permit use of direct compression.



Binders

Binders to form cohesive compacts for directly compressed tablet.



Lubricants: Lubricants are said to:

1. Reduce friction between particles.
2. Improve the rate of flow of tablet granulation.

3. Prevent adhesion of tablet materials to the dye and punch surface.

   Examples include: Ester, amides, fatty acids.

Glidants

Glidants allow the flow of granules by decreasing the friction between the particles. *Example:* Ascorbyl palmitate.

Anti-adherents

Anti-adherents reduce the granules to stick to the walls of tablet press. *Example:* Magnesium stearate.

Table 5.2: Comparison between Lubricant vs. Glidants vs. Anti-adherents

Lubricant	Glidant	Anti-adherent
Lubricant is a substance we use in tablet and capsule formulations in order to reduce the friction.	Glidant is a substance we use to increase the flowability of a powder.	Anti-adherents is a substance that can prevent the tablet from its adhesion properties.
Action		
Lubricants reduce the friction between particles that we use to make the tablet during compression.	Glidants increase the flow rate of the granules of the powder that we use for tablet formation.	Anti-adherents avoid the adhesion of the tablet surface to the wall of the cavity where we produce the tablet.
Examples		
Some common examples of lubricants include stearic acid and calcium or magnesium salts of stearic acid.	Some common examples of glidants include talc, starch, colloidal silica, silicates, etc.	Some common examples of anti-adherents include magnesium stearate, talk and starch.

Disintegrates

Disintegrates are added to the tablet formulations to disintegrate them when it comes in contact with water in GIT. Examples include- cross-linked polyvinylpyrrolidone.

Colouring Agents

The use of colours and dyes in a tablet has three purposes:

(a) Masking of off colour drugs

(b) Product identification

(c) Production of more elegant product.

Flavouring Agents

Flavouring oils are added in dry form to the chewable tablets. *Example:* Spray-dried beadlets

Absorbents

The addition of absorbents is necessary to the substances that have high affinity with water. Hygroscopic materials, if present, render the blend wet and difficult to handle during manufacture.

Methods of Preparations

Tablets are prepared by three methods:

1. Wet granulation method
2. Dry granulation method
3. Direct compression

Wet Granulation Method

It is the most common and widely used method. This method involves various steps like weighing of ingredients, mixing, granulation and screening of damp pass, drying, lubrication and compression of tablets.

Dry Granulation Method

Dry granulation method is used during tablet preparation if the ingredients are very sensitive to moisture or they are unable to

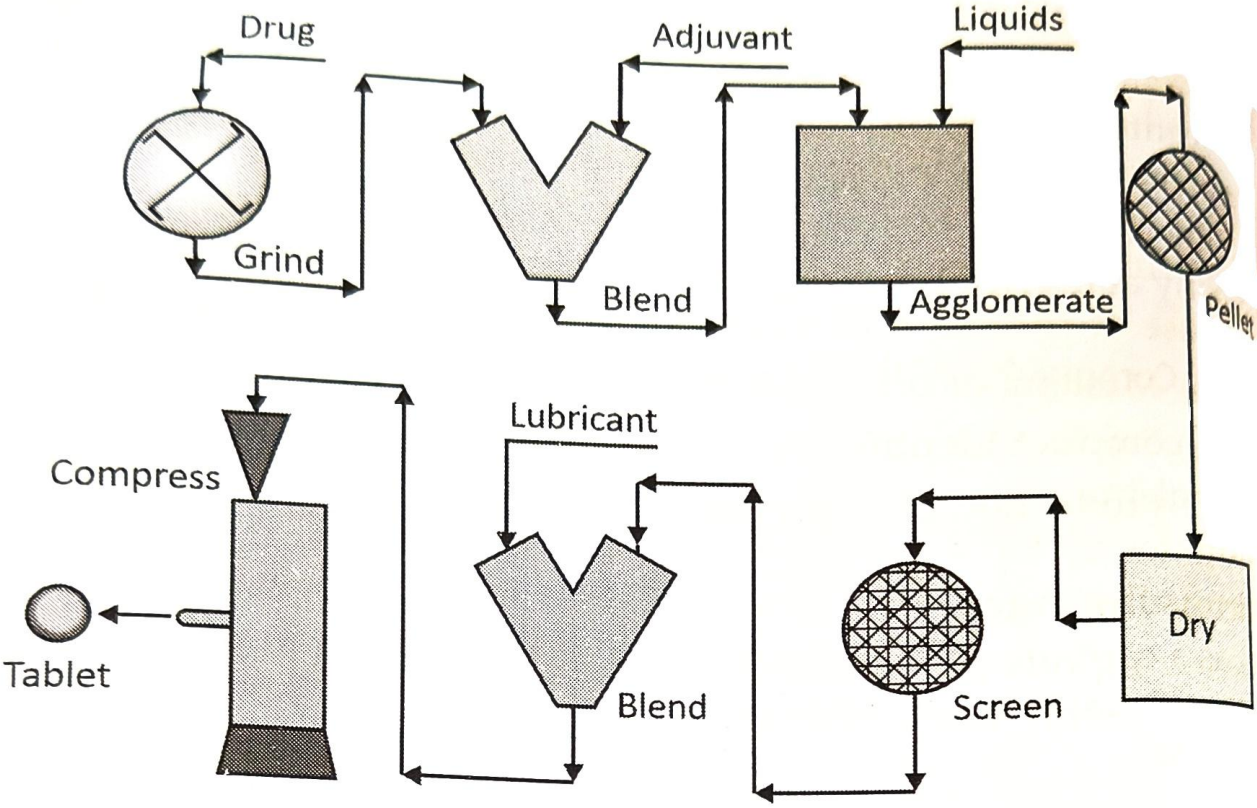


Fig. 5.1: *Wet Granulation Method*

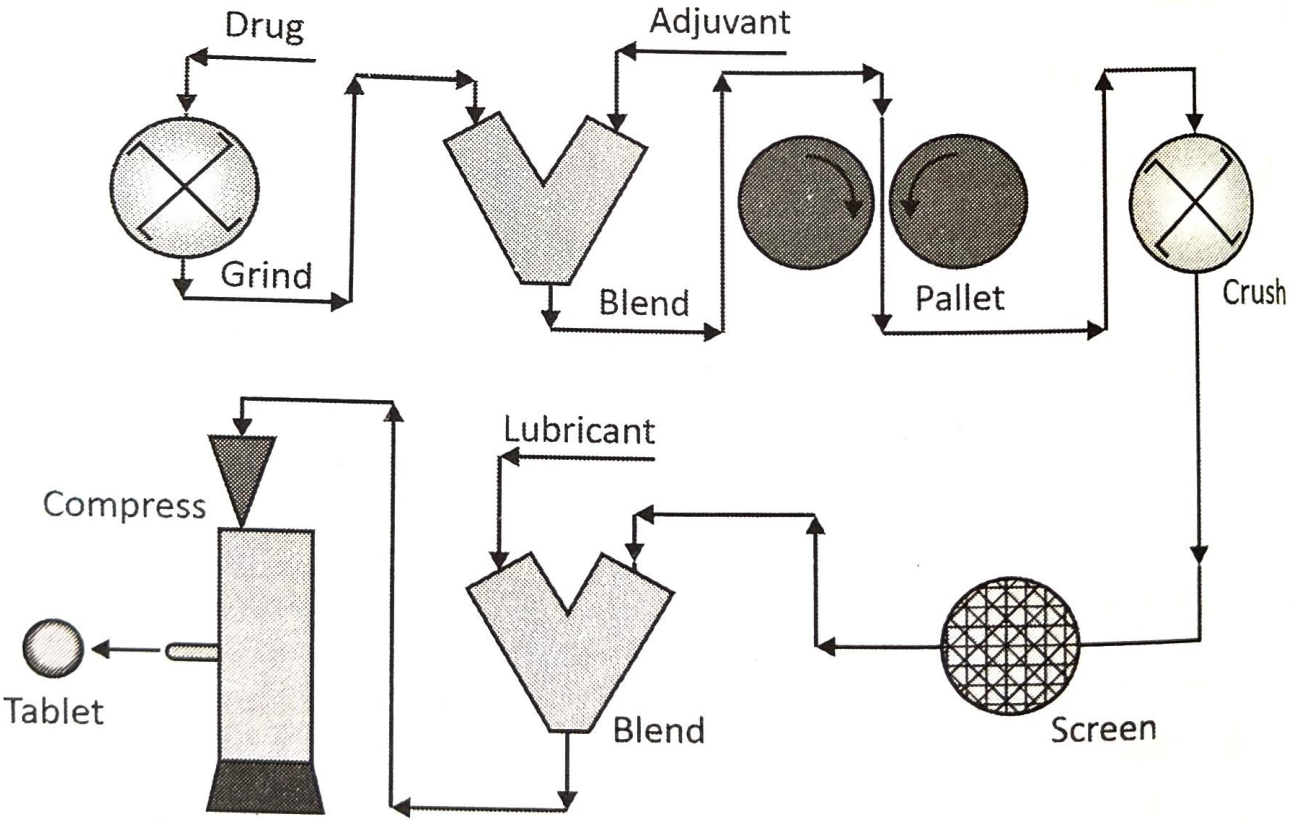


Fig. 5.2: *Dry Granulation Method*

tolerate high temperatures while drying. Slugging of powder mass is prevented in this method. The active ingredient, diluent and lubricant are blended together, to form the slug. Thus, the compressed slug is passed through the mesh or through the mill and the remaining lubricant is added to the granulation, blended properly and compressed to form the tablets.

Direct Compression

Direct compression involves direct compressing the powdered material into tablets. Direct compression is adopted, if drug constitutes major portion of tablet. Tablets containing 25% or less of drug substances can be formulated, with a suitable diluent which acts as a carrier or vehicle for the drug

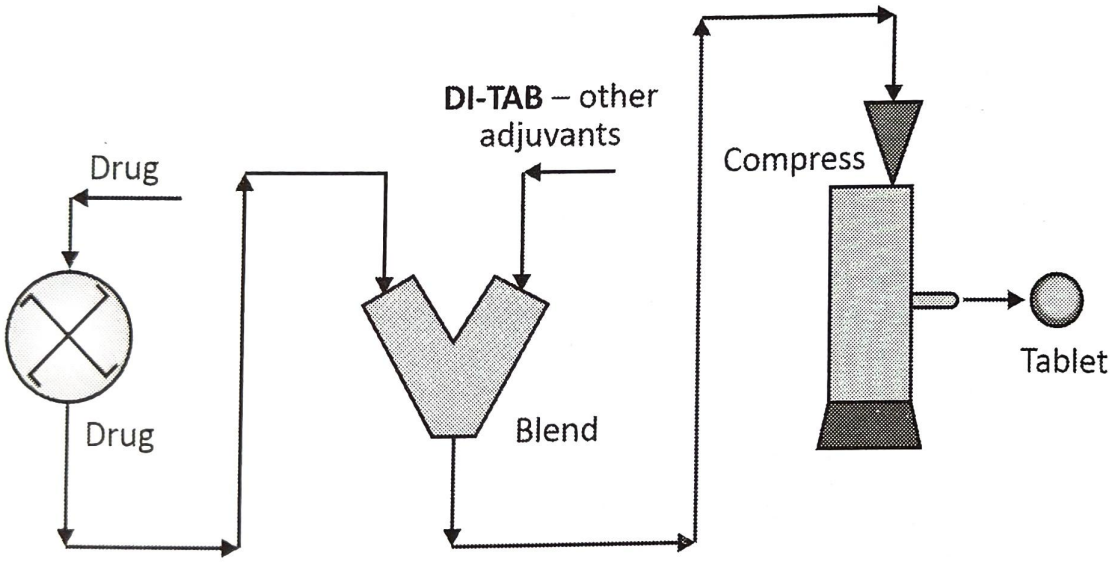


Fig. 5.3: *Direct Compression Method*

CLASSIFICATION OF TABLETS

A. Oral Tablets for Ingestion
   1. Standard Compressed Tablets
   2. Multiple Compressed Tablets
      (a) Compression Coated Tablets
         (i) Sugar Coated
         (ii) Film Coated Tablets

(iii) Gelatin Coated Tablets
(iv) Enteric Coated Tablets
(b) Layered Tablet
(c) Inlay Tablet
3. Targeted Tablets
(a) Floating Tablet
(b) Colon Targeting Tablet
4. Chewable Tablets
5. Dispersible Tablets

B. Tablets used in the Oral Cavity
1. Lozenges and Troches
2. Sublingual Tables
3. Buccal Tablet
4. Dental Cones
5. Mouth Dissolved/Rapidly Dissolving Tablets

C. Tablets Administered by other Routes
1. Vaginal Tablet
2. Rectal Tablet
3. Implants

D. Tablets used to Prepare Solution
1. Effervescent Tablets
2. Moulded Tablets
(a) Hypodermic Tablet
(b) Dispensing/soluble Tablet
3. Tablet Triturate.

E. Action Wise
1. Modified Release Tablet
(a) Sustained Release Tablet
(b) Extended Release Tablet
(c) Fast Dissolving Tablet
(d) Double Layered Tablet

Uncoated Tablets

Uncoated tablets are generally single-layer tablets prepared by a single compression of granules or multilayer tablets consisting of parallel layers prepared by compression of granules of different compositions. Any added substances are not specifically intended to modify the release of their active ingredients.



Fig. 5.4: *Compressed Tablets*

Coated Tablets

Coated tablets are the tablets that contain several layers of mixtures of substances like resins, polymers, sugars, gums etc. In compression coated tablets, the coating is applied by compressing around the tablets granules prepared from tablet excipients such as lactose, calcium phosphate, etc.

Substances used as coatings are usually applied as a solution or suspension in condition in which evaporation of the vehicle occurs. When the coating is thin, the tablets are described as film coated.

Sugar Coated Tablets

Sugar coat acts as the barrier to environment and objectionable taste and odour. It gives glossy and elegant appearance. Patients also prefer these tablets due to sweet taste. Widely utilized in preparing multivitamin and multivitamin mineral combination.

Film Coated Tablets

Film coating on tablets is done to provide strength to the tablet. It is an alternative to sugar coating. The polymers such as HPC (Hydroxypropyl cellulose), HPMC (Hydroxypropylmethyl cellulose) and Ethyl cellulose are used for this technique. It is also a

fast process than the sugar coating technique. It has the advantages over sugar coating in that it is more durable, less bulky and less time consuming to apply, but it is less attractive and elegant in physical appearance than sugar coating. The coating is designed to rupture and expose the core tablet at the desire location in the gastrointestinal tract.

Gelatin Coated Tablets

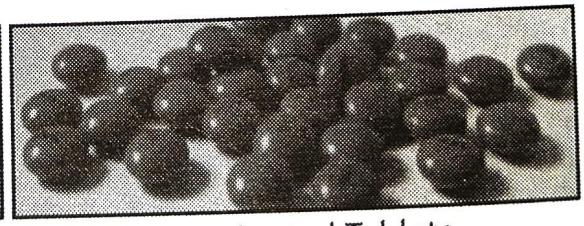
The innovator product, the gel cap is a capsule shaped compressed tablet that allows the coated product to be about one–third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilities swallowing and gelatin coated tablets are more tamper evident than unsealed capsule.

Enteric Coated Tablets

Enteric coated tablets are coated with the material that is resistant to the acidic medium of the stomach. Thus, the drug is not released in the stomach. Drug gets released on reaching intestine where alkaline media is present. Thus, time of release of drug is delayed. Hence, called delayed action tablet.



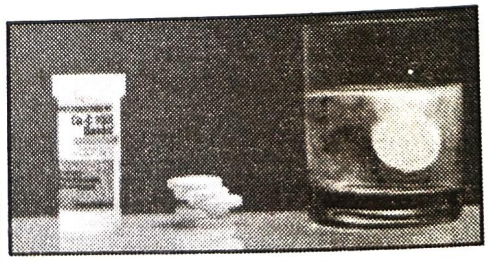
Compressed Tablets



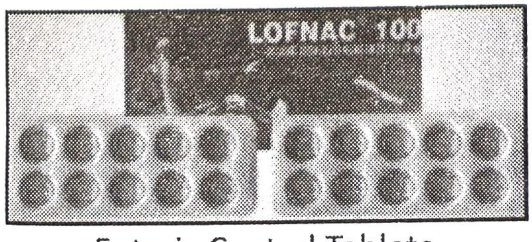
Sugar Coated Tablets



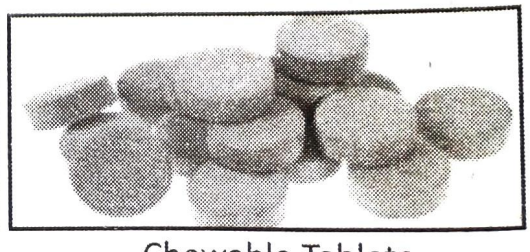
Film Coated Tablets



Effervescent Tablets



Enteric Coated Tablets



Chewable Tablets

Modified Release Tablet

Release the medicament slowly for long time duration after administration of a single tablet. Used to target the site-specific releases. Comparison of blood concentration vs. time any adjuvant that can alter water uptake rate, swelling and gelling characteristics can alter the release rate of API. The drug release can be modified by providing suitable micro-environment pH in the tablet. Inclusion of alkaline polymers results in desirable drug release of acidic drugs.

CAPSULES

INTRODUCTION

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin.

There are two types of capsules, "hard" and "soft". The hard capsule is made of two small cylinders named as cap and body. The soft gelatin capsule is a one-piece capsule.

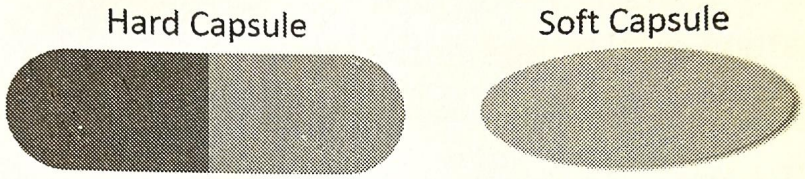
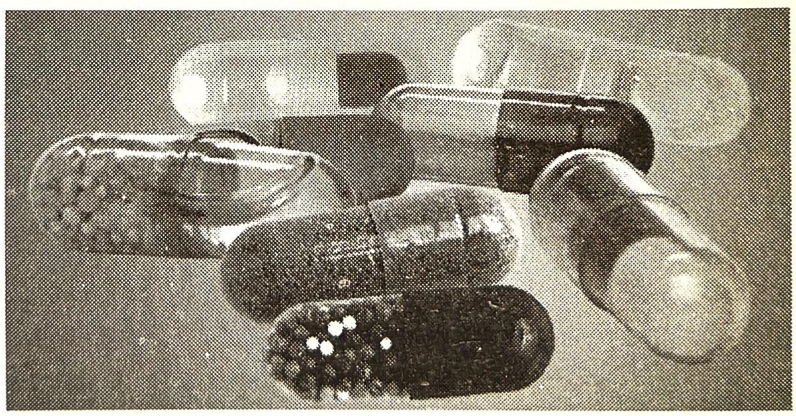


Fig. 5.5: *Types of Capsules*

Capsules are available in many sizes to provide dosing flexibility. Those drugs are enclosed in gelatin shells which have unpleasant taste and odour. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms.



ADVANTAGES OF CAPSULES

- Capsules mask the taste and odour of unpleasant drugs and can be easily administered.
- They are attractive in appearance

- They are slippery when moist and, hence, easy to swallow with a draught of water.
- As compared to tablets less adjuncts are required.
- The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.
- They are economical
- They are easy to handle and carry.
- The shells can be opacified (with titanium dioxide) or coloured, to give protection fromlight.

DISADVANTAGES OF CAPSULES

- Hygroscopic drugs are not suitable for filling into capsules as these drugs absorb water from the capsule shell making it brittle.
- The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of stomach.

RAW MATERIALS FOR CAPSULES

Soft and hard gelatin capsules are made of gelatin, water, colorants, aids and preservatives.

Gelatin

Gelatin is the major component of the capsules and has been the material from which they have traditionally been made. Gelatin has been the raw material of choice because ofthe ability of a solution to gel to form a solid at a temperature just above ambient temperate conditions, which enables a homogeneous film to be formed rapidly on a mould pin.

The reason for this is that gelatin possesses the following basic properties:

- It is non-toxic, widely used in foodstuffs and acceptable for useworldwide.
- It is readily soluble in biological fluids at body temperature.
- It is good film-forming material, producing a strong flexible film
- The gelatin films are homogeneous in structure, which gives them strength.

Some of the disadvantages with using gelatin for hard capsules include: It has a high moisture content, which is essential because this is the plasticizer for the film and under International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) conditions for accelerated storage testing, gelatin undergoes a cross linking reaction that reduces its solubility.

Gelatin is a translucent brittle solid substance, colourless or slightly yellow, nearly tasteless and odorless, which is created by prolonged boiling of animal skin connective tissue or bones.

Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Capsules may be made from either type of gelatin, but mostly amixture of both types is used considering availability and cost. Difference in the physical properties of finished capsules as a function of the type of gelatin used is slight.

Blends of bone and pork skin gelatins of relatively high strength are normally used for hardcapsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend, thereby reducing hazeor cloudiness in the finished capsule.

Physical Properties of Gelatin

Gelatin is a protein product produced by partial hydrolysis of collagen extracted from skin, bones, cartilage, ligaments, etc. The natural molecular bonds between individual collagen strands are broken down into a form that rearranges more easily. Gelatin melts when heated and solidifies when cooled again. Together with water it forms a semi-solid colloidal gel.

Production of Gelatin

On a commercial scale, gelatin is made from by-products of the meat andleather industry, mainly pork skins, pork and cattle bones or split cattle hides. Contrary topopular belief, horns and hooves are not commonly used. The raw materials are prepared by different curing, acid and alkali processes which are employed to extract the dried collagenhydrolysate. The entire process takes several weeks.

Colourants

The colour of pharmaceutical product plays an important role in their use. Colour is used principally to identify a product in all stages of its manufacture and use. In the manufacturing company it assists in complying with GMP norms by helping the operators differentiate between products. The colourants that can be used in capsules are of two types:

Water Soluble Dyes or Insoluble Pigments

To make a range of colours dyes and pigments are mixed together as solutions or suspensions. Three most commonly used dyes are erythrosine, indigo carmine and quinolone yellow. The two types of pigments used are iron oxides- black, red and yellow and titanium dioxide which are white and used to make the capsule opaque. Capsules are coloured by the addition of colourants to the gelatin solution during the manufacturing stage.

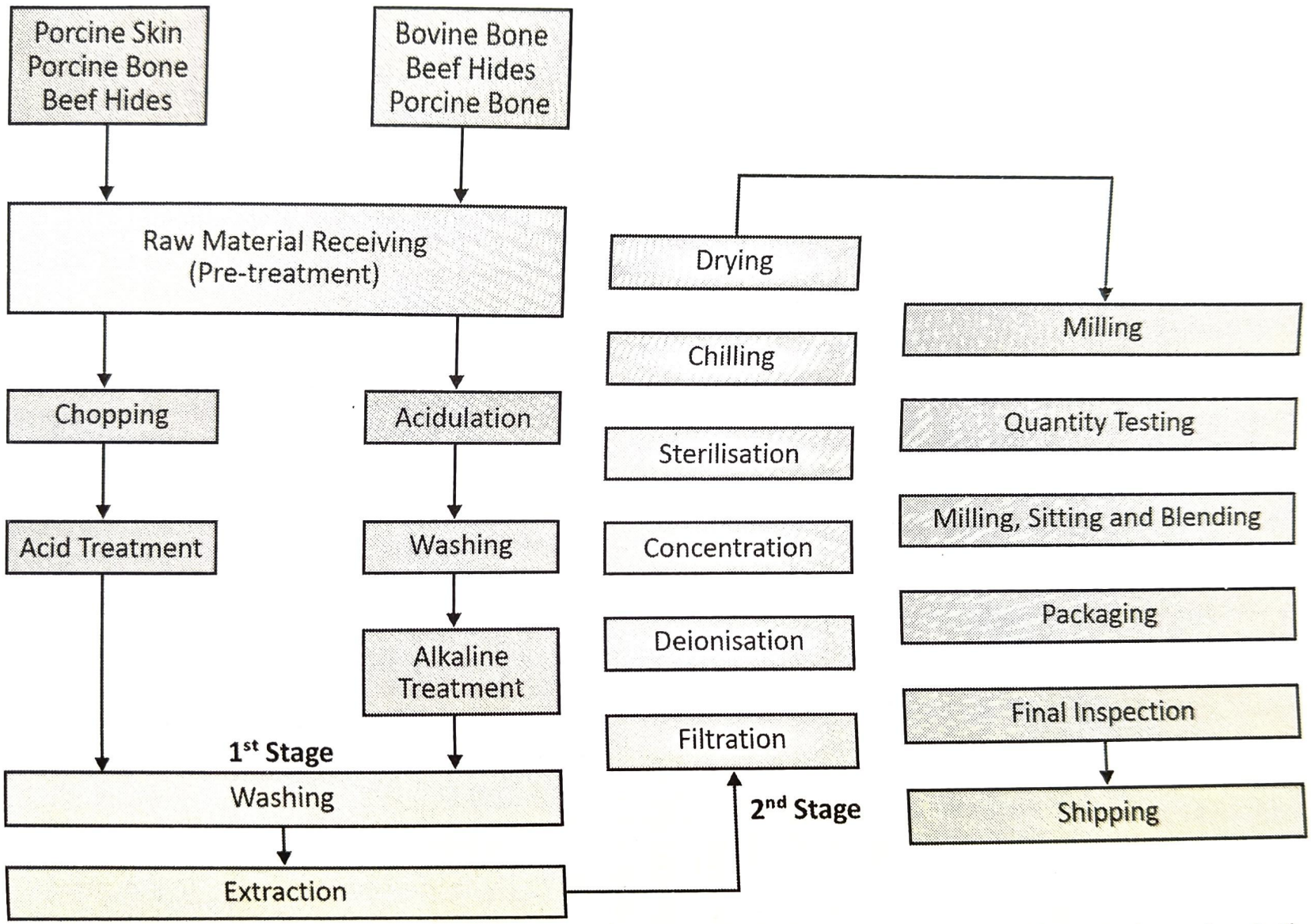


Fig. 5.6: ***(a) Industrial setup for manufacturing and production of porcine/bovine-based gelatin***

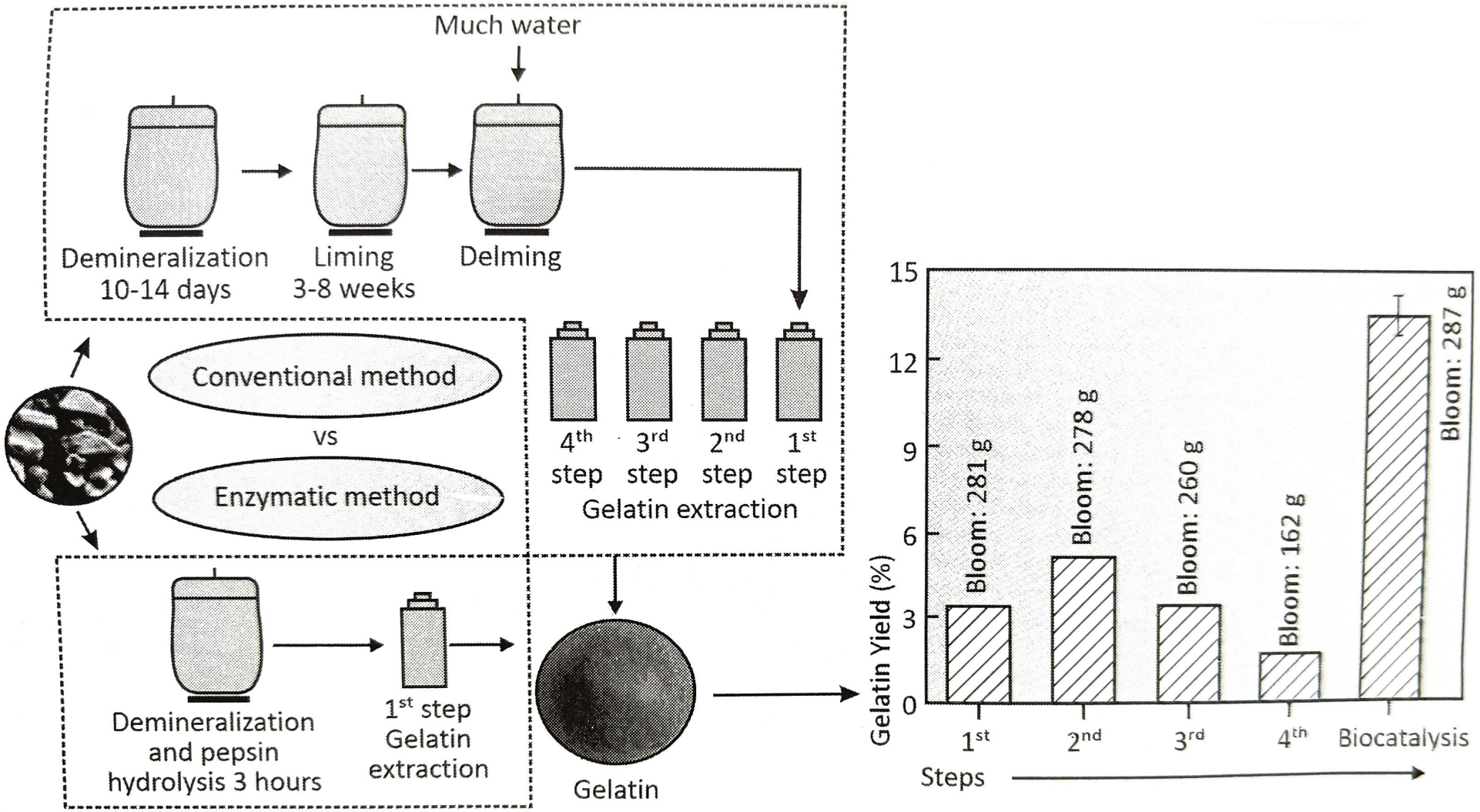


Fig. 5.6: ***(b) Setup to optimized gelatin extraction process from conventional to enzymetic approach***

Process Aids

Preservatives and surfactants are added to the gelatin solution during capsule manufacture to aid in processing. There may occur bacterial growth in the gelatin solutions at a temperature below 55°C. Hence, preservatives are added to the gelatin and colourant solutions to reduce the growth of microorganisms until the moisture content of the gelatin film is below 16% w/v. This is because bacterial population will decline in such moisture content with time. The materials used as preservatives include: sulfur dioxide which is added as the sodium saltsbisulfite or metabisulfite, sorbic acid or the methyl propyl esters of para-hydroxy-benzoic acid and the organic acids, benzoic and propanoic acids.

Some hard gelatin capsules may contain 0.15% w/w of sodium lauryl sulphate which functions as wetting agent, to ensure that the lubricated metal moulds are uniformly covered when dipped into the gelatin solution. Capsules are available in many different sizes and shapes and can be used for the administration of powders, semisolids and liquids. Unpleasant tastes and odours of drugs are effectively masked by the practically tasteless capsule shell which dissolves or is digested in the stomach after about ten to twenty minutes. Capsules also can be used as a means of providing accurately measured doses for administration rectally or vaginally.

Manufacture of Hard Gelatin Capsules

Steps involved in making hard gelatincapsules:

(a) Dipping
(b) Spinning
(c) Drying
(d) Stripping
(e) Trimming and Joining
(f) Polishing

(a) Dipping: Caps and bodies are formed by dipping pairs of the stainless steel pins into the dipping solution. The dippingsolutionis maintainedat atemperature of about 50°C in a heated, jacketed dipping pan.

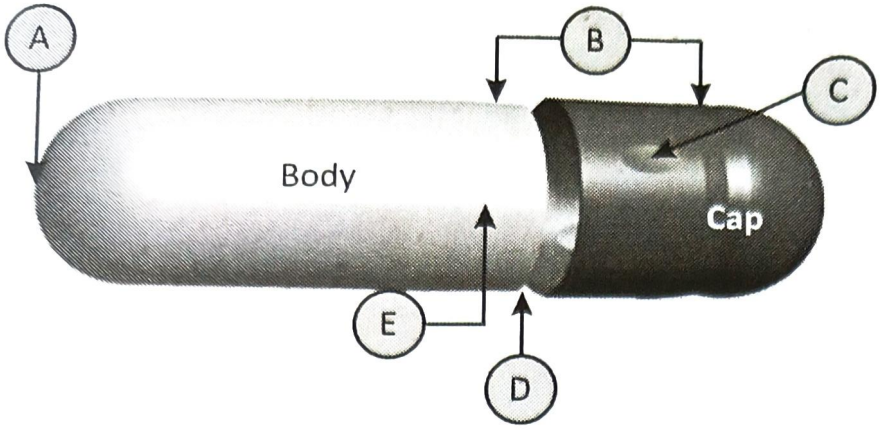


Fig. 5.7: *A. Two aerodynamic air vents allow air to escape from the cap; critical when operating high speed filling machines; B. Closely-matched locking rings provide full-circumference leak-free closure; C. Six elongated dimples maintain precise round capsule diameter, improving filling machine performance; D. Tapered rim of the body engages easily with the cap for problem-free closure; E. Rounded hemispherical ends are mechanically stronger and more resistant to deformation*

(b) **Spinning:** The pins are rotated to uniformly distribute the gelatin over the pins and to prevent the formation of bead at the ends of capsule.

(c) **Drying:** The gelatin is dried by a blast of cool air to form a hard shell.

The pins are moved through a series of air drying kilns to remove water.

(d) **Stripping:** The cap and body of capsules are stripped off from the pins by a series of bronze jaws strip.

(e) **Trimming and joining:** The stripped cap and body portions are trimmed to the required length by stationary knives.

After trimming to the right length,the cap and body portion are joined and ejected from the machine.

(f) **Polishing:**

- *Pan Polishing:* Acela-cota pan is used to dust and polish.
- *Cloth Dusting:* Capsules are rubbed with cloth.
- *Brushing:* Capsules are feed under soft rotating brush.

Types of Materials for Filling into Hard Gelatin Capsules

Dry solids: Powders, pellets, granules or tablets.

Semisolids: Suspensions or pastes.

Liquids: Non-aqueous liquids.

Table 5.3: Size of hard gelatin capsules-capsule size chart

Capsule number	0	0	0	1	2	3	4	5
Approximate capacity in mg	960	665	475	350	260	210	145	90

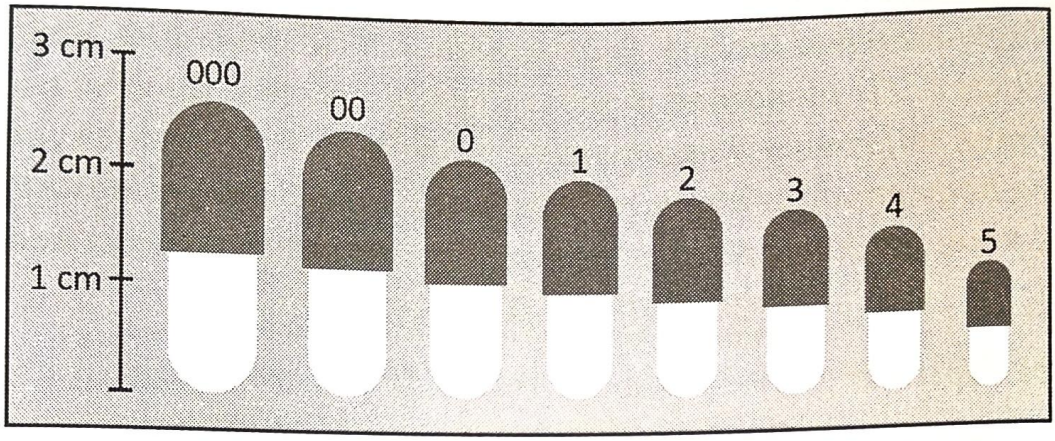


Fig. 5.8: ***Empty Hard Gelatin Capsule Physical Specifications***

Capsule Shell Filling

Hand operated hard gelatin capsule filling machines:

Generally, the capsules are filled with hand operated and electrically operated machines. But for small and quick dispensing hand operated machines are quite economical.

A hand operated gelatin capsule filling machine consists of the following parts and is shown in Fig. 5.9.

1. A bed with 200-300 holes.
2. A capsule loading tray
3. A powder tray
4. A pin plate having 200 or 300 pins corresponding to the number of holes in the bed and capsule loading tray.
5. A lever

6. A handle
7. A plate fitted with rubber top.

All parts of the machine are made up of stainless steel. The machines are generally supplied with additional loading trays, beds and pin plates with various diameters of holes so as to fill the desired size of the capsules. These machines are very simple to operate, can be easily dismantled and reassembled

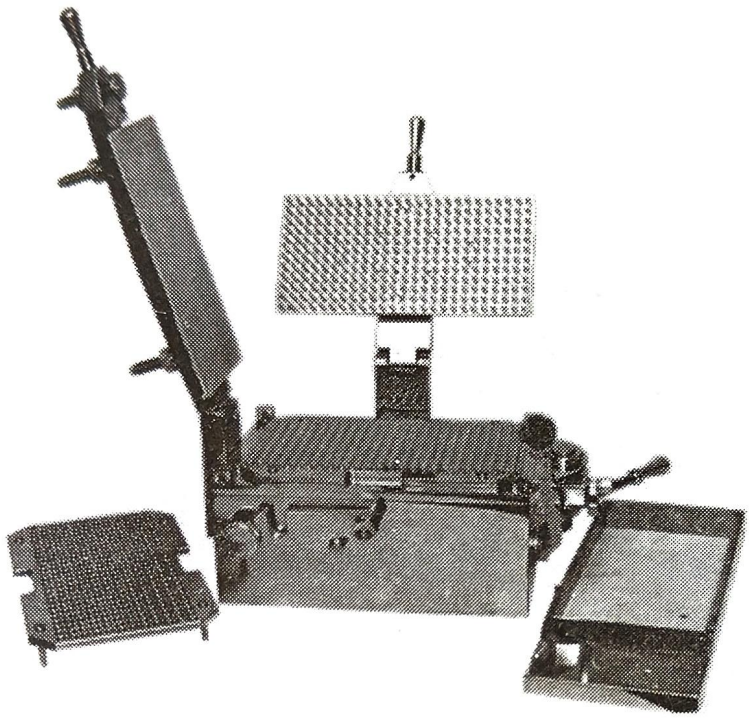


Fig. 5.9: ***Hand operated hard gelatin capsule filling machine***

Working:

1. Empty capsules are placed in the loading tray placed over the bed.
2. Bodies of capsules are separated from caps in the loading tray itself.
3. The required amount of drug to be filled in the capsules is placed in the powder tray present over the bed.
4. Powder is spread with the help of powder spreader.
5. Excess powder is removed.

6. Now the pin plate is lowered to press the powder in the bodies.
7. Now place the caps holding tray in position of powder tray.
8. Caps are pressed with help of plate with rubber top.
9. Filled capsules are collected in the tray.

With 200 hole machine about 5000 capsules can be filled per hour and with 300 hole machine 7500 capsules can be filled per hour.

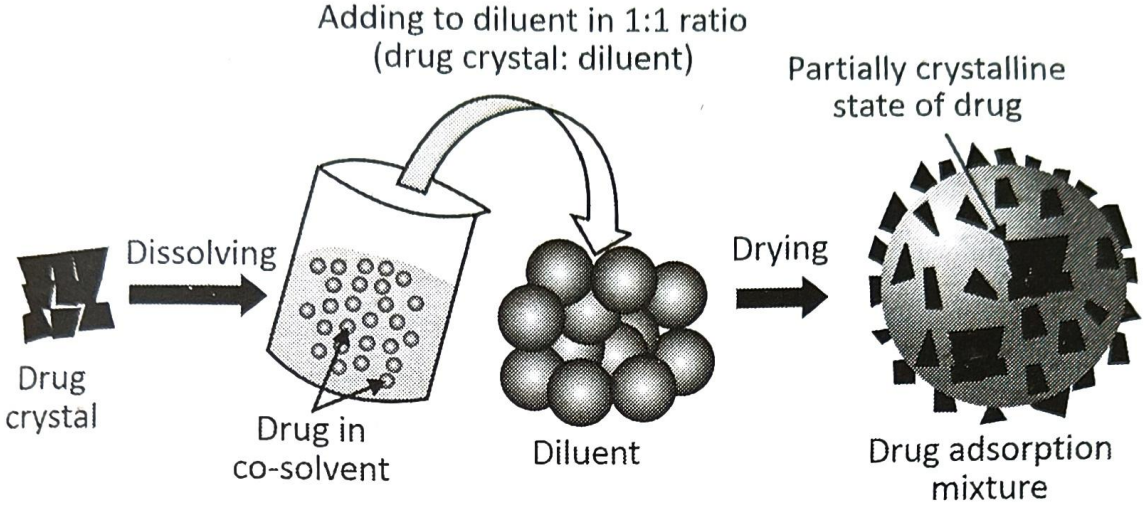
On large-scale manufacturing various types of semi-automatic and automatic machines are used.

They operate on the same principle as manual filling, namely the caps are removed, powder filled in the bodies, caps replaced and filled capsules are ejected out. With automatic capsule filling machines powders or granulated products can be filled into hard gelatin capsules. With accessory equipment, pellets or tablets along with powders can be filled into the capsules.

Difficulties in Filling Capsules

1. **Deliquescent or Hygroscopic Powders:** Hygroscopic drug can absorb the water from the gelatin capsule making it brittle. The addition of an adsorbent like magnesium carbonate, heavy magnesium oxide or light magnesium oxide overcomes this difficulty provided the capsules are packed in tightly closed glass capsule vials.
2. **Eutectic Mixtures:** Certain substances on mixing together forms a mixture with melting point lower than the room temperature. This results in the formation of liquid paste. Before filling in the capsules, such substances are mixed with an absorbent separately and then mixed together for being filled in the capsules. The absorbents used are magnesium oxide and kaolin. Another method in dealing with such type of difficulty is that the substances are mixed together so as to form a eutectic mixture, then an absorbent like magnesium carbonate or kaolin is added.

3. **Addition of Inert Powders:** It is impossible to fill very low amount of drug in the capsule. Hence, inert substance or diluent is added to increase the bulk of powder to be filled easily in capsules.



4. **Use of Two Capsules:** Some of the manufacturers separate the incompatible ingredients of the formulation by placing one of the ingredients in smaller capsule and then placing this smaller capsule in a larger capsule containing the other ingredients of the formulation.
5. **Filling of Granular Powder:** Some powders which lack adhesiveness and most granular powders are difficult to fill in the capsules by punch method because they are not compressible and flow out of the capsule as soon as they are lifted from the pile of powder into which they are punched. To overcome this difficulty, the non-adhesive powders should be moistened with alcohol and the granular powders should be reduced to powder before filling into capsules.

Alternative Material for Hard-Shell Capsules

Several materials have been examined as a substitute for the gelatin in two-piece hard capsules. Hydroxypropylmethyl Cellulose (HPMC) has become a successful alternative material for two- piece capsules and is actually on the market in the world. HPMC capsules have been developed for both pharmaceutical products and dietary

supplements. QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products.

Soft Gelatin Capsule

Soft gelatin (also called soft gel or soft elastic) capsules consist of one-piece hermetically-sealed soft shells. Soft gelatin capsules are prepared by adding a plasticizer, such as glycerine or polyhydric alcohol (e.g., sorbitol), to gelatin. The plasticizer makes gelatin elastic. Soft gelatin capsules come in various shapes such as spherical, elliptical, oblong and special tube shapes with and without twist off. They can contain non-aqueous liquids, suspensions, pasty materials or dry powders. Theyare especially important to contain volatile drug substances or drug materials susceptible to deterioration in the presence of airpresence of air.

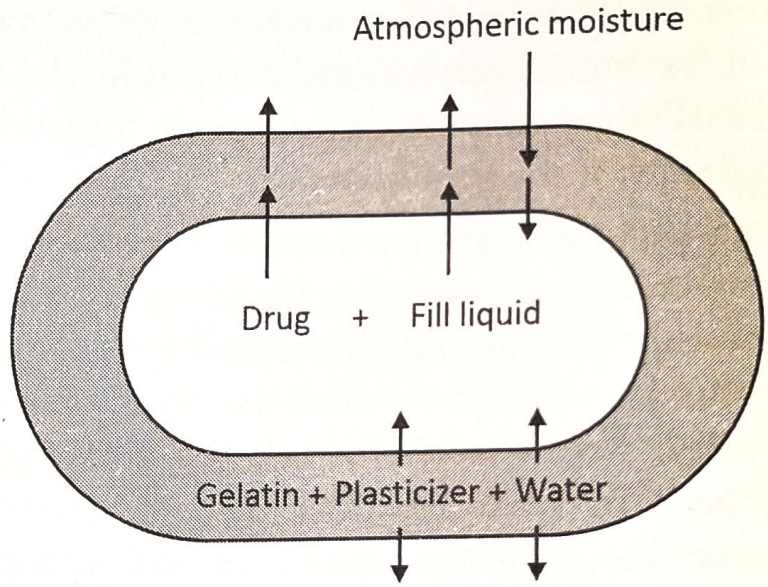


Fig. 5.10: ***Dynamic nature of the soft gelatin capsule***

Solid dosage forms are becoming a popular dosage form for the administration of liquids, suspensions, pastes and dry powders in the dietary supplement industry and they differ from hard gelatin capsules in various terms.

A soft gel capsule is one piece, hermetically sealed soft gelatin shell containing a liquid, a suspension or semisolid referred to as fill. They are formed and filled and sealed in one continuous

operation, preferably by the rotary die process. Depending on the polymer forming the shell, they can be sub divided into two categories, namely soft gelatin capsule and non-gelatin soft capsules. The majority of soft capsules are made from gelatin owing to its unique physical properties that make it an ideal excipient for the rotary die process. Other various components of soft gelatin capsules are given:

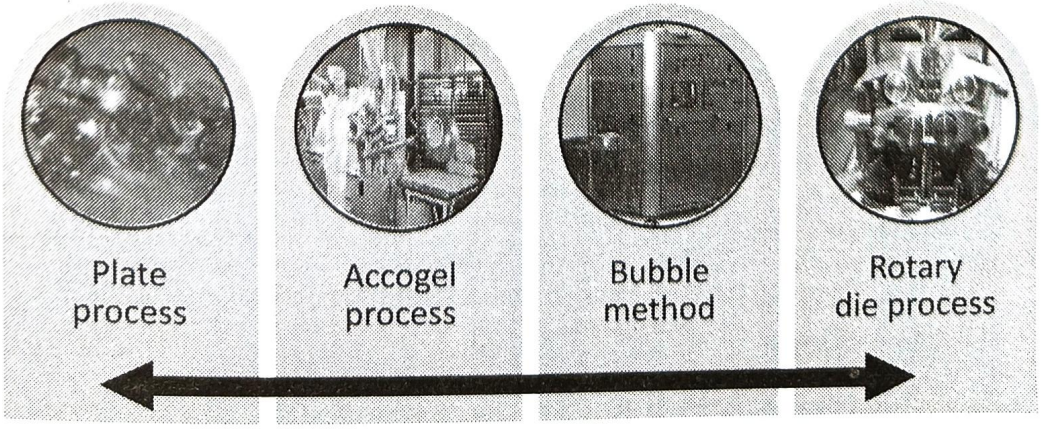
- Gelatin
- Glycerin or polyhydric alcohol
- Water or moisture
- Preservative
- Colourant
- Markings
- Opaquest

Flavours may be added and up to 5% sucrose may be included for its sweetness and to produce a chewable shell.

Manufacturing of Soft Capsules

It is manufactured by four methods. They are:

1. Plate process
3. Accogel capsule machine
4. Bubble method
2. Rotary die process



1. **Plate process:** Gelatin sheet is placed over a die plate having numerous depressions or die pockets. Sheet is drawn in these depressions by applying vacuum. Pockets are filled with liquid or paste. A second sheet of gelatin is placed on top of filled pockets. Now combined plates are sealed and capsules are formed.
2. **Accogel capsule machine:** It consists of mainly 3 parts:
   (a) Measuring roll
   (b) Die roll
   (c) Sealing roll

   Measured doses are transferred in the gelatin linked pockets by the rotation of measuring roll and die roll. The continued rotation of the filled die converges with the rotating sealing roll where a second gelatin sheet is applied to form the other half of the capsule. Pressure developed between the die roll and sealing roll seals and cuts out the capsules.
3. **Bubble method:** The globlex mark II capsulator produces truly seal less, one piece-soft gelatin capsules by a "bubble method". A concentric tube dispenser simultaneously discharges the molten gelatin from the outer annulus and the liquid content from the tube. By means of a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets that consist of a liquid medicament core within a molten gelatin envelope.
4. **Rotary die process:** Rotary die process is used to encapsulate shells with liquids, suspensions or semisolids. The gelatin sheets are feed on rolls contain small orifice hinded up with the die pocket of the die roll Two gelatin ribbons are fed continuously into a rotating die assembly and are simultaneously fed with liquid or paste between the rollers. Appropriate volume of material is filled in the capsule by a pump. Die rolls are mechanically pressed to seal the capsules.

Advantages of Soft Gelatin Capsule

- It is easy to swallow soft gels and contents are released quickly.
- Unpleasant taste and odours are masked by capsules.
- Have an elegant appearance
- Easily soluble in digestive tract.
- They may enhance the bioavailability of the active ingredient
- Dosage Accuracy. Uniformity and precision dosage
- Product Stability. Sealed container, Protection from light for photosensitive formulations, Protects drug from oxidation and degradation

Disadvantages of Soft Gelatine Capsule

- Hygroscopic materials difficult to incorporate as they make capsule brittle.
- Efflorescent material cannot be incorporated, they may cause softening/leaching.
- Deliquescent materials cannot be incorporated. They may cause hardening or brittle capsule.

Ideal Characteristics of Soft Capsules

- To optimize the chemical stability of the active compound.
- To improve bioavailability of the active compound
- To allow for an efficient and safe filling process
- To achieve a physically stable capsule product.
- Final product stability is related to shell compatibility

Types of Soft Gel

1. Enteric Soft Gel
2. Controlled Release Soft Gel
3. Chewable Soft Gels

Table 5.4: Difference between Hard Gelatin and Soft Gelatin Capsule

Characteristics	Hard gelatin capsule	Soft gelatin capsule
Small batches manufacturing ability	Yes	No
Scale up	Simple and in house	Large quantities of drug substances required and must be outscored.
Fill temperature	Max. 70°C	Max. 35°C
Plasticizers in shell	No	Yes
Risk of drug migration	Low	High for drug soluble in plasticizer
Permeability of shell to oxygen	Low	High due to plasticizer and varies with moisture content
Sensitivity to heat and humidity	Low	High due to plasticizers
Hygroscopic excipients	High concentration must be avoided	Can be tolerated due to presence of plasticizer in shell
Capsule dimension	Constant	May vary.

Evaluation Tests for Capsules

1. Content uniformity
2. Disintegration test
3. Weight variation test
4. Dissolution test
5. Moisture permeation test

Content Uniformity

The amount of active ingredient should be within in the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label amount.

Disintegration Test

Place 1 capsule in each of the 6 tubes of the basket and suspend the assembly in water at 370°C ± 20°C, which is repeatedly immersed 30 times per minute. The capsules pass the test if no residue of drug or other than fragments of shell remains No.10 mesh screen of the tubes.

Weight Variation Test

20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight is noted. The capsule passes the test if the weight of individual capsule falls within 90-110% of the average weight.

Dissolution Test

Place 1000 ml of water having a temperature of 36.5° to 37.5° in to the vessel. Place specified number of capsules in basket 7 adjust the speed to 100 rpm. Withdraw the required volume for every 10min. time interval. Filter and determine the amount of active ingredient. The sample passes the test if the amount of active ingredients in the solution is not less than 70% of the standard amount.

Moisture Permeation Test

According to USP the unit dose container is packed along with dehydrated pellets, which have the property of changing colour in the presence of moisture. The weight of test capsule is compared with the under test capsules. Difference in weights gives the amount of moisture absorbed.

Storage, Stability and Packing of Capsules

Capsules should be packed in well closed glass or plastic containers and stored at temperature not exceeding 30°C. Capsules are individually enclosing in strip and blister packing. In strip packing the capsule is hermetically sealed within the strips of an aluminum or plastic film.

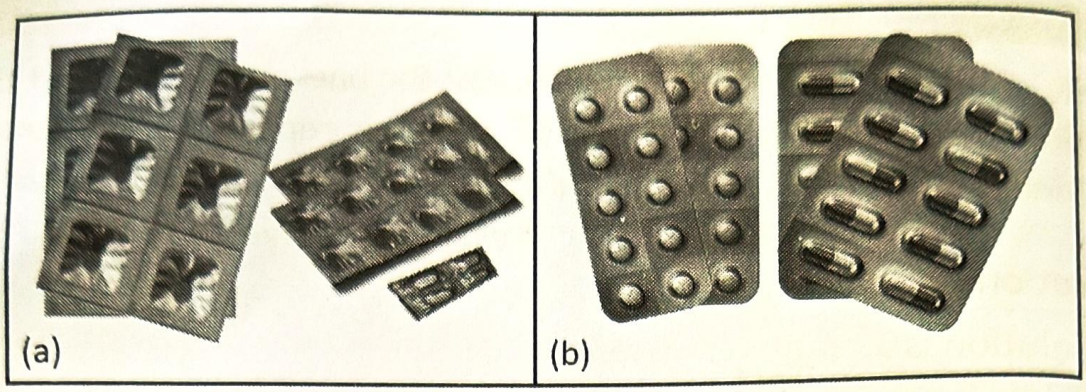


Fig. 5.11: ***(a) Strip Pack; (b) Blister Pack***

In blister packs, a press forces the capsule through the backing strip. Capsules having a larger shelf life in unopened glass bottles than in strip pack and but this is reversed.

Storage: Storage for hard gelatin capsules should be 24° to28°C.The moisture content exceeding between 12-15%. When the capsules are stored at high humidity, it may absorb the moisture content and it may lose it shapeat low humidity they loss the water from the shell and they become brittle. The ambient humidity and temperature levels for storage of hard gelatine capsules are as follows:

- Minimum = 35% RH, 15°C
- Best possible = 50% RH, 20°C
- Maximum = 65% RH, 25°C

Soft gelatin capsules already being high in water content it requires extra caution during storage. They should be stored in air-conditioned area where humidity does not exceed 45% RH at 21-24°C.

Stability: Stability is defined as ability of dosage form to maintain its physical, chemical, microbiological, therapeutic and toxicological identification right from the date of formulation and packing until its therapeutic action.

Accelerated stability tests for capsules are performed to determine the integrity of gelatin capsule shell and for determination of shelf life of capsules. The capsule shells must be equilibrated to known atmospheric conditions with relative humidity of about 20-30% at 21-24°C. The capsules must be used for further tests only after re-established the equilibrium at room temperature.

PHARMACEUTICAL SOLUTIONS

True solution: It is a clear homogenous (one phase) mixture that is prepared by dissolving a solid, liquid or gas in liquid, represent an one phase so also termed as the monophasic liquid dosage form.

Solutions

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquidor gas in another liquid and representsa group of preparations in which the molecules of the solute or dissolved substance are dispersed into the solventor **solutions** are homogeneous mixtures of one or more solutes molecularly dispersed in a suitable solvent or a mixture of mutually miscible solvents. The components of solutions are termed the solute and the solvent depending on their relative proportions (a component in lower proportion is termed solute).

Most solutions are unsaturated with the solute. The strengths of pharmaceutical solutions are expressed in terms of percentage strength, although for very dilute preparations expressions of ratio strength are sometimes used.

w/v, v/v or w/w means percentage weight-in-volume for solutions or suspensions of solids in liquids; percentage weight-in-volume for solutions of gases in liquids; percentage volume-in-volume for solutions of liquids in liquids; and weight-in-weight for mixtures of solids and semisolids pharmaceutical.

Saturated solutions are solutions that, at a given temperature and pressure, contain the maximum amount of solute that can be dissolved in the solvent.

Isotonic solutions have similar tonicity as biological fluids. These solutions cause no swelling or contraction of the tissues with which they come in contact and produce no discomfort when instilled in the eye, nasal tract, blood or other body tissues. Isotonic sodium chloride is a 0.9% w/v concentration of NaCl in water and is also called normal saline. A 5% w/w dextrose, also known as glucose, solution in water is also isotonic.

Pharmaceutical solutions are used for many routes of administration, including oral, rectal, vaginal, ophthalmic, parenteral and otic. The most common solution dosage form is the oral liquid.

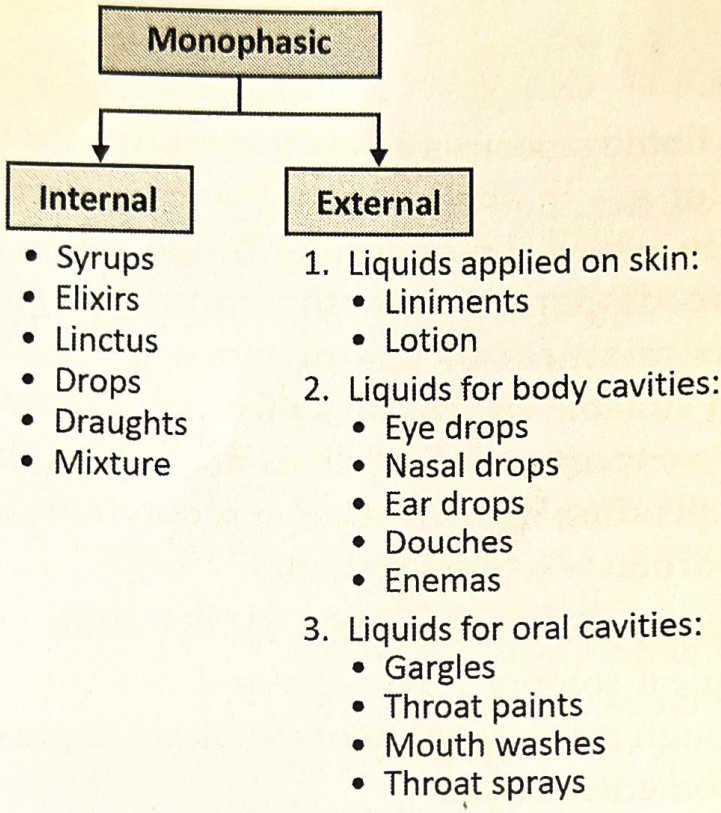


Fig. 5.12: *Classification of Monophasic Liquid Dosage Forms*

LIQUID ORAL PREPARATIONS

Solutions

Solutions are liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

Advantages

- Drug available immediately for absorption, i.e., bioavailability of solutions is greater than that of oral solid dosage forms.

- Flexible dosing.
- Designed for oral route of administration.
- No need to shake container.
- Facilitates swallowing in difficult cases.

Disadvantages

- Drug stability reduced in solutions.
- Bulky, difficult to transport and prone to container breakages.
- Technical accuracy needed to measure dose on administration.
- Measuring device is needed for administration. 5. Some drugs are poorly soluble.

Classification of Solutions

1. Oral solutions
2. Oral syrups
3. Oral elixirs
4. Linctus
5. Mouth washes/gargles

Syrup

The syrup is a saturated or concentrated, viscous aqueous solution of sucrose/sugar substitute with or without flavour/medicinal substances in purified water.

Simple syrup contains **85% w/v** (65% w/w); specific gravity 1.313 (**USP**) or **66.7% w/w** as per **Indian Pharmacopeia/BP**.

Composition of Syrup

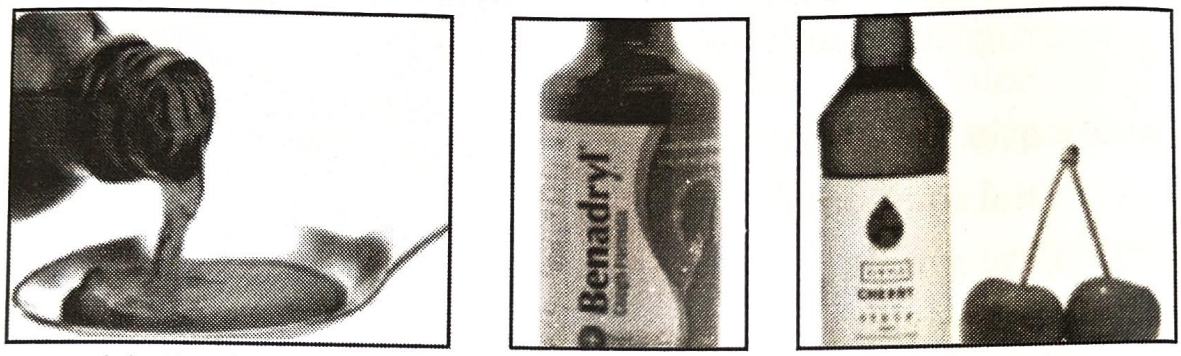
Most syrups contain the following components in addition to the purified water and drug(s):

- Sugar, usually sucrose or other sugar substitutes are used to provide sweetness and viscosity, (Sugar-free alternative-Sorbitol, Saccharine, Aspartame)

- Antimicrobial preservatives,
- Flavorants & colourants,
- Syrups may also contain solubilizing agents, thickeners or stabilizers.

Syrup may contain preservatives. Glycerin, methylparaben, benzoic acid and sodium benzoate may be used to prevent bacterial and mold growth. Glycine, benzoic acid (0.1%-0.2%), sodium benzoate (0.1%-0.2%) and various combinations of methylparaben, propylparaben and butylparaben or alcohol are commonly used as antimicrobial preservatives.

Types of Syrup



(a) Simple Syrup (b) Medicated Syrup (c) Medicated Syrup

Fig. 5.13: *Types of Syrup*

1. **Simple Syrup:** Simple syrup is concentrated solution of sucrose in purified water. The concentration of sugar is 66% w/w
2. **Medicated Syrup:** Medicated syrups are aqueous solutions containing sugar and atleast one water soluble active ingredient.

   The sugar concentration should be between 65-67%.

   Syrups may contain the following excipient:

   (a) **Sugar polyols:** Glycerol, manitol, sorbital

   (b) **Preservatives:** Parabens, benzoates, antioxidants (like BHT and sodium metabisulfite)

   (c) Acids-citric acid to prevent recrystallisation

(d) Buffering agents

(e) Chelating agents

(f) Flavouring agents and flavour enhancers

(g) Colouring agents

(h) Ethyl alcohol (3-4% volume)

3. **Flavoured Syrup:** Syrups with flavouring agents and without medicinal substances. Containing Aromatic/ Flavoured – Flavoured syrup (Cherry & Raspberry syrup)

Preparation of Syrups

Syrups are prepared using one of four techniques:

1. Solution with heat
2. Solution by agitation/agitation without heat
3. The addition of sucrose to a liquid medication or flavoured liquid
4. Percolation.

1. **Solution with Heat:** This method is suitable for preparation when constituents are non-volatile or do not get degraded by heat. Purified water is heated upto 85 degrees Celsius. Sucrose is then added while agitating vigorously. The heat stable components are then added to hot solution. Mixture is let to cool down. Then purified water is added to adjust the volume upto proper level. In instances in which heat-labile agents or volatile substances, such as flavors and alcohol, are added, they are incorporated into the syrup after cooling to room temperature.

   Invert sugar: While heating the syrups during their preparations, sucrose gets hydrolysed into glucose and fructose. This hydrolytic reaction is referred as inversion. The sugar is dextrorotatory whereas monosaccharides formed are laevorotatory. Thus, inversion of sugar taken place. The rate of inversion is increased greatly by the presence of acids; the hydrogen ion acts as a catalyst in this

hydrolytic reaction. Fructose is responsible for the darkening of syrup. Invert sugar is more readily fermentable than sucrose and tends to be darker in colour. But, its two reducing sugars prevent the oxidation of other substances.

$$C_{12}H_{24}O_6 \rightarrow C_6H_{12}O_6 \text{ (Glucose)} + C_6H_{12}O_6 \text{ (Fructose)}$$

2. **Agitation without Heat:** This method is used for those substances in which constituents either degrade on heating or are volatile in nature.
3. **Addition of Sucrose to a Liquid Medication or Flavoured Liquid:** This method is often used with fluidextracts or tinctures.
4. **Percolation:** In the percolation method, either purified water or the source of the medicinal component is passed slowly through a bed of crystalline sucrose, thus, dissolving it and forming a syrup. Example: Ipecac syrup

Preservation of Syrups

Where special facilities cannot be employed for preservation of syrups, they should be made only in small quantities that can be used within a few months.

There are several ways of preserving syrups:

1. Low temperature not above 25°C.
2. Concentration without supersaturation.
3. Addition of preservatives to prevent bacterial and mold growth, e.g., glycerin, methyl parabens, benzoic acid and sodium benzoate added particularly when concentration of sucrose is syrup is low.

Elixirs

Elixirs are clear, liquid, flavoured hydroalcoholic preparation intended for oral use. They contain one or more medicaments, pleasantly flavoured, usually attractive colour containing high

proportion of alcohol or sucrose or suitable polyhydric alcohols together with suitable additives (including antimicrobial agents). The alcoholic contents in elixir vary from 5% to 40%. In general they are more stable than mixture as sufficient alcohol is added to maintain the drug in solution. Most of the elixirs become turbid when moderately diluted by aqueous fluids.

Types of Elixirs

Elixirs are mainly of two types:

1. **Non-medicated elixir:** They are used purely as diluting agents or solvents for drugs containing approximately 25 percent alcohol, e.g., simple elixir, Iso-alcoholic elixir or low alcohol elixir (containing 8-10% alcohol), High alcoholic elixir (containing 75-78% alcohol).
2. **Medicated elixirs:** Elixirs containing therapeutically active compounds are known as medicated elixirs, e.g., Phenobarbital elixir USP, Dexamethasone elixir USP, Chlorpheniramine Maleate elixir USP, Diphenhydramine Hydrochloride elixir USP, Piprazine Citrate elixir, Terpin Hydrate elixir etc.



Fig. 5.14: ***Types of Medicated Elixirs***

The elixir is used as a vehicle for other drugs in many commercially available cough syrups *viz.*, dextromethorphan hydrobromide, codeine phosphate, pyrilamine maleate, ammonium chloride, creosote, chloroform and a wide variety of other drugs with expectorant and anti-tussive properties.

Formulation

Generally elixirs contain following ingredients:

Vehicles

About 10% to 20% of alcohol is used for keeping oils, vegetable extracts, tannin etc., in solution form. Faint opalescence from flavouring agents containing essential oils and light precipitants from vegetable extracts are not considered acceptable in elixirs. Glycerol and propylene glycol are used as solvents.

Stabilizers

In neomycin elixir, citric acid is used to adjust pH 4.0 to 5.0 to minimize the darkening that occurs on storage. Disodium edetate should be used to sequester heavy metals that catalyse decomposition of the antibiotics.

Flavouring Agents

Sweetening agents and fruit flavors are used in many medicinal preparations, e.g., Black currant syrup in chloral elixir, Concentrated raspberry juice with inverted syrup in paracetamol elixir, Lemon spirit with invert syrup in ephedrine elixir, compound orange spirits with glycerol in phenobarbital elixir.

Preservatives

In elixir, fermentation and mould growth are inhibited when it contains more than 20% of alcohol, propylene glycol or glycerol. Syrup containing saturated solution of sucrose is also inhibitory to many microorganisms because of high osmotic pressure. The commonly used preservatives are double strength chloroform, spirit and benzoic acid and methyl ester of p-hydroxy benzoic acid.

Method of Preparation

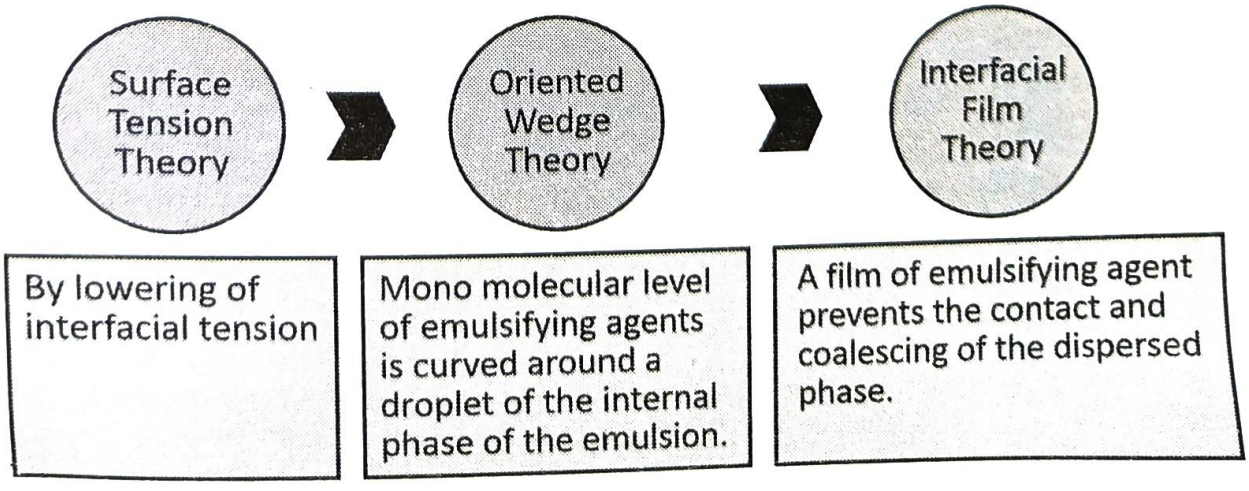
Elixirs are prepared by dissolving the ingredients with agitation/or by admixture of two or more liquid components in the suitable solvent. Usually, the alcohol soluble substances are dissolved in alcohol and water soluble in water separately. As a rule, the aqueous solution is always added to alcoholic solution.

The aqueous solution is then added to the alcoholic solution with constant stirring and make up the volume with the solvent or vehicle specified in the formulation. At this stage the product may not be clear due to the separation of some of the flavouring agents because the alcoholic strength is reduced. In such case the elixir is allowed to stand for some time to ensure the saturation of the hydroalcoholic solvent and permit the oil globules to coalesce. Talc (upto 3%) can be used to absorb the excess of oils and assist in their removal from solution. Filtration gives a bright clear product.

EMULSIONS

An emulsion is a biphasic liquid preparation containing two immiscible liquids, one of which is dispersed as minute globule is called the 'dispersed phase' and the liquid in which the globules are dispersed is called the 'continuous phase'. Normally, two immiscible liquids cannot be dispersed for a long period. So an emulsifying agent is added to the system. It forms a film around the globules in order to scatter them indefinitely in the continuous phase, so that a stable emulsion is formed.

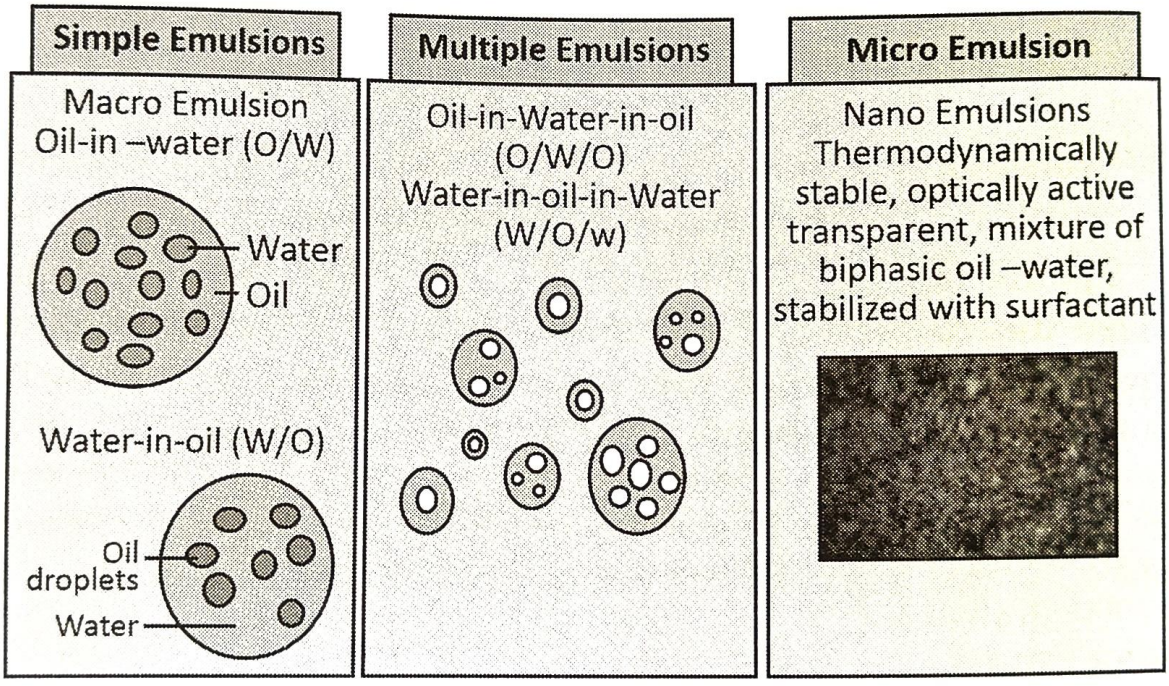
Theory of Emulsification



Difference between O/W and W/O Emulsion

O/W Emulsion	W/O Emulsion
Water is the dispersion medium and oil is the dispersed phase.	Oil is the dispersion medium and Water is the dispersed phase
Non greasy and easily remove from the skin	Greasy and not water soluble
Used externally to provide cooling, e.g., vanishing cream	Used externally to prevent evaporation of moisture from the surface of skin, e.g., cold cream
Preferred for internal use	For external use

Classification of Emulsion



Emulsifying Agents

Emulsifying agents are also known as emulgents or emulsifiers. Emulsifying agents reduce the interfacial tension between two phases, that is oil phase and aqueous phase and so it make them miscible with each other and form a stable emulsion.

Ideal Properties

1. It should be capable of reducing the interfacial tension between the two immiscible liquids.

2. It should be compatible with other ingredients of the preparation.
3. It should be non toxic
4. It should be capable to produce and maintain the required consistency of the emulsion.
5. It should be chemically stable.
6. It should be capable of keeping the globules of dispersion liquid distributed indefinitely throughout the dispersion medium.

Classification of Emulsifying Agent

Emulsifying agents can be divides as follows:

1. **Natural:**
   (a) Vegetable source, e.g., Gum acacia, Tragacanth, agar, pectin, starch, irish moss (Chondrus)
   (b) Animal Source: wool fat, egg yolk, gelatin.
2. **Semi-Synthetic; Methyl cellulose, Sodium carboxymethyl cellulose**
3. **Synthetic:**
   (a) *Anionic:* Sodium lauryl sulphate
   (b) *Cationic:* Cetrimide, Benzalkonium chloride etc.
   (c) *Non-ionic:* Glyceryl esters etc.
4. **Inorganic:** Milk of magnesia, magnesium oxide, Magnesium trisilicate, Magnesium aluminium silicate, Bentonite.
5. **Alcoholes:** Carbowaxes, Lecithins, Cholesterols

1. Natural emulsifying agent can be classified into two types:

(a) Vegetable source: These are carbohydrates which include gums and mucilaginous substances. They are anionic in nature and they produce o/w emulsion. The following are some of the emulsifying agent in this class.

(i) Acacia: It is best emulsifying agent for preparing extemporaneous preparation meant for internal use that are stable over wide pH range (2-10). Emulsion prepared by using acacia has low viscosity therefore creaming takes place, to overcome this problem it can be used

along with other emulsifying agent like tragacanth gum agar pectin etc.

(ii) **Tragacanth:** It is rarely used alone as it produces very viscous emulsion, stability and appearance can be improved by passing through an homogenizer. Tragacanth can be used with other emulsifying agent.

(iii) **Pectin:** 1% mucilage is used as emulsifying agent. It is incompatible with alkalis, strong alcohol, tannic acid and salicylic acid.

(iv) **Starch:** Starch mucilage is rarely used as it coarse emulsion, it is generally used for preparation of enemas

(v) **Irish moss:** It is used as thickening agent, it is used along with gum acacia to mask unpleasant odour in preparation of cod liver oil emulsion.

(b) **Animal sources:**

(i) **Wool fat:** It is used for emulsion meant for external use, it produces o/w emulsion and can absorb about 50% of water.

(ii) **Egg yolk:** Meant for preparing extemporaneous emulsion meant for internal consumption, it can get spoiled during transportation. It is used in concentration of 12-15%, it has to be stored properly in a refrigerator.

(iii) **Gelatin:** It is used in concentration of 1% as emulsifying agent. It is used for emulsification of liquid paraffin, emulsions prepared by gelatin are white but they need preservative.

Preparation of Emulsion

1. Wet gum method
2. Dry gum method
3. Bottle method
4. Other method

Primary Emulsion

Primary emulsion is biphasic liquid preparation having two immiscible liquid with emulsifying agent with nearly white appearance.

Primary **emulsifying agents:** Acacia, Tragacanth

Secondary **emulsifying agents:** Cetrimide, benzethonium chloride and glyceryl monostearate.

1. **Wet gum method:**
   (a) Calculate the quantity of oil, water and gum required for preparing primary emulsion

Oil		Water		Gum
4	:	2	:	1

   (b) Powder the gum acacia in a mortar. Add water and triturate it with gum so as to form mucilage
   (c) Add required quantity of oil in small portions with rapid triturating until a clicking sound is produced and the product becomes white. At this stage emulsion is known as primary emulsion.
   (d) Add more of water in small proportion to the primary emulsion with triturating to produce the required volume. Stir thoroughly so as to form a uniform emulsion
   (e) Transfer the emulsion to a bottle, cork, label and dispense.
2. **Dry gum method for preparation of emulsion:**
   (a) Measure the required quantity of oil in a dry measure and transfer it into a dry mortar.
   (b) Add the calculated quantity of gum acacia into it and triturate rapidly so as to form a uniform mixture.
   (c) Add required quantity of water and triturate vigorously till a clicking sound is produced and the product becomes white or nearly white due to the total internal reflection of light. The emulsion produced at this stage is known as primary emulsion.
3. **Bottle Method or Forbes Bottle Method:** It contains volatile oil or oil with low viscosity.

Gum + Oil (dry bottle)

↓

Shake

↓

Gum + Oil (dry bottle) shake, water (Volume equal to oil) is added in portion with vigorous shaking to form primary emulsion

↓

Remaining quantity of water is added to make the final emulsion

Types of oils	Examples	Quantity for primary emulsion		
		Oil	Water	Gum
1. Fixed Oil	Almond Oil Arachis Oil Castor Oil Cod liver Oil	4	2	1
2. Mineral Oil	Liquid Paraffin	3	2	1
3. Volatile Oil	Turpentine Oil Cinnamon Peppermint	2	2	1
4. Oleoresin	Male fern extract	1	2	1

Test for Identification of Emulsion

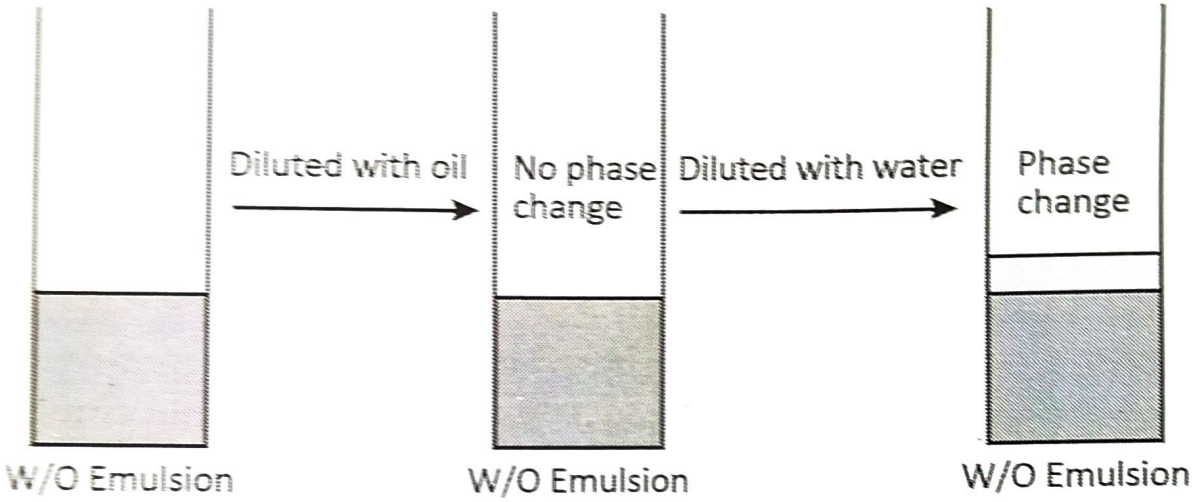
1. Dilution test
2. Dye test
3. Conductivity test
4. Fluorescence test

1. Dilution Test:

Emulsion diluted with water:

(i) Emulsion remains stable then it is o/w emulsion

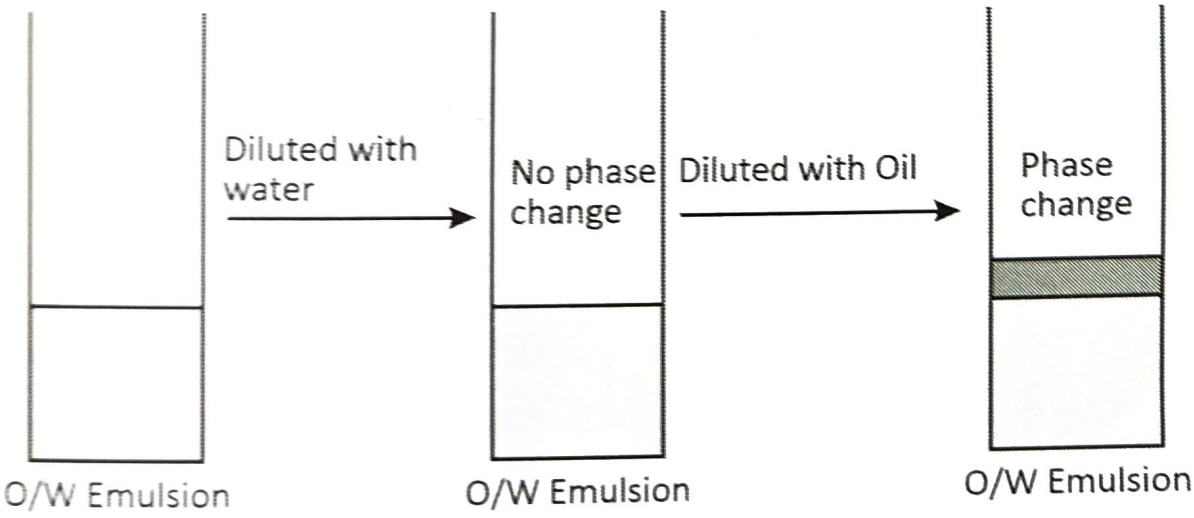
(ii) Emulsion break, it is w/o emulsion



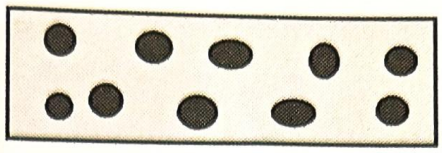
Emulsion diluted with oil:

(i) Emulsion remains stable then it is w/o emulsion

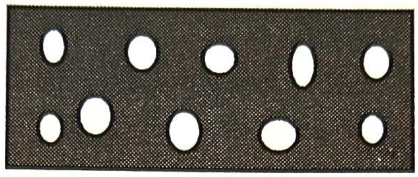
(ii) Emulsion break it is o/w emulsion



2. **Dye Test:** Emulsion diluted with scarlet red dye:

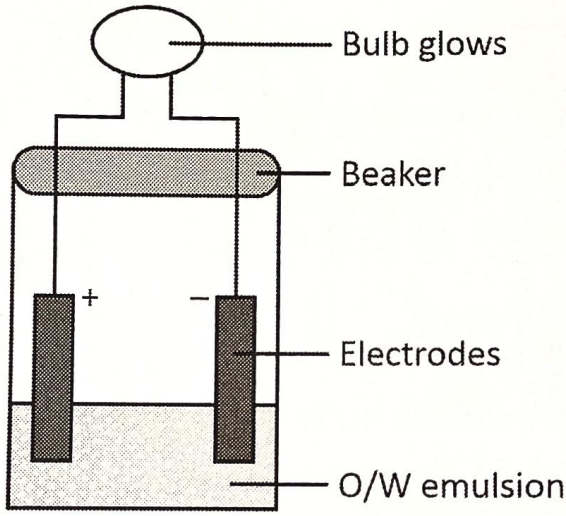


(i) Dispersed globules appear red & background is colorless then it is o/w type.

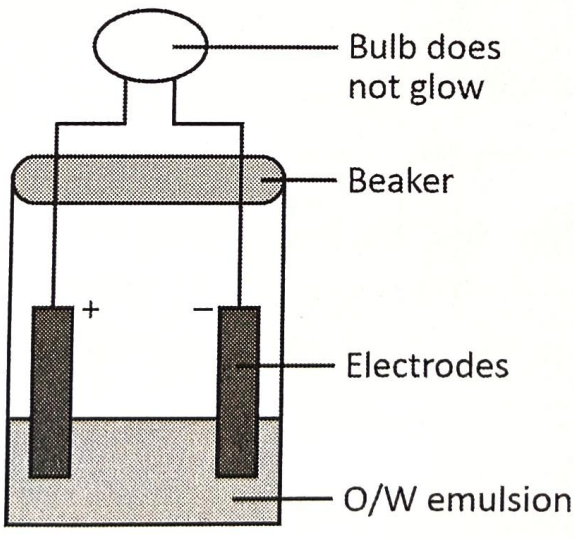


(ii) Dispersed globules appear colourless & background is red then it is w/o type.

3. **Conductivity Test:** This type of emulsion show bulb glowing on passing electric current.



If bulb glows the emulsion is o/w type.



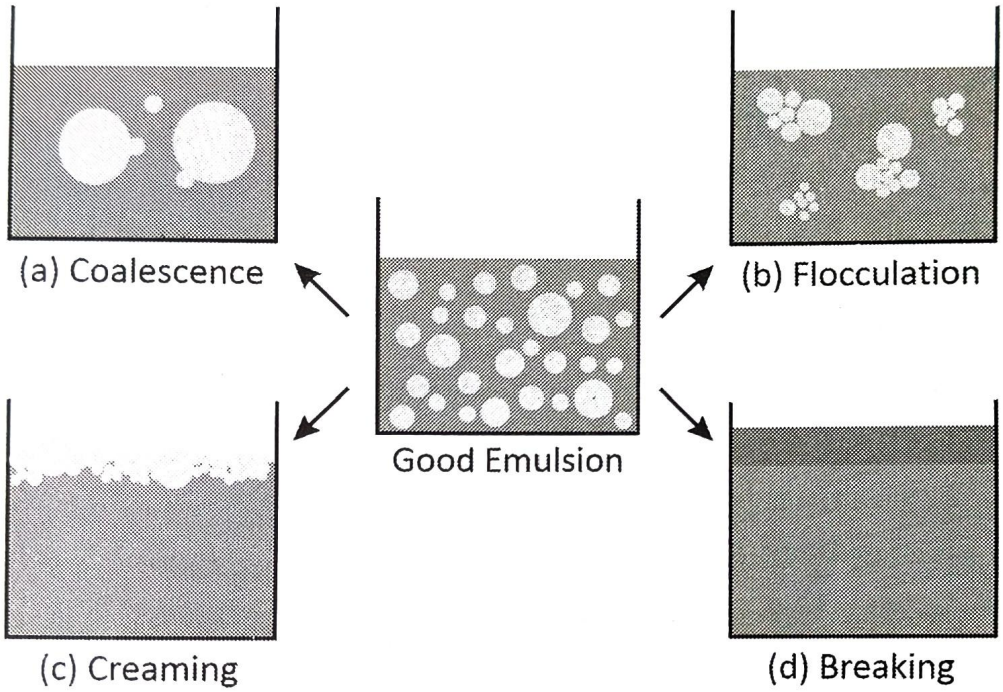
If bulb does not Glow the emulsion is w/o type

4. **Fluorescence Test:** If an emulsion on exposure to ultraviolet radiations shows continuous fluorescence under microscope, then it is w/o type

   If it shows only spotty fluorescence, then it is o/w type.

5. **Cobalt Chloride Test:** When a filter paper soaked in cobalt chloride solution is dipped in to an emulsion and dried, it turns from blue to pink, indicating that the emulsion is o/w type.

Stability of Emulsion



1. **Cracking:** Cracking means the separation of two layers of disperse and continuous phase due to coalescence of disperse phase globules which are difficult to redisperse by shaking.

   Factor responsible for cracking of emulsion.

   The following factors results in the cracking of emulsion:

   (i) Addition of emulsifying agent of opposite type:
   (ii) Growth of microorganism
   (iii) Decomposition of the emulsifying agent
   (iv) Addition of common solvent
   (v) Change in temperature
   (vi) By creaming.

(i) **Addition of emulsifying agent of opposite type:** Soaps of monovalent metal produces o/w emulsion, & Soaps of divalent metal produces w/o emulsion. But addition of monovalent soap to divalent soap emulsion & vice versa may leads to cracking.

(ii) **Growth of microorganism:** Preservative should be present otherwise bacteria may destroy emulsifying agent & cause cracking.

(iii) **Decomposition of emulsifying agent:** When acid is added to alkali soap emulsion it causes decomposition of emulsifying agent & thus, leading to cracking of emulsion.

(iv) **Addition of common solvent:** Addition of common solvent in which both disperse & continuous phase are soluble forms one phase system & destroys the emulsion, e.g., Turpentine, soft soap & water are soluble in alcohol.

(v) **Change in Temperature:** Increase in temperature leads to reduction in viscosity; encourage creaming thus leads to cracking. Low temperature causes freezing of water content.

(vi) **By creaming:** A creamy emulsion is more liable to crack than a homogenous emulsion.

2. **Creaming:** Creaming may be defined as the upward movement of dispersed globules to form a thick layer at the surface of the emulsion.

According to a stokes law, the rate of creaming is depends upon various factors as follows:

$$V = 2r^2 (d_1 - d_2)g/9n$$

where,

V = rate of creaming, r = radius of globules, d1 = density of dispersed phase, d2 = density of dispersion medium, g = gravitational constant, n = viscosity of the dispersion medium.

(i) **Radius of the globules:**

- The rate of creaming is directly proportional to the radius of the globules.

- Larger the size of the globules more will be creaming and smaller the size of globules lesser will be creaming.
- The small globules will rise less quickly than larger globules. Hence, creaming can be reduced by reducing the size of the globules by passing the emulsion through a homogenizer.

(ii) **Difference in densities of the disperse phase and continuous phase:** Greater the difference, more will be the creaming. This is not desirable because it is not required therapeutically.

(iii) **Viscosity of the dispersion medium:**

- The rate of creaming is inversely proportional to the viscosity of the continuous phase.
- Too much viscosity is undesirable because it may becomes difficult to redisperse the material which have settled at the bottom, also difficult to pour the emulsion from the container.

(iv) **Storage condition:**

- The emulsion should be stored in cool place because the rise in temperature reduces the viscosity, may lead to creaming.
- Freezing should be avoided because it may lead to cracking of emulsion.

Table 5.5: Strategies to reduce Creaming

Principal	Method
Reduce Droplet size	Homogenizer
Reduce Density Difference	Add weighting agents like oil
Increase the viscosity of continuous phase	Add thickening or gelling agent, e.g., methylcellulose

3. **Phase inversion:** Means change in the type of emulsion, i.e., o/w to w/o or *vice versa.*

Reasons for phase inversion:

1. Addition of electrolyte.
2. Changing phase volume ratio.
3. Temperature change.
4. Changing the emulsifying agent.

Phase inversion can be reduce by:

1. Using proper emulsifying agent in proper concentration.
2. Using 30-60% dispersed phase
3. Storing the emulsion in cool place.

Evaluation of Emulsion

A stable suspension can be dispersed homogeneously with moderate shaking and can be easily poured throughout its shelf life. Their stability can be evaluated by following method:

(a) **Sedimentation Method:** Sedimentation volume is the most important parameter in the Evaluation of the stability of suspension. The sedimentation volume F = Hu/Ho, where, Hu is the ultimate height of the total suspension and Ho is the initial height, than the graph of sedimentation volume can be plotted against time indicating sedimentation pattern

(b) **Rheological Method:** The viscosity of suspension is studied at different time interval by using a good viscometer which provide good information about stability of suspension

(c) **Electro kinetic Method:** The determination of surface electric charge or zeta potential helps in determining the stability of suspension, Zeta potential can be calculated from migration velocities of the particles measured by electrophoresis method.

(d) **Micrometric Method:** Stability of suspension depends on particle size so any change in particle size with reference to time will provide useful information, particle size distribution and crystal habit can be studied by microscopy and coulter counter method.

Formulation of Emulsions

The formulation includes vehicle, oil, emulsifier, antioxidants, flavouring agents and preservatives. The selection of oil and emulsifier depends on the type of an emulsion type (o/w, w/o or multiple).

Vehicle

In emulsion, there are two liquid phases- aqueous and non-aqueous. The aqueous phase include purified water for the emulsions used externally or topically, but when the emulsion is intended for parenteral use, then Sterile Water for Injection (SWFI) is used. In this phase, buffers like citrate, phosphate can be included. While in non-aqueous phase, oils are used.

Oils

The various types of oils that can be used in emulsions are simple esters, volatile oils, fixed oils, turpenoid derivatives and hydrocarbons. Oils act as carrier for drug, but the disadvantage is that it undergoes oxidation and therefore, there is a need of antioxidant, preservatives to be added. The emulsions that are used for external use, mineral oils are used, individually or in combination with hard or soft paraffins. Oils like castor oil, cottonseed oil, arachis oil are used in emulsions.

Emulsifiers (Emulsifying Agents)

These provide emulsification during manufacturing of emulsion and also control the stability of it. It can be used alone or in combination.

Emulsifiers can be classified as follows:

1. Surface active agents
2. Natural polymers (macromolecular)
3. Finely divided solids

1. **Surface active agents:** These are also called as surfactants. These are obtained from natural and synthetic sources. They are fur-

ther classified as anionic, cationic and non-ionic surfactants. As cationic surfactants are toxic in nature, so non-ionic are widely used.

Table 5.6: Synthetic surfactants

Type of surfactants	Example	Type of emulsion for used
Anionic (pH > 8)		
Organic sulfates	Sodium lauryl sulphate	o/w
Alkali and ammonium soaps	Sodium stearate	o/w
Cationic (pH 3-7)		
Quaternary ammonium compounds	Cetrimonium bromide	o/w
Pyridium compounds	Hexadecyl pyridinium chloride	o/w
Non-ionic (pH 3-10)		
Fatty acid polyethylene glycol esters	Polyethylene glycol 40 stearate	o/w
polyethylene glycol esters	Polyoxyethylene sorbitan monooleate (Tween 80)	o/w
Polymeric		
Polyoxyethylene-polyoxy-propylene block co-polymers	Poloxomers, Pluronic F-68	o/w
Amphiphiles		
Fatty acids	Stearic acid	w/o
Fatty alcohols	Cetyl alcohol	w/o

2. **Natural polymers (macromolecular):** These may be obtained from vegetable or animal sources. As they are obtained from the natural sources, there are chances of degradation. Examples include–polysaccharides. The synthetic polymers used are cellulose derivatives like methylcellulose, sodium carboxy ethyl cellulose etc.

3. **Finely divided solids:** The examples of these include–clays that are used in dermatological preparation that act as structuring agents.

Anti-oxidants

As oils present in the emulsion, are liable to undergo oxidation. So, to prevent the oxidation these are added to prevent oxidation. The examples of antioxidants include – Butylated Hydroxyanisole (BHA) in concentration 0.02 – 0.5% w/w, Butylated Hydroxytoluene (BHT) in concentration 0.02 – 0.5% w/w, proply gallate – 0.1 % w/v

The characteristics required for antioxidants are as follows:

- Should be non-irritant
- Should be non-toxic
- Should be compatible with other ingredients
- Should be stable
- Should be effective in low concentration

Flavouring Agents

These are added to mask the unpleasant flavour and improve acceptance of the formulation. Examples of it include – mint, cherry, peach, raspberry, banana, pineapple flavours.

Preservatives

The microbial contamination of emulsions may arise due to use of impure raw materials, contamination during preparation or development of emulsion, poor sanitation conditions, so to prevent this microbial contamination preservatives are added. Various preservatives can be added for example – methyl, propyl parabens, organic mercurials like phenylmercuric acetate, nitrates, cresol derivatives as chlorocresol, organic acids like benzoic acid, ascorbic acid and miscellaneous agents like sodium benzoate etc.

Methods of Formulation of Emulsion

1. **Trituration method:** This method again is classified in two types as–dry gum method and wet gum method.

A. **Dry gum method:** In this method, oil is triturated first with gum and small quantity of water is added, to prepare a primary emulsion. This trituration is continued, till a "clicking" sound is heard and white cream is formed. Once this is formed, the remaining water is added to prepare the final emulsion.

   This method includes "4:2:1" formula, that denotes – 4 parts (volume) of oil, 2 parts of water and 1 part of gum.

B. **Wet gum method:** In this method, gum and water are mixed together to form a mucilage. Oil is gradually added in small proportions with continuous trituration to form a primary emulsion. Once this is formed, the remaining quantity of water is added to make the final emulsion.

2. **Bottle method:** This method is used to prepare emulsion that contains volatile or non-viscous oils. In this method, in a bottle, water and oil are shaken thoroughly and vigorously with the required amount of gum. Once this is emulsified, the second liquid, either water or oil, is added and again the bottle is vigorously shaken to form primary emulsion. Water is added, in small portions, with continuous agitation to prepare the final volume.

   The equipment used for formulation of emulsion is – mechanical stirrers, propeller type mixers – homogenizers, turbine mixers, colloid mills, ultrasonifiers etc.

Selection of Emulsifying Agents

The inclusion of emulsifying agent is for the stability of the emulsion. The selection of it depends on the type of emulsion desired, the use and toxicity of the emulsion. Generally the anionic are used for external formulations. The HLB (Hydrophilic Lipophilic Balance) scale is used for the selection of emulsifying agents.

Griffin devised the concept of Hydrophile–Lipophile Balance (HLB) and still it is being used for the selection of correct emulsifying agent.

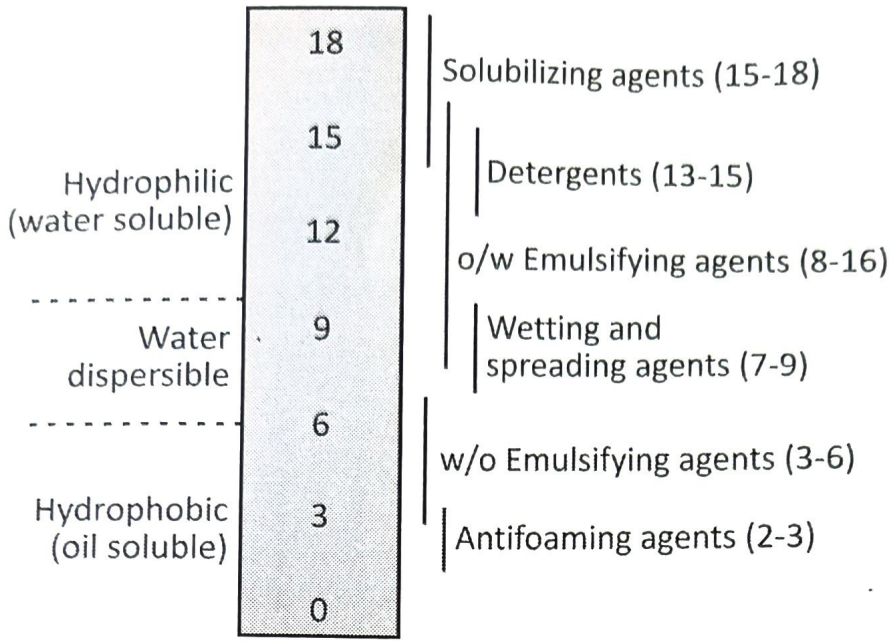


Fig. 5.15: *HLB scale*

The selection of emulsifying agent is important and it should possess characteristics as follows:

- Should be inert
- Should reduce the interfacial tension between immiscible liquids
- Should be compatible with ingredients used in emulsion
- Should be stable
- Should be non-toxic, non-irritant
- Should not impart any odor, colour, taste to the formulation
- Should impart the necessary viscosity to the formulation
- Should prevent coalescence of the droplet of dispersed phase
- Should be able to form coherent film around the globules of the dispersed phase

Instability of Emulsions

An emulsion is said to be stable, when on storage there is no separation of phases and no growth of microbial growth is observed, no colour change or formation of odour.

The emulsion instability may be reversible or irreversible and include:

1. Cracking (Irreversible instability)
2. Creaming
3. Flocculation
4. Phase inversion

1. Cracking

It means there is separation of two phases. The reasons behind this cracking are–due to the coalescence of globules of the disperse phase and it is difficult to redisperse even on shaking. If emulsifying agents are added of opposite type –monovalent metal soaps form o/w while divalent metal soaps form w/o emulsions, anionic and cationic surfactant are incompatible, by adding common solvent like castor oil, water, soft soap are soluble in ethanol, due to degradation or precipitation of emulsifying agent like alkali soaps are decomposed by acids, non-ionic are incompatible with phenol, gums, gelatine, casein are insoluble in alcohol, due to that it leads to cracking, presence of microorganisms, temperature change – the high temperature, causes collisions and this further cause cracking of the emulsions.

2. Creaming

When dispersed globules form a thick layer on the surface of emulsion, then it is termed as creaming. It is temporary phenomenon that can be redistributed by mild shacking or stirring. The factors that affect creaming are given by **Stoke's law:**

$$V = 2r^2 (d_1-d_2)\ g/9\eta$$

where,

V = Rate of creaming

r = Radius of globules

d_1 = Density of dispersed phase

d_2 = Density of dispersion medium

g = Gravitational constant

η = Viscosity of the dispersion medium

The approaches that can reduce creaming are, as follows:

- Control of the radius of globules
- Increasing viscosity, of dispersion media
- By difference in the density of the disperse and continuous phase
- Proper storage conditions

3. Flocculation

Here, the globules form loose masses within the emulsion. In this, the van der waals forces maintain the droplets at defined distance of separation. Shaking the formulation, redipserse the droplets to get homogeneous formulation. Though this help to stabilize the emulsion, but there are chances that the nearby droplets coalesce and the properties are affected.

4. Phase Inversion

As the name reveals that, there is change in the type of one emulsion into other that is o/w changes to w/o and w/o changes to o/w. Example an o/w with Na Stearate can be converted to w/o by addition of Calcium chloride to form Ca Stearate (addition of electrolyte), other example include alteration in phase inversion if phase volume ratio is changed. Example is mixing of o/w emulsifiers with oil and small addition of water, which is now dispersed in oil.

Preservation of Emulsions

The presence of natural emulsifying agents and some excipients in emulsion, provide favourable environment for growth of the micro-organisms. Natural emulsifiers cause deterioration of emulsions and oils promote growth of the microorganisms. There may be contamination of emulsions due to the vehicle used that is deionized water used, equipment and contaminated emulsifying agent if used

Thus, to preserve the emulsions, from such conditions, preservatives are added in it. Examples of preservatives are methyl and propyl parabens, sodium benzoate, sorbic acid, mercurial soaps and salicylic acid etc.

The concentration of preservatives is important factor to be considered when it is added in emulsion. As emulsions are hetergenous systems, the preservatives tend to partition between the two phases–water and oil. Due to the presence of water, there is growth in it, so if preservative that partitions in oil phase, then it will not be effective in preservation of emulsion. Hence, preservative that partitions strongly in oil phase, is to be considered, here volume ratio is also important.

The preservative should be unionized, so as to penetrate the bacteria membrane, the activity of weak acid preservative decreases as pH of aqueous phase raises.

The characteristics that preservative should have are as follows:

- They should be free, not bound to the other components
- Should be non-toxic, non-irritating
- Should be rapid in action
- Should be effective in less concentration
- Should be compatible with other excipients
- Should be stable to heat
- Should be effective against bacteria, fungi
- Should be cost effective

The preservative efficacy depends on the type of emulsion, the degree of aeration, type of container used and the nutritive value of product.

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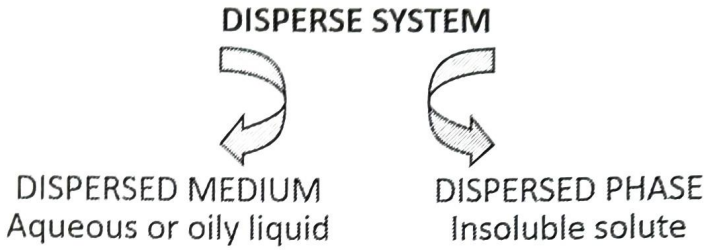
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SUSPENSIONS

Suspensions are heterogeneous system consisting of two phases:

1. Oil
2. Water.

A solid in liquid dispersion in which the particles are colloidal type.



Definition

Suspension are the biphasic liquid dosage form of medicament in which the finely divided solid particles are dispersed in a liquid or semisolid vehicle.

The internal phase consists of insoluble solid particles having a range of size 0.5 to 5 microns which is maintained uniformly throughout the suspending vehicle with the aid of single or combination of suspending agent.

The external phase suspending medium is generally aqueous in some instance, may be organic or oily for non oral use.

The reasons for the formulation of pharmaceutical suspension:

1. When the drug is insoluble or poorly soluble in the delivery vehicle, e.g., prednisolone suspension.
2. To mask the bitter taste of the drug, e.g., chloramphenicol palmitate suspension.
3. To increase the drug stability, e.g., oxytetracycline suspension.
4. To achieve controlled/sustained drug release.

Advantages of Suspension

1. Suspension can improve chemical stability of drugs, e.g., procaine penicillin G.
2. Suspension can mask the unpleasant/bitter taste of drug, e.g., chloramphenicol.
3. Duration and onset of action can be controlled, e.g., zinc insulin suspension.
4. Suspension show higher rate of bioavailability of drug.

Solution > Suspension > Capsule > Compressed tab. > Coated tab.

Disadvantages of Suspension

1. Care must be required in handling and transport, because it is in bulk.
2. It is difficult to formulate.
3. Uniform and accurate dose cannot be achieved in multiple dose container.
4. Physical stability difficult to maintain.

Classification of Suspension

Based on General Classes

1. Oral Suspension, e.g., Paracetamol suspension, antacid
2. Externally applied suspension, e.g., Calamine lotion
3. Parenteral suspension, e.g., Procaine penicillin G
4. Ophthalmic suspension

Based on Electrokinetic Nature of Solid Particles

1. Flocculated suspension
2. Deflocculated suspension

1. Flocculated suspension:

(i) In this system forms loose aggregates of solid particle by forming a network like structure.

(ii) Rate of sedimentation is high.
(iii) Sediment forms rapidly.
(iv) Sediment is easy to redisperse.
(v) Sediment is loosely packed and dose not form a hard cake.
(vi) Supernatant liquid is clear.
(vii) Suspension is not pleasing in appearance.

2. **Deflocculated suspension:**
   (i) Solids are present as individual particles and also form aggregates but lower than flocculated suspension.
   (ii) Rate of sedimentation is slow.
   (iii) Sediment forms slowly.
   (iv) Sediment is difficult to redisperse.
   (v) Sediment is very closely packed and hard cake is formed.
   (vi) Supernatant liquid is not clear.
   (vii) Suspension is pleasing in appearance.

Ingredients for Formulation of Suspension

1. **Wetting agent:** They reduce the interfacial tension between solid particles and liquid, i.e., continuous phase. They increase the affinity of the solid particles of the surrounding and reduce the Inter particular force. For example, Glycerin in sodium alginate, alcohol in Tragacanth mucilage.

   Excessive use of wetting agent cause foaming or give bad taste to suspension.

2. **Flocculating agent:** Added to floc the drug particles. The flocculating agent added to reduce the interfacial tension, e.g., tween, span, sodium Lauryl sulphate, Carbo wax.
3. **Thickening agent:** They increase the viscosity of continuous phase, they are classified in Fig. 5.16.
4. **Preservatives:** Benzoic acid, sodium benzoate, methyl paraben and propyl paraben are used as a preservative to preserve the suspension from bacterial growth.

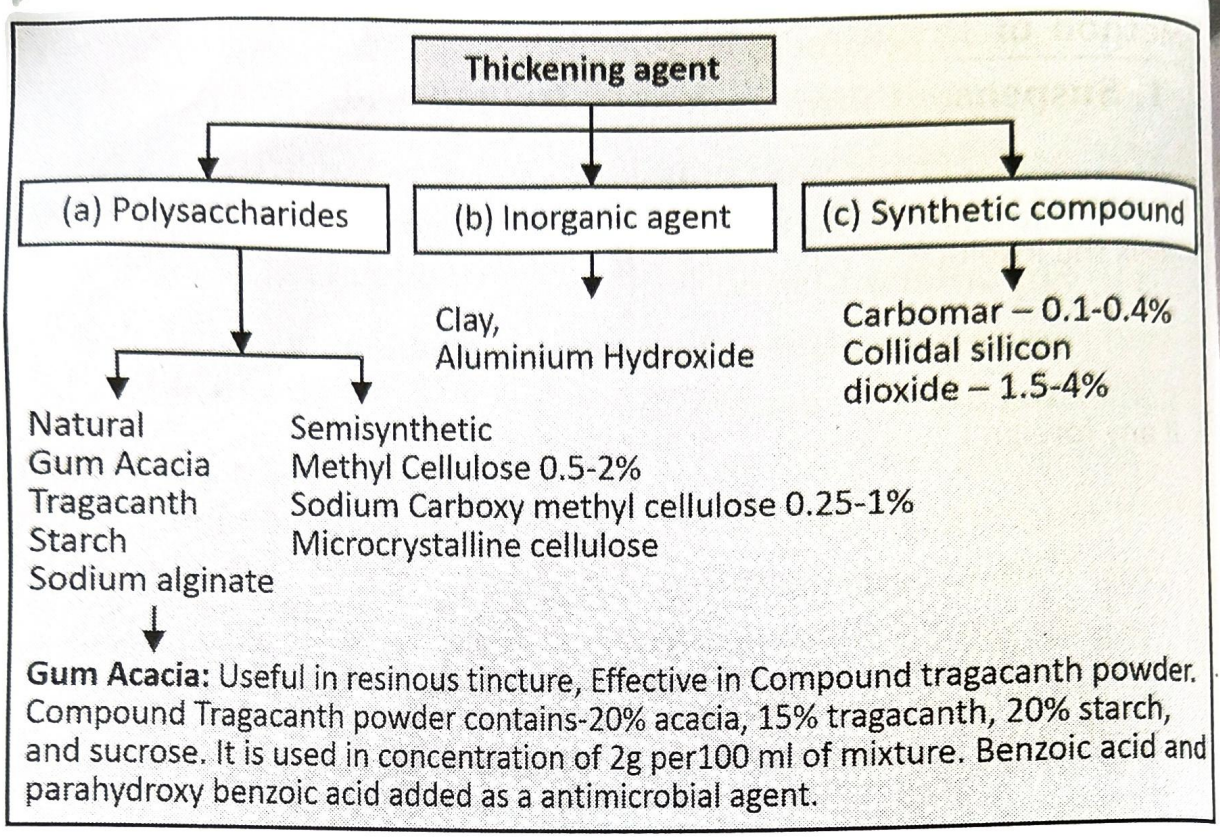
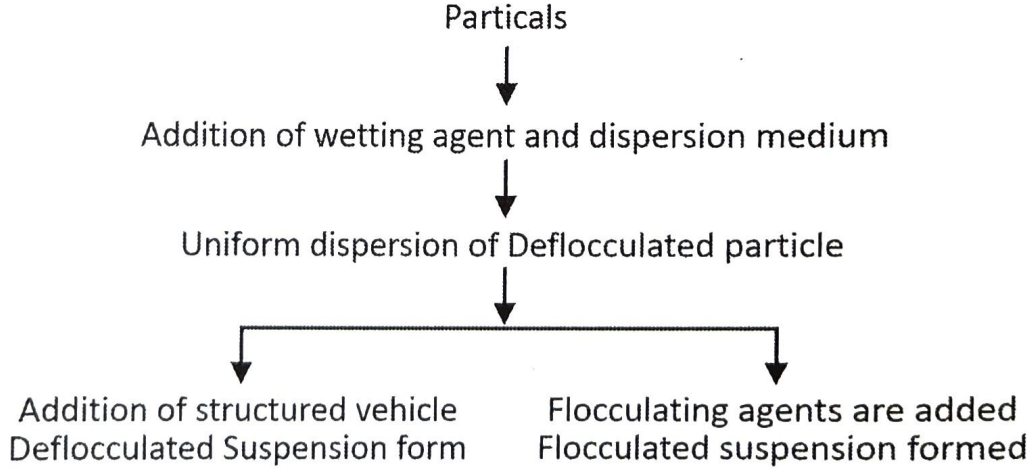


Fig. 5.16: *Classification of Thickening Agent*

5. **Organoleptic additives:** Sweetening agent, coloring agent, flavouring agent are added in oral suspension. Perfumes and colouring agents are added in external use suspension.

Formulation of Suspension

Theory involved in formulation – Wetting of particles, particle interaction, aggregation, sedimentation



Method of Dispensing Suspension

1. Suspension containing Diffusible Solid:

Finely powder the solid ingredients

↓

Mix the insoluble powder in a mortar and add vehicle to form smooth cream

↓

Add more vehicle to make it pourable

↓

If any foreign particle observed, then pass through muslin cloth in to container

↓

Rinse the mortar, add any liquid ingredient

↓

Add more vehicle to produce require volume

Gum Acacia

2. Suspension containing Indiffusible Solid:

Finely powder the solid ingredients

↓

Mix them together in a mortar and add compound tragacanth powder

↓

Add ¾ vehicle and triturate to form a smooth cream

↓

If any foreign particle observed, then pass through muslin cloth in to container

↓

Rinse the mortar, add any liquid ingredient

↓

Add more vehicle to produce require volume

Gum Acacia

3. **Suspension containing precipitate forming Solid:** It contains resinous matter and when mixed with water it form precipitation of resin and may stick to side of bottle which will difficult to rediffuse by shaking. To prevent this Tragacanth mucilage or compound tragacanth powder is used.

Finely indiffusable and diffusible powder the ingredients

↓

Mix them together in a mortar and add compound tragacanth powder

↓

↓

Add ¾ vehicle and triturate to form a smooth cream
Measure the precipitate forming liquid in a dry mortar and add it in a slow stream in the center of cream with stirring

↓

If any foreign particle observed, then pass through muslin cloth in to container

↓

Rinse the mortar, add any liquid ingredient

↓

Add more vehicle to produce require volume
Gum Acacia

Container: Suspension should be packed in a wide mouth bottle and container which is having adequate space above the liquid.

Labelling: "Shake well before use" must be mentioned on the label. In case of dry suspension marking for addition of vehicle is clearly mentioned on the label.

Storage: Should be stored in a cool place, not in a refrigerator.

Stability of Suspension

For evaluation of physical stability of suspension following methods are used:

1. **Sedimentation Method:** Suspension to be filled in a measuring cylinder in undisturbed position for definite period of time and height of solid will be measured. The graph of sedimentation volume plotted against time. A stable suspension shows horizontal or less steep curve.
2. **Micromeritics Method:** By using microscope and coulter counter method, particle size will be studied. So any change in particle size with reference to time will provide useful information regarding stability of suspension.
3. **Rheological Method:** The viscosity of suspension is studied by using viscometer.
4. **Electrokinetic Method:** By using zeta potential or by surface electric charge useful to find out the stability.

DRY POWDER FOR RECONSTITUTION

Some drugs have the ability to lose their potency when mixed in solution. Hence, these drugs are stored in powdered form. Before administering, these drugs have to be reconstituted or mixed with liquid called diluent. Depending on the product, the powder may be stable for about 24 months. After reconstitution, the solution or suspension is stable in the quantities usually dispensed for up to 10 days at room temperature or 14 days under refrigeration.

Reconstitution may result in the preparation of suspension or clear solution depending on the product's formulation. Volume of the product equals the sum of the volume of diluent and that of suspended powder. These products generally are intended for infants and children but also may be used by adults who have difficulty swallowing tablets and capsules.

1. **Suspension:** Preparation containing finely divided drug particles dispersed in a liquid vehicle.
2. **Solution:** Liquid preparation that contains one or more solutes in a solvent or mixture of solvents.
3. **Syrup:** Concentrated aqueous solution of a sugar or sugar substitute; may or may not be medicated.

For children and adults, reconstituted products for oral solution or suspension generally are formulated such that the usual dose of the drug is contained in teaspoonful amounts of the product. For infants, paediatric drops, which also require reconstitution, may be used. Sometimes these products must be mixed, changing their normal concentration, to make dosing easier for the patient.

TROPICAL PREPARATIONS

OINTMENTS

Ointments are homogenous translucent, viscous, semi-solid preparation intended for external application to skin or mucous membrane. Ointment may be medicated or not.

It is used as emollient, occlusive, application of ingredients to the skin.

Characteristics of an Ideal Ointment

- It should be chemically and physically stable.
- It should be smooth and free from grittiness.
- It should melt or soften at body temperature and be easily applied.
- The base should not possess any therapeutic action and must be non-irritant.
- In ointment base, finely divided active ingredients should be uniformly distributed.

Ointment Bases

Carrier or vehicle of the medicament is referred as ointment base.

Properties of an Ideal Ointment Base

1. It should be inert and stable.
2. It should be non-irritating in nature.
3. Incorporated medicaments should be released readily.
4. It should not irritate the skin.

Classification of Ointment Bases

1. Oleaginous bases
2. Absorption bases
3. Water-miscible bases
4. Water soluble bases

Table 5.7: Properties of Ointment Base

Composition	Oleaginous compounds	oleaginous base + w/o surfactant	oleaginous base + water (<45% w/w) + w/o surfactant (HLB <8)	Oleaginous base + water (>45% w/w) + o/w surfactant (HLB >9)	Polyethylene Glycols (PEGs)
Water Content	Anhydrous	Anhydrous	Hydrous	Hydrous	Anhydrous, hydrous
Affinity for Water	Hydrophobic	Hydrophilic	Hydrophilic	Hydrophilic	Hydrophilic
Spread ability	Not easy	Not easy	Easy	Easy	Easy
Wash ability	Non-washable	Non-washable	Non- or poorly washable	Washable	Washable
Stability	Oils poor; hydrocarbons better	Oils poor; hydrocarbons better	Unstable, especially alkali soaps and natural colloids	Unstable, especially alkali soaps and natural colloids; non-ionics better	Stable
Drug Incorporation Potential	Oil solubles only	Solids, oils and aqueous solution	Solids, oils and aqueous solutions	Solid and aqueous solutions	Solid and aqueous solutions
Drug Release Potential*	Poor	Poor	Good	Good	Good
Occlusiveness	Yes	Yes	Sometimes	No	No

Uses	Protectants, emollients (+/-), vehicles	Protectants, emollients (+/-), vehicles	Emollients, cleansing, vehicles	Emollients, vehicles	Drug vehicles
Examples	White Petrolatum, White Ointment	Hydrophilic Petrolatum, Anhydrous Lanolin, Aquabase™, Aquaphor®	Cold Cream, Rose Water Ointment, Hydrocream™, Nivea®	Hydrophilic Ointment, Dermabase™, Unibase®	PEG Ointment, Polybase™

Ointment act as carrier or vehicle for the medicament.



Oleaginous Base Absorption Base Water Soluble Base Emulsion Base

1. **Oleaginous Bases:** These bases consist of oils and fats. The most important are the hydrocarbons, i.e., petrolatum, paraffins and mineral oils.

   The animal fat includes lard.

   The combination of these materials can produce a product of desired melting point and viscosity.

   (a) **Petrolatum (Soft paraffin):** This is a purified mixture of semi-solid hydrocarbons obtained from petroleum or heavy lubricating oil.

   Yellow soft paraffin (Petrolatum; Petroleum jelly)

   This a purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain suitable stabilizers like, antioxidants, e.g., α-tocopherol (Vitamin E), Butylated Hydroxy Toluene (BHT) etc.

   Melting range: 38 to 56°C.

   White soft paraffin (White petroleum jelly, White petrolatum)

   This a purified mixture of semisolid hydrocarbons obtained from petroleum and wholly or partially decolourized by percolating the yellow soft paraffin through freshly burned bone black or adsorptive clays.

   Use: The white form is used when the medicament is colourless, white or a pastel shade. This base is used in

   Dithranol ointment B.P.

   Ammoniated Mercury and Coal tar ointment B.P.C.

   Zinc ointment B.P.C.

(b) **Hard paraffin (Paraffin):** Solid hydrocarbons obtained from petroleum are mixed to form hard paraffin.

It is colourless or white, odourless, translucent, wax-like substance. It solidifies between 50 and 57°C and is used to stiffen ointment bases.

(c) **Liquid paraffin** (Liquid petrolatum; White mineral oil)

It is obtained by mixing liquid hydrocarbons obtained from petroleum. It is transparent, colourless, odourless, viscous liquid.

Antioxidants like tocopherol or BHT are added to prevent its oxidization to peroxides.

It is used along with hard paraffin and soft paraffin to get a desired consistency of the ointment. Tubes for eye, rectal and nasal ointments have nozzles with narrow orifices through which it is difficult to expel very viscous ointments without the risk of bursting the tube. To facilitate the extrusion upto 25% of the base may be replaced by liquid paraffins.

Advantages of hydrocarbons bases:

- They are not absorbed by the skin. They remain on the skin for prolonged period of time without drying. Thus, they are highly occlusive in nature.
- Being sticky in nature, it ensures prolonged contact between skin and medicament.
- They are almost inert. They consist largely of saturated hydrocarbons, therefore, very few incompatibilities and little tendency of rancidity are there.
- They can withstand heat sterilization, hence, sterile ophthalmic ointments can be prepared with it.
- They are readily available and cheap.

Disadvantages of hydrocarbon bases;

- If applied for prolonged period, water logging followed by maceration of skin may occur.

- It may cause an uncomfortable feeling of warmth due to its ability to retain body heat.
- They are immiscible with water; as a result, rubbing onto the surface and removal after treatment both are difficult.
- It may contaminate the clothes due to its sticky nature.
- Water absorption capacity is very low, hence, these bases are poor in absorbing exudate from moist lesions.

2. **Absorption Base:** The term absorption base is used to denote the water absorbing or emulsifying property of these bases and not to describe their action on the skin.

   These bases (sometimes called emulsifiable ointment bases) are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantity of water yet retaining its ointment-like consistency.

   Preparations of this type do not contain water as a component of their basic formula but if water is incorporated a W/O emulsion results.

   Wool Fat (anhydrous lanolin): It is the purified anhydrous fat like substance obtained from the wool of sheep.

   - It is insoluble in water but it can absorb twice its weight in water.

     Therefore it is used in ointments in which proportion of aqueous liquids to be incorporated is too large for incorporation into hydrocarbon base.
   - Due to its sticky nature it is not used alone but is used along with other bases in the preparation of a number of ointments, e.g., Simple ointment B.P. contains 5% and the B.P. eye ointment base contains 10% woolfat.

   Hydrous Wool Fat (Lanolin):

   - It is a mixture of 70% w/w wool fat and 30% w/w purified water. It is a w/o emulsion. Aqueous liquids can be emulsified with it.
   - It is used alone as an emollient.

- *Example:* Hydrous Wool Fat Ointment B.P.C., Calamine Coal Tar Ointment.

Wool Alcohol: It is the emulsifying fraction of wool fat. Wool alcohol is obtained from wool fat by treating it with alkali and separating the fraction containing cholesterol and other alcohols. It contains not less than 30% of cholesterol.

Use:

- It is used as an emulsifying agent for the preparation of w/o emulsions and is used to absorb water in ointment bases.
- It is also used to improve the texture, stability and emollient properties of o/w emulsions.

  Examples: Wool alcohol ointment B.P. contains 6% wool alcohol and hard, liquid and soft paraffin.

Beeswax: It is purified wax, obtained from honey comb of bees.

It contains small amount of cholesterol. It is of two types: (a) yellow beeswax and (b) white beeswax.

Use: Beeswax is used as a stiffening agent in ointment preparations.

Examples: Paraffin ointment B.P.C. contains beeswax.

Cholesterol: It is widely distributed in animal organisms. Wool fat is also used as a source of cholesterol.

Use: It is used to increase the water absorbing power of an ointment base.

Example: Hydrophilic petroleum U.S.P. contains:

- Cholesterol: 3%
- Stearyl alcohol: 3%
- White beeswax: 8%
- White soft paraffin: 86%

Advantages of absorption bases:

- Less occlusive and good emollient.
- They help in penetration of oil soluble medicaments into the skin.

- They are easier to spread.
- They are compatible with majority of the medicaments.
- They are relatively heat stable.
- The base may be used in their anhydrous form or in emulsified form.
- They can absorb a large quantity of water or aqueous substances.

Disadvantage: Inspite of their hydrophilic nature, absorption bases are difficult to wash.

3. **Water-miscible Bases:** They are miscible with an excess of water. Ointments made from water-miscible bases are easily removed after use.

   There are three official anhydrous water-miscible ointment bases:

   Example:

   Emulsifying ointment B.P. — contains anionic emulsifier.

   Cetrimide emulsifying ointment B.P. — contains cationic emulsifier

   Cetomacrogol emulsifying ointment B.P. — contains non-ionic emulsifier

   Uses: they are used to prepare o/w creams and are easily removable ointment bases, e.g., Compound Benzoic Acid Ointment (Whitfield's Ointment) – used as antifungal ointment.

   Advantages of water miscible bases:

   - Readily miscible with the exudates from lesions.
   - Does not interfere with normal functioning of skin.
   - Due to their surfactant content, they remain in contact with skin.
   - High cosmetic acceptability, hence there is less likelihood of the patients discontinuing treatment.
   - Can be easily removed from the hair.

4. **Water Soluble Bases:** Water soluble bases contain only the water soluble ingredients and not the fats or other greasy substances, hence, they are known as grease-less bases.

Water soluble bases consists of watersoluble ingredients such as Polyethylene Glycol Polymers (PEG) which are popularly known as "carbowaxes" and commercially known as "macrogols".

They are a range of compounds with the general formula:

$$CH_2OH . (CH_2OCH_2)_n CH_2OH$$

The PEGs are mixtures of polycondensation products of ethylene and water and they are described by numbers representing their average molecular weights. Like the paraffin hydrocarbons they vary in consistency from viscous liquids to waxy solids.

Examples:

Macrogols 200, 300, 400 — viscous liquids

Macrogols 1500 — greasy semi-solids

Macrogols 1540, 3000, 4000, 6000 — waxy solids.

Different PEGs are mixed to get an ointment of desired consistency.

Advantages of PEGs as ointment base:

- They are water soluble; hence, very easily can be removed from the skin and readily miscible with tissue exudates.
- Easily absorbed by the skin
- Good solvent properties. Some water-soluble dermatological drugs, such as salicylic acid, sulfonamides, sulfur etc., are soluble in this bases.
- Non-greasy.
- Hydrolysis does not occur.
- Compatibility with many dermatological medicaments.

Disadvantages:

- Limited uptake of water. Macrogols dissolve when the proportion of water reaches about 5%.

- Reduction in activity of certain antibacterial agents, e.g., phenols, hydroxybenzoates and quaternary compounds.
- Solvent action on polyethylene and bakelite containers and closures.
- Certain other substances which are used as water soluble ointment bases include tragacanth, gelatin, pectin, silica gel, sodium alginate, cellulose derivatives, etc.

Factors Governing Selection of an Ideal Ointment Base

1. Dermatological factors
2. Pharmaceutical factors

1. Dermatological Factors:

(a) Absorption and Penetration:

- 'Penetration' means passage of the drug across the skin, i.e., cutaneous penetration and 'absorption' means passage of the drug into blood stream.
- Medicaments which are both soluble in oil and water are most readily absorbed through the skin.
- Whereas animal and vegetable fats and oils normally penetrate the skin.
- Animal's fats, e.g., lard and wool fat when combined with water, penetrates the skin.
- o/w emulsion bases release the medicament more readily than greasy bases or w/o emulsion bases.

(b) Effect on the skin:

- Greasy bases interfere with normal skin functions i.e., heat radiation and sweating. They are irritant to the skin.
- o/w emulsion bases and other water miscible bases produce a cooling effect due to the evaporation of water.

(c) Miscibility with skin secretion and serum: Skin secretions are more readily miscible with emulsion bases than with greasy bases. Due to this the drug is more rapidly and completely released to the skin.

(d) **Compatibility with skin secretions:** The bases used should be compatible with skin secretions and should have pH about 5.5 because the average skin pH is around 5.5. Generally neutral ointment bases are preferred.

(e) **Non-irritant:** All bases should be highly pure and bases specially for eye ointments should be non-irritant and free from foreign particle.

(f) **Emollient properties:** Dryness and brittleness of the skin causes discomfort to the skin therefore, the bases should keep the skin moist. For this purpose water and humectants such as glycerine and propylene glycol are used. Ointments should prevent rapid loss of moisture from the skin.

(g) **Ease of application and removal:** The ointment bases should be easily applicable as-well-as easily removable from the skin by simple washing with water. Stiff and sticky ointment bases require much force to spread on the skin and during rubbing newly formed tissues on the skin may be damaged.

2. Pharmaceutical factors:

(a) **Stability:** Fats and oils obtained from animal and plant sources are prone to oxidation unless they are suitably preserved. Due to oxidation odour comes out. This type of reactions are called rancidification. Lard, from animal origin, rancidify rapidly. Soft paraffin, simple ointment and paraffin ointment are inert and stable. Liquid paraffin is also stable but after prolonged storage it gets oxidized. Therefore, an antioxidant like tocopherol (Vitamin E) may be incorporated. Other antioxidants those may be used are Butylated Hydroxy Toluene (BHT) or Butylated Hydroxy Anisole (BHA).

(b) **Solvent properties:** Most of the medicaments used in the preparation of ointments are insoluble in the ointment bases therefore, they are finely powdered and are distributed uniformly throughout the base.

(c) **Emulsifying properties:** Hydrocarbon bases absorbs very small amount of water.

Wool fat can take about 50% of water and when mixed with other fats can take up several times its own weight of aqueous solution.

Emulsifying ointment, cetrimide emulsifying ointment and cetomacrogol emulsifying ointment are capable of absorbing considerable amount of water, forming w/o creams.

(d) **Consistency:** The ointments produced should be of suitable consistency. They should neither be hard nor too soft. They should withstand climatic conditions. Thus, in summer they should not become too soft and in winter not too hard to be difficult to remove from the container and spread on the skin.

The consistency of an ointment base can be controlled by varying the ratio of hard and liquid paraffin.

Classification of Ointments

According to their therapeutic properties based on penetration of skin.

According to their therapeutic uses.

Ointments classified according to their therapeutic properties based on penetration are as follows:

(a) Epidermic, (b) Endodermic, (c) Diadermic

(a) **Epidermic ointments:**

- These ointments produce local effect on the surface of skin.
- They are not absorbed.
- They have antiseptic or parasiticidic properties.

(b) **Endodermic ointments:** These ointments tend to release the medicaments deeper into the skin. They are partially absorbed and acts as emollients, stimulants and local irritants.

(c) **Diadermic ointments:** These ointments are intended to release the medicaments that pass through the skin and produce systemic effects.

Preparation of Ointments

A well-made ointment is:

(a) Uniform throughout, i.e., it contains no lumps of separated high melting point ingredients of the base, there is no tendency for liquid constituents to separate and insoluble powders are evenly dispersed.

(b) Free from grittiness, i.e., insoluble powders are present in fine form.

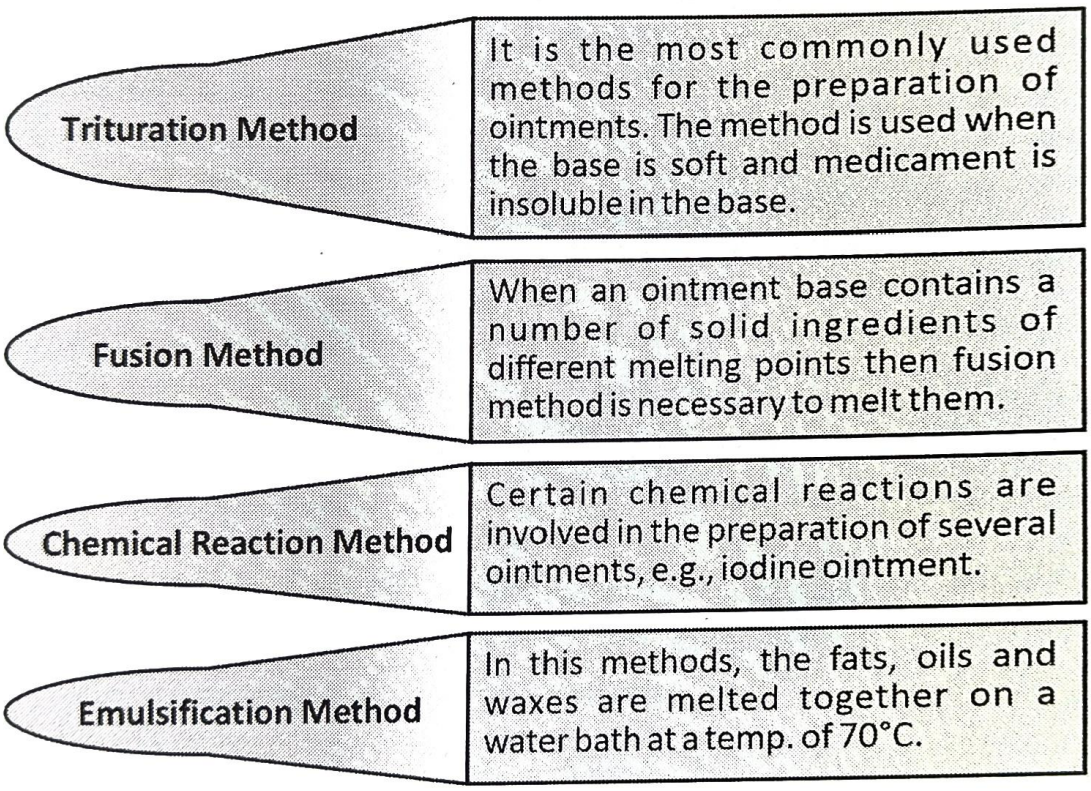
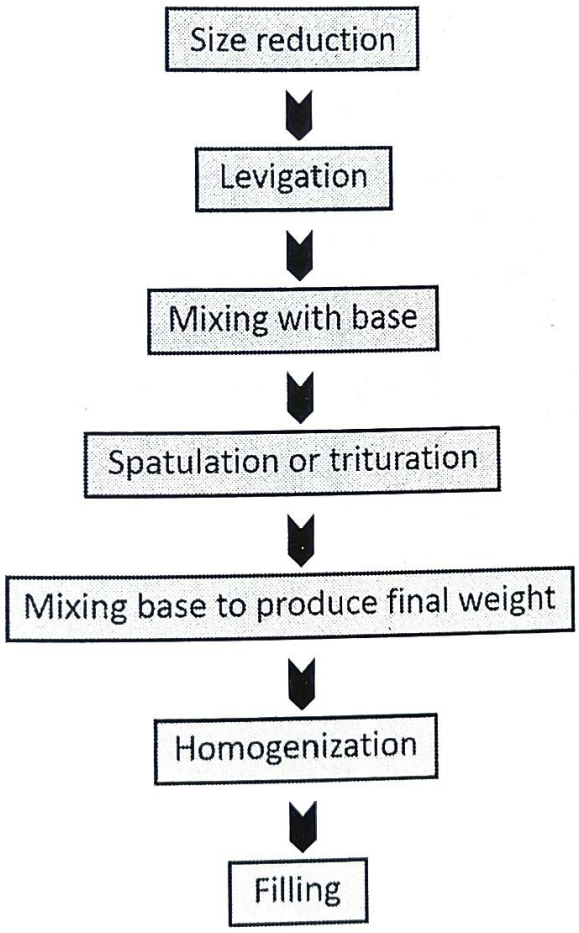


Fig. 5.17: *Methods for preparation of Ointments*

1. Ointment Prepared by Trituration Method

- This method is used if the quantity of base or liquid is small.
- Fine powder of solids is formed, which is then passed through sieve (# 250, # 180, #125).

- The powder is taken on an ointment-slab and triturated with a small amount of the base. A steel spatula with long, broad blade is used. To this additional quantities of the base are incorporated and triturated until the medicament is mixed with the base.
- Finally liquid ingredients are incorporated. There may occur loss of liquid due to splashing. To prevent this, small volume of liquid is taken in depression of ointment and more is added just after thorough incorporation of previous added liquid. Splashing is more easily controlled in a mortar than on a tile.



Example:

(i) **Whitfield ointment** (Compound benzoic acid ointment B.P.C.)

Formula:

Benzoic acid, in fine powder—6 gm

Salicylic acid, in fine powder—3 gm

Emulsifying ointment—91 gm

Method: Benzoic acid and salicylic acid are sieved through No. 180 sieves. They are mixed on the tile with small amount of base and levigated until smooth and dilute gradually.

(ii) Salicylic acid sulphur ointment B.P.C.

2. Ointments Prepared by Fusion Method

When number of solid ingredients in an ointment base are more, then all are melted together and then stirred. The melting can be done in two methods:

Method-I:

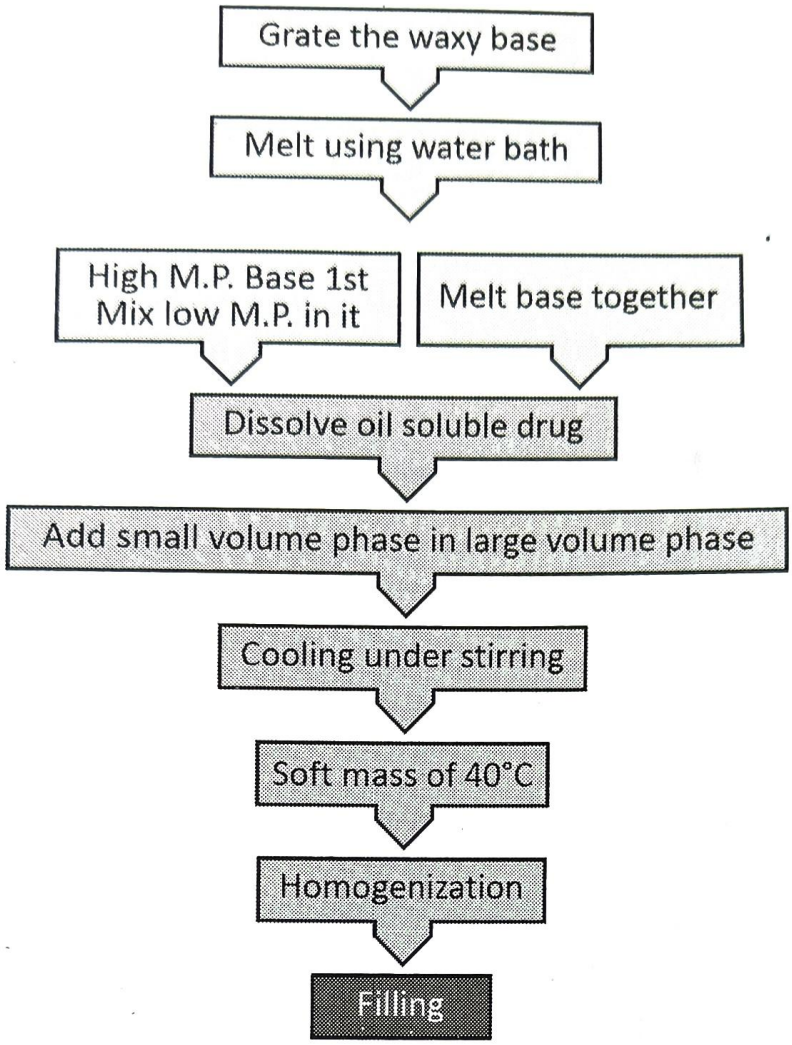
Different components in the base are melted in order of their decreasing melting points that is substances that have high melting point are melted first compared to substances with low melting point. Medicament is then added slowly till temperature lowers down to form homogeneous mixture.

Advantages: This will avoid over heating of substances having low melting point.

Method-II:

All the components subdivided in finely state and melted together.

Advantages: The maximum temperature reached is lower than Method-I and less time was taken possibly due to the solvent action of the lower melting point substances on the rest of the ingredients.



Cautions:

- Melting time is shortened by grating waxy components (i.e., beeswax, wool alcohols, hard-paraffin, higher fatty alcohols and emulsifying waxes) by stirring during melting and by lowering the dish as far as possible into the water bath so that the maximum surface area is heated.
- Some ingredients undergo discoloration due to oxidation like in wool fats and wool alcohols. Such discoloured layers must be removed before use.
- After melting all the constituents, cooling is done. While cooling, it is ensured that cooling should be done uniformly to prevent separation of hard lumps.
- Vigorous stirring after thickening of ointment may result in excessive aeration. Thus, it should be avoided.

- Many constituents attract dirt due to their greasy nature. These dirt are seen after melting. Thus, dirt is allowed from melt by the process of sedimentation and decantation. In both instances the clarified liquid is collected in another hot basin.
- If the product is granular after cooling, due to separation of high m.p. constituents, it should be remelted, using the minimum of heat and again stirred and cooled.

Example:

(i) Simple ointment B.P. contains

Wool fat: 50 g

Hard paraffin: 50 g

Cetostearyl alcohol: 50 g

White soft paraffin: 850 g

Type of preparation: Absorption ointment base

Procedure: Hard paraffin and cetostearyl alcohol on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted.

If required decanted or strained and stirred until cold and packed in suitable container.

(ii) Paraffin ointment base:

Type of preparation: Hydrocarbon ointment base

(iii) Wool alcohols ointment B.P.

Type of preparation: Absorption base

(iv) Emulsifying ointment B.P.

Type of preparation: Water-miscible ointment base.

(v) Macrogol ointment B.P.C

Type of preparation: Water soluble ointment base

Formula: Macrogol 4000 and Liquid Macrogol 300

Method: Macrogol 4000 is melted and previously warmed liquid macrogol 300 is added. Stirred until cool.

3. Ointment Preparation by Chemical Reaction Method

Chemical reactions were involved in the preparation of several famous ointments of the past, e.g., Strong Mercuric Nitrate Ointment, both of the 1959 B.P.C.

(a) **Ointment containing free iodine:** Iodine is less soluble in oils or fats but readily soluble in concentrated solution of KI due to formation of molecular complexes $KI.I_2$, $KI.2I_2$, $KI.3I_2$ etc.

These solutions may be incorporated in absorption-type ointment bases.

For example, Strong Iodine Ointment B. Vet. C (British Veterinary Pharmacopoeia) is used to treat ringworm in cattle. It contains free iodine. At one time this type of ointments was used as counter-irritants in the treatment of human rheumatic diseases but they were not popular because:

- They stain the skin a deep red colour.
- Water gets dried up after improper storage, which may cause iodine crystals to irritate the skin. Hence, this can be prevented by adding glycerol instead of water to dissolve iodine-KI complex.

Example: Strong Iodine Ointment B. Vet. C.

Iodine

Woolfat

Yellow soft paraffin

Potassium iodide

Water

Procedures:

- Iodine is dissolved in solution of potassium iodide in water.
- Woolfat and yellow soft paraffin are melted together over water bath. Melted mass is cooled to about 40°C.

- I_2 solution is added to the melted mass in small quantities at a time with continuous stirring until a uniform mass is obtained.
- It is cooled to room temperature and packed.

Use: Ringworm in cattle.

(b) **Ointment containing combined iodine:** Fixed oils and many vegetable and animal fats absorb iodine which combines with the double bonds of the unsaturated constituents, e.g.,

$$CH_3.(CH_2)_2.CH = CH.(CH_2)_7.COOH + I_2 \rightarrow \begin{matrix} CH_3.(CH_2)_2.CHI \\ CHI.(CH_2)_7.COOH \end{matrix}$$

Examples:

- Non-staining Iodine Ointment B.P.C. 1968
- Iodine
- Arachis Oil
- Yellow Soft Paraffin

Methods:

- Iodine is finely powdered in a glass mortar and required amount is added to the oil in a glass-stoppered conical flask and stirred well.
- The oil is heated at 50°C in a water-bath and stirred continuously till brown colour changes to greenish black.
- From 0.1 g of the preparation the amount of iodine is determined by B.P.C. method and the amount of soft paraffin base is calculated to give the product the required strength.
- Soft paraffin is warmed to 40°C. The iodized oil is added and mixed well. No more heat is applied because this causes deposition of a resinous substance.
- The preparation is packed in a warm, wide-mouthed, amber colour, glass bottle. It is allowed to cool without further stirring.

4. Preparation of Ointments by Emulsification

An emulsion system contains an oil phase, an aqueous phase and an emulsifying agent.

For o/w emulsion systems the following emulsifying agents are used:

(i) Water soluble soap
(ii) Cetyl alcohol
(iii) Glyceryl monostearate
(iv) **Combination of emulsifiers:** Triethanolamine stearate + cetyl alcohol
(v) **Non-ionic emulsifiers:** Glyceryl monostearate, glyceryl monooleate, propylene glycol stearate.

For w/o emulsion creams the following emulsifiers are used:

(i) Polyvalent ions, e.g., magnesium, calcium and aluminium are used.

(ii) Combination of emulsifiers: Beeswax + divalent calcium ion

The viscosity of this type of creams prevents coalescence of the emulsified phases and helps in stabilizing the emulsion.

Example: Cold cream:

Procedures:

- Water immiscible components e.g., oils, fats, waxes are melted together over water bath (70°C).
- Aqueous solution of all heat stable, water soluble components are heated (70°C).
- Aqueous solution is slowly added to the melted bases with continuous stirring until the product cools down and a semi-solid mass is obtained.
- N.B. The aqueous phase is heated otherwise high melting point fats and waxes will immediately solidify on addition of cold aqueous solution.

Stability of Ointments

- The stability of ointment should be there from time of preparation till its consumption by the user.
- Preservatives such as p-hydroxyl benzoates, phenol, benzoic acid are added to stop microbial growth.
- Preservatives should be unreactive to any component of the formulation. Plastic containers should not be used for storing preservatives as it may absorb the preservative, thereby reducing its concentration available for killing bacteria.
- Suitable antioxidants must be added to prevent oxidation of some ingredients like wool fat and wool alcohols.
- Incompatible drugs, emulsifying agents and preservatives must be avoided. The drugs which are likely to hydrolyze must be dispensed in an anhydrous base.
- Humectants such as, glycerin, propylene glycol and sorbitol may be added to prevent the loss of moisture from the preparation.
- Ointment must be stored at an optimum temperature otherwise separation of phases may take place in the emulsified products which may be very difficult to remix to get a uniform product.

CREAMS

Pharmaceutical Creams (topical preparation) are homogeneous, semi-solid or viscous preparations that possess a relatively fluid consistency and are intended for external application to the skin or certain mucous membranes for protective, therapeutic or prophylactic purposes especially where an occlusive effect is not necessary.

In recent times, creams are emulsions of either the O/W or W/O type. Pharmaceutical creams are classified as water-removable bases in the USP and are described under Ointments.

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They are semi-solids usually consisting of solutions or dispersions of one or more medicaments in suitable bases. They are formulated using hydrophilic or hydrophobic bases to provide preparations that are essentially miscible with the skin secretion.

Creams can be also used for administering drugs via the vaginal route.

Classification of Creams

The creams can be classified on various basis

1. **According to function,** e.g., cleansing, foundation, massage, etc
2. **According to characteristics properties,** e.g., cold creams, vanishing creams, etc.
3. **According to the nature or type of emulsion:**
   - o/w emulsion type cream
     - — Vanishing creams
     - — Foundation creams.
   - w/o emulsion type creams
     - — Cleansing cream,
     - — Cleansing milk,
     - — Cleansing lotion
     - — Cold cream or moisturizing creams/Winter cream
4. **Others creams:**
   - All-purpose cream and general creams.
   - Night cream and massage creams.
   - Skin protective cream
   - Hand and body creams.

Cold Cream

It is a W/O emulsion. It produces cooling effect on being applied to skin due to slow evaporation of water present in emulsion.

Cold creams are in general O/W type emulsions which inverts to W/O emulsion after being applied to akin due to evaporation of water.

Cleansing Cream

Cleansing creams used to remove facial makeup, dead cells, sebum and improve the health of skin.

Pepsin is added to cleansing cream to make the facial skin smooth.

Cleansing Cream are three types:

1. Liquefying cleansing cream
2. Emulsified creams of o/w type
3. Emulsified creams of w/o type

Vanishing Cream

Vanishing creams are the creams which easily spread on skin and then rapidly vanish on being rubbed on skin.

Vanishing creams are an **o/w type of emulsions which when applied to the skin leave an almost invisible layer on it so-called** vanishing creams.

Vanishing creams can be quickly washed off with water due to the presence of o/w emulsifiers

Foundation Cream

These are applied to the face to provide a smooth emollient base for the application of facial makeup.

Foundation creams act as skin protective's to prevent the damage caused by environmental factors like sun, wind, dirt, etc.

Mostly O/W type emulsion

Moisturing Cream

These creams are said to be left on skin. There occurs very slow trans epidermal water loss due to its occlusive layer. Hence, skin doesn't dry up.

Cream Base

The base for cream should:

- Not produce irritation or sensitization of the skin
- Not retard wound healing
- Smooth, inert, odourless or almost odourless
- Physically and chemically stable and compatible with the skin and with incorporated medicaments.

Antimicrobial Preservatives in Creams

Creams may contain suitable antimicrobial preservatives unless the active ingredients or the bases themselves have sufficient bactericidal or fungicidal activity. They may contain other suitable auxiliary substances such as antioxidants, stabilizers, thickeners and emulsifiers.

Formulation of Creams

Pharmaceutical Cream can be either water in oil (w/o) or oil in water (o/w) emulsion, consisting of waxes, emollients and lubricants dispersed in an oil phase and a water phase containing emulsifying, stabilizing and thickening agents, preservatives and in some cases, colourant. Active ingredients are dispersed in either phase or added when the emulsion has been formed and allowed to cool.

A typical manufacturing process breaksdown into four individual operations:

1. **Preparation of the Oil Phase**: Flake/powder ingredients, sometimes dry blended in advance, are dispersed into mineral oil or silicone oil. Heating may be required to melt some ingredients.
2. **Hydration of aqueous phase ingredients**: Emulsifiers, thickeners and stabilizers are dispersed into water in a separate vessel. Heating may be required to accelerate hydration.
3. **Forming the emulsion**: The two phases are blended under vigorous agitation to form the emulsion.

4. **Dispersion of the active ingredient**: The active ingredient often makes up only a small proportion of the formulation; this must be efficiently dispersed to maximize yield and product effectiveness.

Using conventional agitators a number of problems can be encountered:

- Thickening, stabilizing and emulsifying agents gets agglomerated on being added to water, which cannot be even broken by agitators.
- Shear is required to disperse the lumps formed by oil phase ingredients.
- Ingredients must be fully hydrated to obtain the required viscosity and develop yield.
- Partially hydrated materials can build up on the vessel wall, in-tank baffles and parts of the agitator.
- Agitators cannot sufficiently reduce droplet size to form a stable emulsion.
- Active ingredients are sensitive to temperature. Processing time can be increased if product is cooled before the addition of active ingredient.
- Poor dispersion of the active ingredient impairs product effectiveness.
- Homogeneous and stable finished products can be obtained by prolonged mixing.
- These problems can be overcome by using silverson mixer which can disperse solids into liquids, break down agglomerates and finely reduce size of particles to form emulsions and suspensions.

Test For Evaluation of Cream

1. Uniformity of weight
2. Sterility (For Sterile cream)
3. Irritancy study
4. Determination of pH
5. Physical appearance

6. Spreadability
7. Saponification value & Acid value (If oily base is used)
8. Viscosity
9. Homogeneity

PASTES

Pastes are semi-solid dosage forms for topical application. These Pastes hold on to skin and used for management of chronic lesions. Pastes contain high content of insoluble solids (generally 50% or more) that are dispersed in proper vehicle. These solids are incorporated by levigation with base to form paste.

Pastes have good adhesive property and are less greasy than ointments. Due to solid contents, pastes are porous, are more stable than other semisolid dosage forms. Pastes are the semisolid preparations intended for external application to the skin.

Composition of Pastes

1. Bases Used in Paste
2. Additives Used in Paste

1. Bases Used in Paste

Hydrocarbon Bases: The commonly used bases are Soft paraffin and liquid paraffin. For example:

- Compound Zinc Paste B.P. Zinc oxide – Soft Paraffin
- Zinc Oxide & Salicylic Acid – Soft Paraffin
- Aluminium Paste B.P.C. – Liquid Paraffin

Water miscible Base: These include emulsifying ointments and emulsifying wax for pastes. For example:

- Resorcinol & Sulfur Paste B.P.C – Emulsifying Ointment
- Zinc & Coal tar Paste – Emulsifying wax

Water soluble Base: These consist of mixture of high and low molecular weight polyethylene glycols. For example:

- Triamcinolone Dental Paste B.P.C.

2. Additives Used in Paste

Toxic toothpaste: Potassium citrate, Triclosan Potassium nitrate, Sodium lauryl sulphate, Sodium mono fluorophosphates, Artificial sweeteners, Triclosan Flouride, Strontium chloride Propylene glycol Diethanol Amine (DEA).

Method of Preparation

1. Trituration method
2. Fusion methods

The ingredients are taken in subdivided state and together melted. The melting of the ingredients is done in decreasing order and then drug is added and stirred thoroughly, till it cools, e.g., Zinc and coal tar Paste B.P.C

Packing of Pastes

Filling tubes

Difference Between Ointment and Paste

Sl. no	Ointment	Paste
1.	They contain drugs that are generally dissolved/suspended/ emulsified in the base.	These contain high content of finely powdered solids such as starch, zinc oxide, calcium carbonates etc.
2.	These are soft	These are very thick and stiff, due to high content of solids (50%)
3	Are more greasy	Less greasy
4	Are used as protective or emollient for skin	These form a protective coating on the area applied
5	Are used for the protection of lesions	As these contain high content of solids, become porous which help in removal of perspiration
6	Are more macerating in action	Are less macerating than ointments

GELS

A gel is a solid or semi-solid system of at least two constituents, consisting of a condensed mass enclosing and interpenetrated by a liquid.

Advantages:

- Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH.
- Gels do not get affected by enzymes and do not get affected with food and drinks.
- They are good substitutes to oral medications.
- They can avoid the first pass effect, that is, the initial pass of drug substance through the human body.
- They avoid systemic and portal circulation following gastrointestinal absorption.
- They get unaffected by liver enzymes.
- They are non-invasive and have patient compliance.
- They are applied over skin for slow and prolonged absorption.
- Gels have also been applied in pharmacy to some viscous suspension for oral use for example Aluminium hydroxide gel.
- They have localized effect with minimum side effects.

Disadvantages:

- It may cause allergic reactions.
- Epidermal enzymes may denature the drugs of gel.
- Large particle size of drugs are difficult to absorb by the skin.
- They have poor permeability of some drugs through the skin.

- Selection of area to be examined carefully during application of gels.
- Gels should be sterilized before being introduced into body cavity or eyes.
- They may cause application side reactions.
- They may cause skin allergy during application.

Delivery through Skin: Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin.

Advantages of this Route:

- Largest surface area is provided by this route.
- Gastrointestinal irritation and first pass effects are avoided.
- It avoids metabolic degradation associated with oral administration.

Mechanism of Drug Absorption

The principal mechanisms of drug absorption are:

1. Passive diffusion
2. Pore transport
3. Facilitated diffusion
4. Active transport
5. Ionic or electrochemical diffusion
6. Ion-pair transport
7. Endocytosis

Classification

Classification of Gels is following:

- Controlled release gels
- Organogels

- Extended release gels
- Amphiphilic gels
- Hydrophilic gels
- Non aqueous gels
- Bioadhesive gels
- Thermosensitive sol-gel reversible hydrogels
- Complexation gels
- Hydrogel

Controlled Release Gels

Drug delivery to nasal or ocular mucosa for either local or systemic action suffers from many obstacles. Gel formulations with suitable rheological and mucoadhesive properties increase the contact time at the site of absorption. However, drug release from the gel must be sustained if benefits are to be gained from the prolonged contact time.

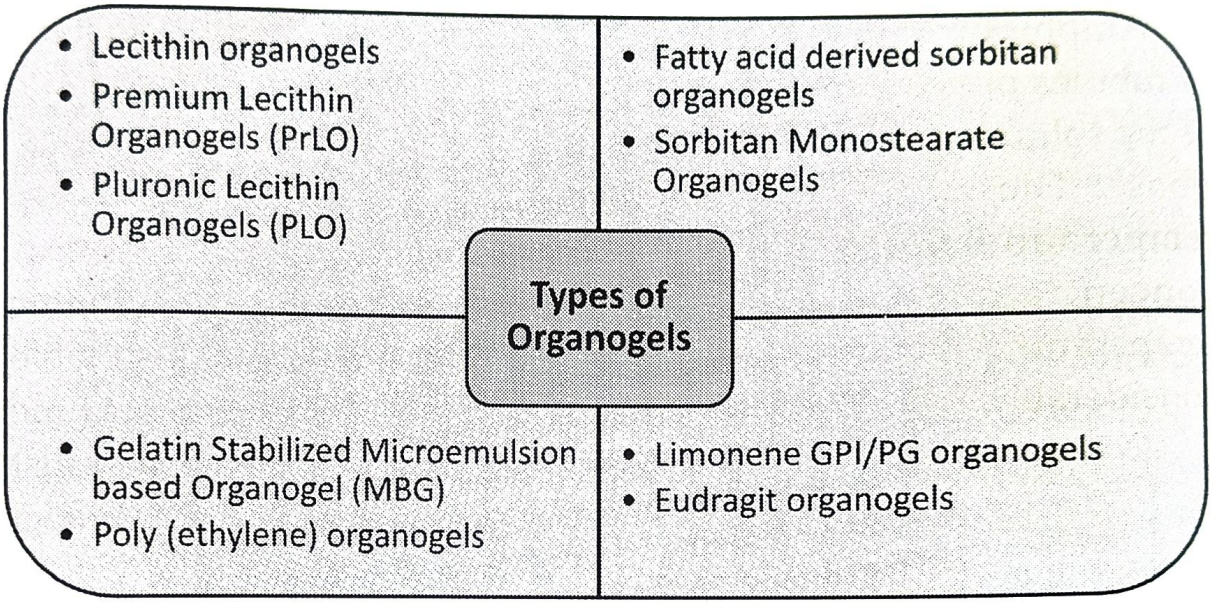
These gels were formed in simulated tear fluid at concentrations of polymer as low as 0.1% and it was shown that sodium was the most important gel-promoting ion in vivo. Rheology, although it may be a questionable technique for evaluating mucoadhesive properties of polymers, showed that interactions between mucin and polymers were most likely to be seen with weak gels.

Organogels

Sorbitan monostearate, a hydrophobic nonionic surfactant and numbers of organic solvents such as hexadecane, isopropyl myristate and a range of vegetable oils are present. Gelation is achieved by dissolving/dispersing the organogelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel state.

Such organogels are affected by the presence of additives such as the hydrophilic surfactant, polysorbate 20, which improves gel stability and alters the gel microstructure from a network of

individual tubules to star-shaped "clusters" of tubules in the liquid continuous phase. Another solid monoester in the sorbitan ester family, sorbitanmonopalmitate, also gels organic solvents to give opaque, thermo reversible semisolids. Like sorbitan monostearate gels, the microstructure of the palmitate gels comprises an interconnected network of rod like tubules.



Extended Release Gels

It is a controlled release technology consists of an agglomerated, hydrophilic complex that, when compressed, forms a controlled-release matrix. It consisting of xanthan and locust bean gums (two polysaccharides) combined with dextrose surrounds a drug core. In the presence of water, interactions between the matrix components form a tight gel while the inner core remains unwetted.

The drug is encapsulated in the pores of the gel and as the matrix travels through the patient's digestive system, the tablet swells and begins to erode. This erosion allows the drug to "back-diffuse" out through the gel-matrix at a controlled rate until the matrix erodes and a majority of the drug is released. The fundamental component controlling the rate of release lies in the properties of the gel matrix.

Amphiphilic Gels

Amphiphilic gels can prepare by mixing the solid gelator like sorbitan monostearate or sorbitanmonopalmitate and the liquid phase like liquid sorbitan esters or polysorbate and heating them at 60°C to form a clear isotropic sol phase and cooling the sol phase to form an opaque semi-solid at room temperature.

Amphiphilic gel microstructures consisted mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, forming a 3D network throughout the continuous phase. The gels demonstrated thermoreversibility. Gelation temperature and viscosity increased with increasing gelator concentration, indicating a more robust gel network. At temperatures near the skin surface temperature, the gels softened considerably, this would allow topical application.

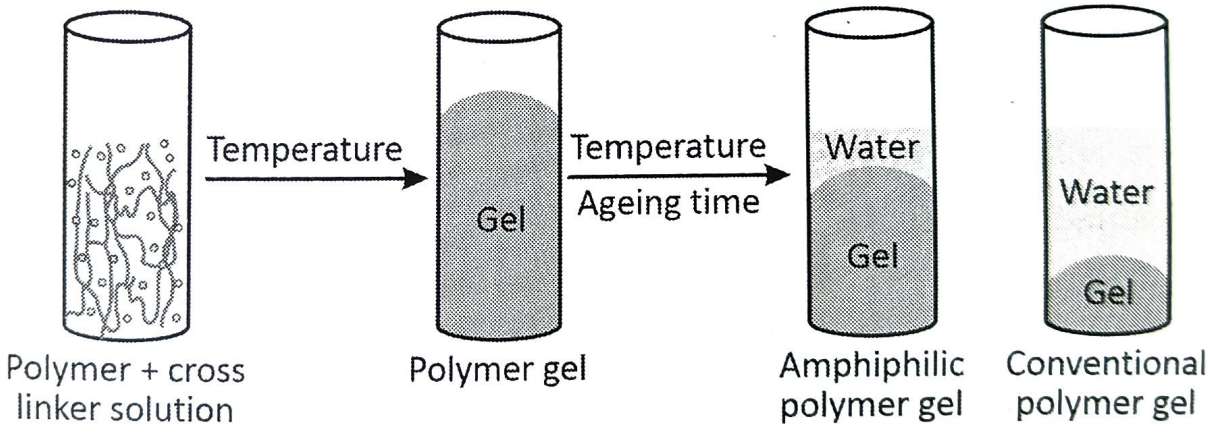


Fig. 5.18: *Bulk gel stability of polymer gel at 85°*

Hydrophilic Gels

Hydrophilic gels are composed of the internal phase made of a polymer producing a coherent three-dimensional net-like structure, which fixes the liquid vehicle as the external phase. Intermolecular forces bind the molecules of the solvent to a polymeric net, thus decreasing the mobility of these molecules and producing a structured system with increased viscosity.

Non-Aqueous Gels

Ethylcellulose was successfully formulated as a non-aqueous gel with propylene glycol dicaprylate/dicaprate. The novel non-aqueous gel exhibited rheological profiles corresponding to a physically cross-linked three-dimensional gel network, with suitable mechanical characteristics for use as a vehicle for topical drug delivery. Molecular conformation of the solvent was found to influence the molecular interactions associated with formation of ethyl cellulose gel networks.

The gel matrices exhibited prominent viscoelastic behaviour, yield stress and thixotropy. Rheological and mechanical properties showed significant upward trends with increased polymeric chain length and polymer concentrations. Good linear correlations were obtained between rheological and mechanical properties. The solvent molecular conformation was found to play a role in affecting the formation of gel networks via intermolecular hydrogen bonding between ethyl cellulose polymer chains.

Bioadhesive Gels

Bioadhesive gels were formulated for nasal delivery of insulin. A nasal perfusion test was carried out to study the toxicity of four absorption enhancers like saponin, sodium deoxycholate, Ethylenediamine Tetraacetic Acid (EDTA) and lecithin.

The gels contained 4000 Iu/dl insulin, 2% or 4% of low and medium molecular weight of chitosan and lecithin or EDTA. Drug release was studied by a membrane less diffusion method and bioadhesion by a modified tensiometry test. The optimized gel was administered nasally in diabetic rats. The serum insulin levels were analyzed by an insulin enzyme immunoassay kit and serum glucose by glucose oxidase method kits.

Thermosensitive Sol-Gel Reversible Hydrogels

They are polymeric solutions which undergo reversible sol to gel transformation under the influence of environmental conditions like temperature and pH which results in insitu hydrogel formation.

Complexation Gels

The goal of oral insulin delivery devices is to protect the sensitive drug from proteolytic degradation in the stomach and upper portion of the small intestine.

The insulin remained in the gel and was protected from proteolytic degradation. In the basic and neutral environments of the intestine, the complexes dissociated which resulted in rapid gel swelling and insulin release. Within 2 hours of administration of the insulin-containing polymers, strong dose-dependent hypoglycemic effects were observed in both healthy and diabetic rats. These effects lasted for up to 8 hours following administration.

Hydrogels

Hydrogels are gel systems in which water immobilised by insoluble polymer. The elements of hydrogels are water and a polymeric substance that is hydrophilic, but not water soluble. When exposed to water, the dry polymer swells and absorbs liquid. The polymer strands are cross-linked either chemically or by physical forces. For convenience, hydrogels may be defined by the type of polymer employed and/or the cross-linking mechanism.

LINIMENTS AND LOTIONS

Lotion

Lotions are either liquid or semi-liquid preparations that contain one or more active ingredients in an appropriate vehicle.

A lotion is a viscous (low to medium viscous) medicated or nonmedicated topical preparation, meant for application to **unbroken skin.** Lotions are usually applied to external skin with bare hands, a clean cloth, cotton wool or gauze without friction. Solid particles incorporated in lotions should be in a finely divided state to avoid grittiness.

Lotions are used for the topical application of medications such as antibiotics, antiseptics, antifungals, corticosteroids, antiacne agents and soothing/protective agents.

Lotion may be types of o/w (mostly) or w/o emulsion. Some Lotions are solutions or suspensions of solids in an aqueous medium (the insoluble matter should be divided very finely). Key Ingredients of lotion are the aqueous and oily phases, an emulsifying agent (to prevent separation of these two phases), and, the drug substance. Other excipients such as fragrances, glycerol, petroleum jelly, dyes, preservatives and stabilizing agents are commonly added to lotions for improved organoleptic and preservation characteristics.



Fig. 5.19: *Calamine Lotion*

Lotions may be prepared by triturating the ingredients or High speed mixers or colloid mills for large scale production.

Liniments

Liniments are usually alcoholic and oily liquid preparations (Monophasic) or emulsion (Biphasic).

- Also known as embrocations.
- Liniments are Liquid or semisolid preparation.
- Meant for application to skin with friction & Rubbing of the skin.
- May contain alcohol or oily solution or emulsion.
- Liniment should not be applied to broken skin or broken skin.
- Liniment should be dispersed in colouredfluted Bottles in order to distinguish it from preparation meant for internal use Label – External Use only; shake well before use & not to be applied to open wound and broken skin.

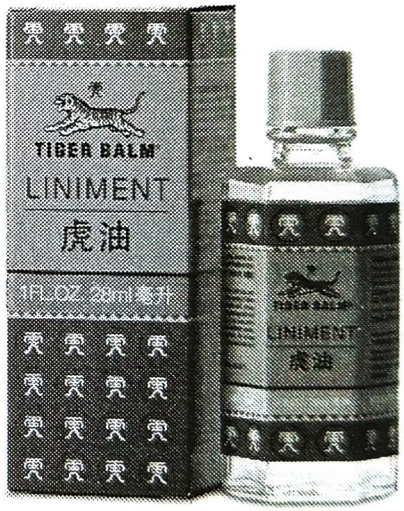


Fig. 5.20: *Tiger Balm Liniment*

Table 5.7: Difference between Liniment & Lotion

Liniment	Lotion
• Liquid or semisolid preparation. • They are applied to skin with friction and rubbing of skin. • May contain alcohol or oily solution or emulsion. • It should not be applied on open wounds. • Liniment should be dispersed in **coloured fluted Bottles in order to distinguish it from preparation meant for internal use.** • Label – External Use only; shake well before use & not to be applied to open wound and broken skin.	• They are externally applied with help of cotton wool or gauze soaked in it without friction. • Used for soothing, cooling and antiseptic properties. • Dispensed in **Fluted bottles in order to distinguish it from preparation meant for internal use** • External Use only; shake well before use
Example: Terpintine liniment	Example: Bentonite lotion, Calamine lotion

SUPPOSITORIES AND PESSARIES

Definition

Suppositories are the solid medications that are inserted into rectum, vagina or urethra. On insertion these melt and soften due to body temperature, that may have systemic or local effect.

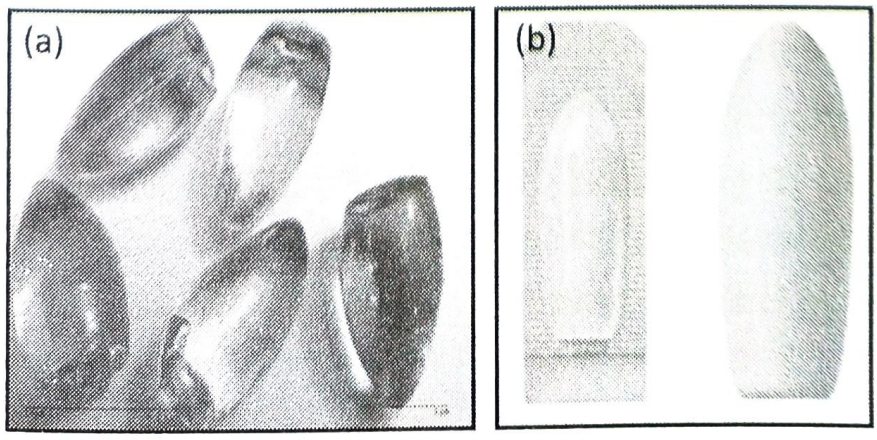


Fig. 5.21: *(a) Suppositories; (b) Pessaries*

Merits of Suppositories

- Not use for oral route.
- It can be given to patients that have GIT problems or have nauseating problems of have undergone surgery.
- Suitable for drugs having GI side effects or not stable at GI pH or susceptible to enzymatic attack in the GI tract, undergo first pass metabolism.
- Drugs with an unacceptable taste can be administered.
- Melt at body temperature.
- Can be used for direct effect to rectum.
- May be used for bowel evacuation.
- Can exert local and systemic effect.
- Administered to unconscious person.

Demerits of Suppositories

- May cause mucosal irritation
- Leakage issues
- Sometimes incomplete absorption
- Inter and intra subject variation
- May cause Proctitis (inflammation of the lining of the rectum)
- Large scale production difficult and costly shelf life (stringent storage conditions)
- The GI state may affect the absorption
- Cause embarrassing situation to the patients
- Expensive
- Drug degradation may take place due to the presence of microbial flora present in the rectum
- Drugs that cause irritation can't be given

Types of Suppositories

1. **Rectal suppositories:** These are inserted into the rectum. It is Cone or torpedo shaped of weight 1-2 g.



Fig. 5.22: *Rectal Suppositories*

2. **Vaginal suppositories (Pessaries):** These are Globular, oviform, cone or wedge shaped of the weight 2-8 g. These are made from glycero-gelatin or macrogol base.



Fig. 5.23: *Vaginal suppositories*

3. **Urethral bougies:** Thin pencil shaped pointed at one end, Male bougies – 4 g and 100-150 mm Female bougies – 2 g and 60-75 mm, thin pencil shaped with pointed ends.

4. **Nasal bougies:** These are to be introduced in nasal cavity. Generally glycerol-gelatin base is used for it. They are 1.2 g and 9-10 mm long.
5. **Ear cones:** These are introduced into the ear. Are pencil shaped and about 1 g in weight.

Suppository Bases

Various substances are used for the suppository base. The physical and chemical properties have provided the basis for setting standards for suppository bases.

The following are the standards and specifications for suppository bases:

- **Origin and chemical composition:** It indicates the origin of the base, whether it is natural or synthetic.
- **Melting Range:** As the suppository bases do not have sharp melting points, due to their composite mixture of triglycerides.
- **Solid Fat Index (SFI):** This determines the melting ranges and solidification of fatty bases, with its hardness at room temperature and molding characteristics.
- **Hydroxyl Value:** It represents the amount of potassium hydroxide that would neutralize the acetic acid used to aceylate 1 gm of fat.
- **Solidification Point:** It is defined as the time required for a base to congeal when it is freezed. When the difference in temperature is 10°C, the time is decreased by use of refrigeration.
- **Saponification Value:** It is defined as the amount of potassium hydroxide essential to nullify the free acids and saponifying the esters present in the 1 gm of fat is an indicator of glycosides and amount of glycosides present.
- **Iodine Value:** It is the volume of iodine that reacts with 100 gm of fat or alternative unsaturated materials. The decomposition of materials increases with high iodine value.
- **Water Number:** The volume of water in grams that can be included in 100 gm of fat is exhibited by this value. The

water number may be enhanced by incorporation of surface active agent, monoglycosides and other emulsification.

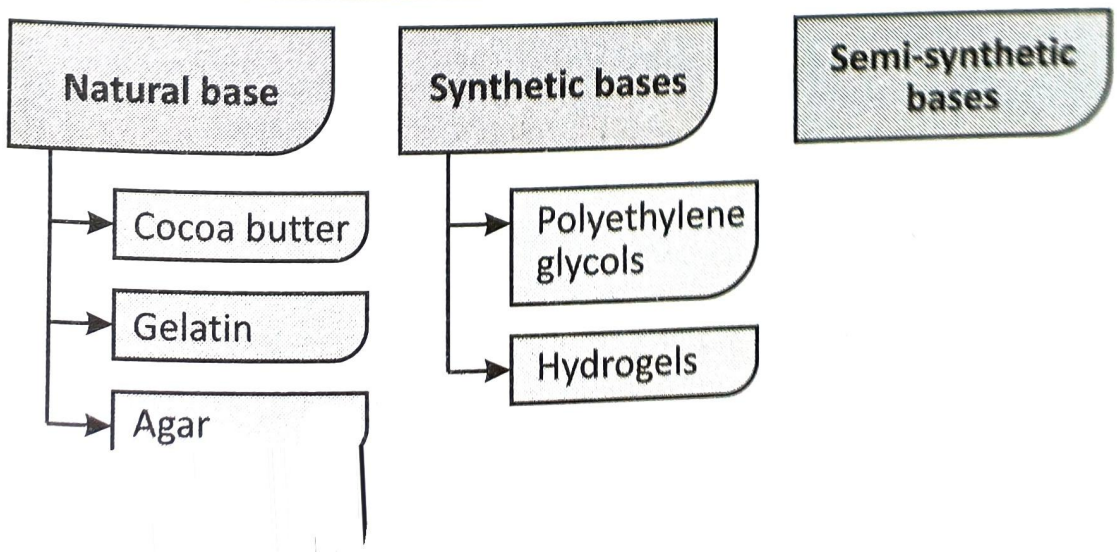
- **Acid Value:** The number of milligram of potassium hydroxide essential to nullify the free acid in 1 gm of substrate is exhibited by this value. The suppository bases are considered to be best when the acid value are low or absent.

The Ideal Properties of a Suppository Base

The ideal properties of a suppository base described as follows:

1. Should be nontoxic, nonirritant.
2. It should be compatible with most of the drugs.
3. Should not have meta stable forms.
4. Should shrink adequately on cooling, so as to release from the mould, without need of lubricant.
5. Should be nonsensitizing.
6. Should have good wetting and emulsifying effects.
7. Should have high water number, so as maximum water can be incorporated in the suppositories.
8. Higher melting mixtures can be used for eutectic mixtures.
9. Should be durable, on storage and there should be no color change, odor change and should not affect drug release properties.

Types of Suppository Bases



Natural Bases

- **Theobroma oil (cocoa butter):** It is the solid fat obtained from roasted seeds of theobroma cocoa.
- **Appearance:** Yellowish white, solid fat, odor agreeable and resembling that of cocoa.
- **Solubility:** Freely soluble in chloroform, in ether and in petrol (B.P from 40°-60°C), slightly soluble in ethanol.
- **Melting Point (M.P.):** 31°C to 34°C.
- **Saponification value:** 188 to 196.
- **Acid Value:** Not more than 4.0.
- **Applications:** As suppository base.

Hydrogenated Vegetable Oils

- It is derived from palm, palm kernel and oil producing plants, composed of triglycerides, Glyceryl Monostearate (GMS) and polyoxy stearate.
- Requires no storage conditions and is water insoluble.
- As it has good lubrication property, so no lubricator is required.
- **M.P.:** 35-37°C.

Agar

- It is derived from rhodophycae family, that belongs to genus Geladium.
- It is colourless or pale yellow translucent, odorless.
- Available in flakes or powder form and becomes brittle on drying.
- It is soluble in hot water but insoluble in cold water.
- The swelling index of it is less than 10 and pH is 3 to 11.

Glycerin (Glycerol)

- It is syrupy, odor free liquid

- It has sweet taste and generates sensation of warmth.
- It dissolves in aqueous media and alcohol, but insoluble in chloroform, diethyl ether, fixed oils.
- It is used as pharmaceutical aid.

Gelatin

- It is pale yellowish transluscent flakes or sheets.
- It has slight odor and taste.
- It is soluble in hot water, insoluble in solvents like ethanol, chloroform, ether, but insoluble in cold water.
- It swells and softens when immersed in cold water.
- It is used as binding, coating, diffusing and encapsulating agent.

Polyethylene Glycols

- These are also known as PEG, carbowax, macrogols, borox PEG.
- It is derivative of ethylene oxide in water and chemically represented as H $(O-C-H_2C-H_2)_n-OH$ where 'n' is the mean number of oxy-ethylene.

Type of macrogol	Viscosity (cps) (100°C)	Density (g/cc)	Hydroxyl value
PEG 1000	20.4-27.7	1.080	107-118
PEG 4000	102-158	1.080	25-32
PEG 6000	185-250	1.080	16-22

Additives

The presence of the additives can affect the properties of suppository bases or affect dissolution of the drug.

Some of the additives which can be used in suppository are:

1. **Polyvinyl Pyrolidine (PVP):**
   - It is coloured, odorless, tasteless, granular or fibrous particles.
   - It dissolves in water and solvents like chloroform, ethanol, propanol.
   - **M.W.:** 10,000 to 700,000.
   - It is used as binder, suspending and dispersing agent and for preparation of solid dispersions.
2. **Sodium-carboxymethylcellulose (Na-CMC):**
   - It is white, odorless, white nut hygroscopic.
   - It is insoluble in solvents like ethanol, ether, toluene, acetone.
   - It is sodium salt of moderately displaced poly (carboxy-methyl) ether of cellulose.
   - Used as viscosity modifier, suspending agent.
3. **Hydroxyproply Methyl Cellulose (HPMC):**
   - It is Cellulose-2-hydroxypropyl methyl ether.
   - It is odor free and tasteless. Has white or creamy white color coarse powder form.
   - **M.W.:** 10000-1500000.
   - Used as Pharmaceutical aid.

Preparation of Suppositories

Hand Molding

It is one of the easiest method for preparation, using cocoa butter as base. The base is first minced, blended with drug in mortar, till product is plastic and blended properly. The drug used is in powder form or dissolved in water and then blended with some quantity of wool fat, for incorporating the base. Then this, bleneded mixture is hand rolled into cylindrical shape of desired diameter and length. The cylindrical rod is further sliced in small portions and one end

is pointed. This method is economical and easy when number of suppositories is less.

Compression Moulding

Elegant suppositories can be prepared by this method. A wheel that is turned by hand, pushes a psiton, against suppository bases, present in the cylinder and the mass is extruded in moulds. This method is more better than hand molding. The advantage of it is that the sedimentation of solids from suppository base is avoided, but the disadvantage is that, for large scale its slow process and also air entrapment may take place by this method.

Fusion Molding or Pour Molding

This is the widely used method for preparation of suppositories. The base is first melted, on water bath, to avoid overheating and then the drug is added that is suspended or emulsified in it. Then the mass is poured in cool metal moulds that are made of chrome or nickel plated.

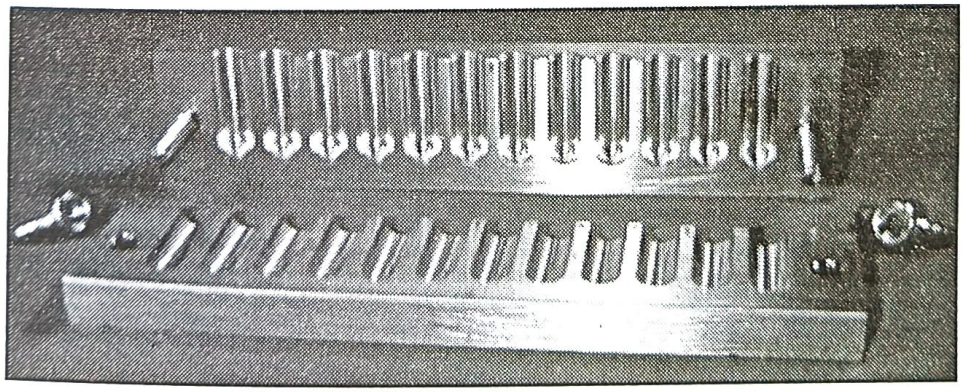


Fig. 5.24: *Molds for preparation of Suppositories*

Packaging of Molded Suppositories

Storage conditions are one of the major parameter to be considered for suppositories. The suppositories should be kept in such containers that they do not come in contact with each other. They can be packed in aluminium foils, of plastic and papers can also be used for wrapping of the suppositories. The contact of the [illegible] with the outer container.

Sometimes, the suppositories are packed in compartments, of 6 to 12 suppositories, in cardboard sheets. The volatile or hygroscopic contents of suppositories require glass or plastic containers for their storage.

In Package Moulding

Due to the advancement in the machinery, the packing of suppositories, is done by machine itself in wrapping materials. Aluminium foils, laquer laminates can be used.



Fig. 5.25: *Marketed Suppositories*

PESSARIES

These are basically used for vagina. These are used for local medication and also for systemic effect. Large molds are used for its preparation of 4 and 8 g moulds.

The major ingredients used for pessaries are for treatment of bacterial, trichomonal and monilial infections. They are used for local anaesthetics, contraceptive agents, antiseptics.

These are single dose and solid. Are available in various shapes, mainly ovoid, with volume and consistency such as that can be

inserted into vagina. They contain drug dispersed or dissolved in base, that is dispersible or soluble in water and melt at body temperature. Various additives are added to make it like adsorbents, surface active agents, antimicrobial preservatives, colouring matter, lubricants, diluents etc.

Hydrated vaginal suppositories can be prepared by use of hydrophilic polymers like polyacrylic acids, sodium carboxymethyl cellulose with the drug. Pessaries weigh 3 to 5 gm and are in oviform shape or conical.

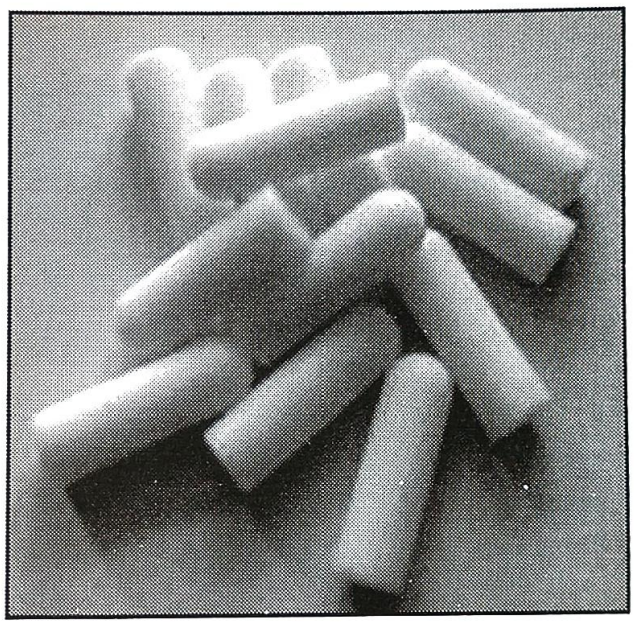


Fig. 5.26: *Pessaries*

NASAL DRUG DELIVERY

Nasal drug delivery is a useful delivery method for drugs that are active in lowdoses and show no minimal oral bioavailability. The nasal route circumvents hepaticfirst pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication.

Currently, two classes of nasally delivered therapeutics are on the market.

1. The first one comprises low molecular weight and hydrophobicdrugs for the treatment of the nasal mucosa

and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products.

2. The second class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in gastrointestinal tract, poor absorption properties and their rapid and extensive biotransformation.

Therefore, nasal delivery is promising alternative route for the administration of peptides and protein drugs in particular.

Advantages of Nasal Drug Delivery System

1. Many drugs undergo first pass elimination if administered orally or rectally. Hence, nasal route is one of the alternative in that case.
2. Drugs which are less stable in gastrointestinal fluids are given by nasal route.
3. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.
4. Some drugs like peptides or proteins get destroyed by GIT fluids or don't get absorbed into systemic circulation after oral administration. Such drugs can be administered nasally.

Limitations of Nasal Drug Delivery Systems

1. Some of the constituents of dosage form may damage cilia of nasal mucosa.
2. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
3. The common cold or any pathological conditions involving mucociliary dysfunction, can greatly affect the rate of nasal Clearance and subsequently the therapeutic efficacy of the drug administered nasally.
4. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

EAR OR OTIC PREPARATIONS

Otic preparations are products applied to or in the ear to treat conditions of the external and middle ear. These products are used to treat dermatitis of the ear, cerumen build up and ear infection.

TYPES OF OTIC PREPARATIONS

Please refer to the drug classes listed below for further information.

- Cerumenolytics
- Miscellaneous otic agents
- Otic anesthetics
- Otic anti-infectives
- Otic steroids
- Otic steroids with anti-infectives

POWDERS AND GRANULES

INTRODUCTION

Powder is the simplest dosage form and the basis of many other solid dosage forms such as tablets, capsules, etc.

DEFINITION

Powder is an intimate mixture of finely divided drug and/or chemicals in a dry form that may be intended for internal use (oral powders) or external use (topical or dusting powder).

Minimum Weighable Quantity

Minimum weighable quantity for a powder is 2 grain, because it is very impractical to weigh below 2 grain and also to avoid the error in weighing on dispensing balance.

Classifications

1. Divided powders.
2. Simple and compound powders for internal use.
3. Powders for reconstitution.
4. Bulk powders for internal use.
5. Bulk powders for external use.

Advantages

1. Used both internally and externally.
2. Good chemical stability as compared to fluid.
3. Rapid onset of action.
4. Easy to swallow even in large bulk, especially if mixed with drink food.
5. Easy to carry than the liquid dosage form.
6. It is suitable for small children's and elderly patients.

Disadvantages

1. Not suitable for drugs unstable in atmospheric conditions.
2. Not suitable for bitter, nauseating, deliquescent and hygroscopic drugs.
3. Dispensing of powder is time consuming.
4. Quantity less than 100 mg cannot possible for dispensing.

FORMULATION OF POWDER AS DOSAGE FORMS

Formulation of powder as dosage forms is performed according to the following step:

1. To obtain powder as raw material from an original drug (animal, vegetable drugs or animal or synthetic chemical entities) by different methods of division.
2. Mixing of various powder with or without excipient as a function of the powders characteristics (e.g., flow properties)
3. Packaging of the finished product for an easy patient's use.

MANUFACTURING OF POWDERS

Methods involved in manufacturing of powders:

1. Method of Particle Size reduction
2. Method of Mixing of Powder
3. Packaging of Powder

1. Methods of Particle Size reduction:

(i) **Trituration:** Process of grinding the powder in mortar and pestle to reduce its particle size.

(ii) **Pulverization by intervention:** Is the reduction of particle size with the aid of a second agent which can readily be removed from the pulverized product.

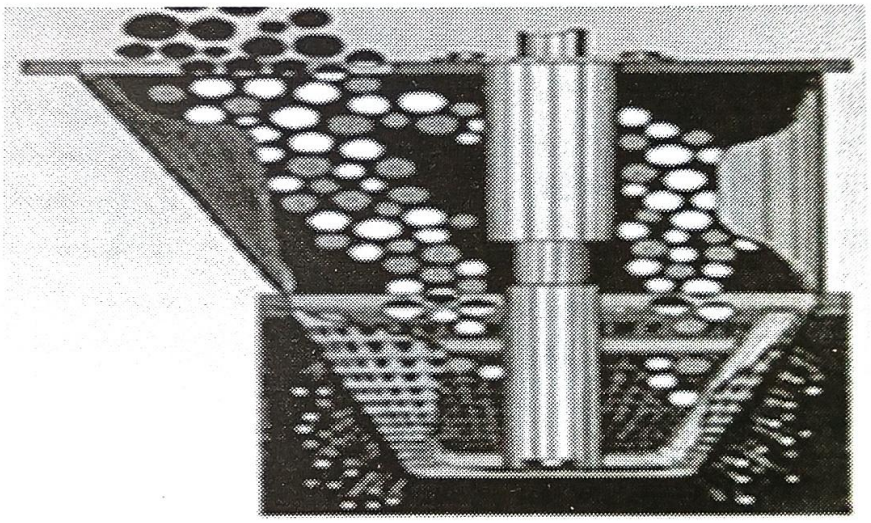


Fig. 5.27: ***Equipments for reducing particle size***

(iii) **Levigation:** Is the process of reducing particle size by first forming a paste of the solid with a minimum amount of a levigating agent and then triturating the paste in a mortar or on slab with a spatula.

(iv) **Milling:** Milling equipment is used to improve flow, reduce segregation, enhance drying and limit wide particle size distribution.

2. Method of Mixing of Powder: If these factors are not under control, segregation can occur. Mixing of powders:

(i) The aim of mixing is to obtain a homogeneous association of several solid products.

(ii) Factors influencing the mixing of powders-nature of surface, density, particle size and particle shape, particle charge proportion of materials.

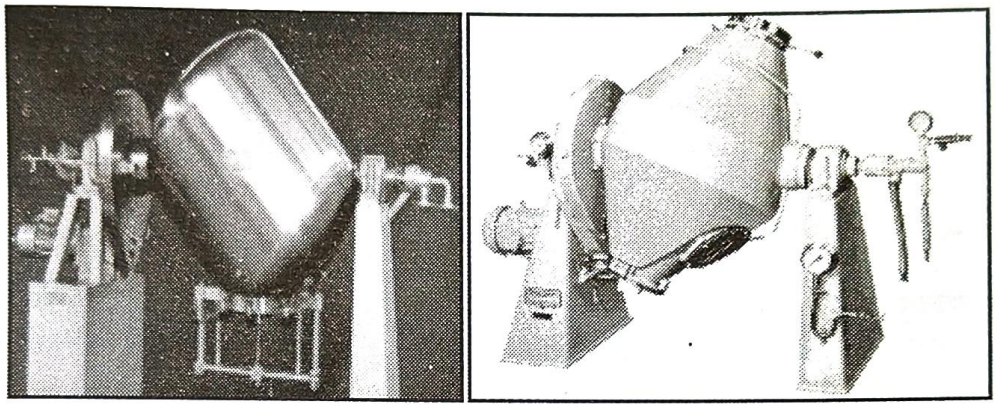


Fig. 5.28: ***Single and double cone blender for mixing of powder***

(iii) If these factors are not under control, segregation (demixing) can occur.

(iv) Type of segregation includes percolation, trajectory and densification.

Different Method of Mixing:

(i) Spatulation: Spatula + tile

(ii) Trituration: Mortor + Pestle

(iii) Geometrical dilution

(iv) Tumbling: wide mouth closed container

3. **Packaging of Powder:** Powders are wrapped in paper or dispensed in bulk powder in a wide mouth bottle:

(a) *Wrapping of Powder:* Require quantity of powder should be weigh and then wrap in the white glazed paper.

(b) *Double wrapping of Powder:* For Volatile, hygroscopic and deliquescence substance white glazed paper is not sufficient to protect, so waxed paper is used. It is again wrapped externally in aluminum foil.

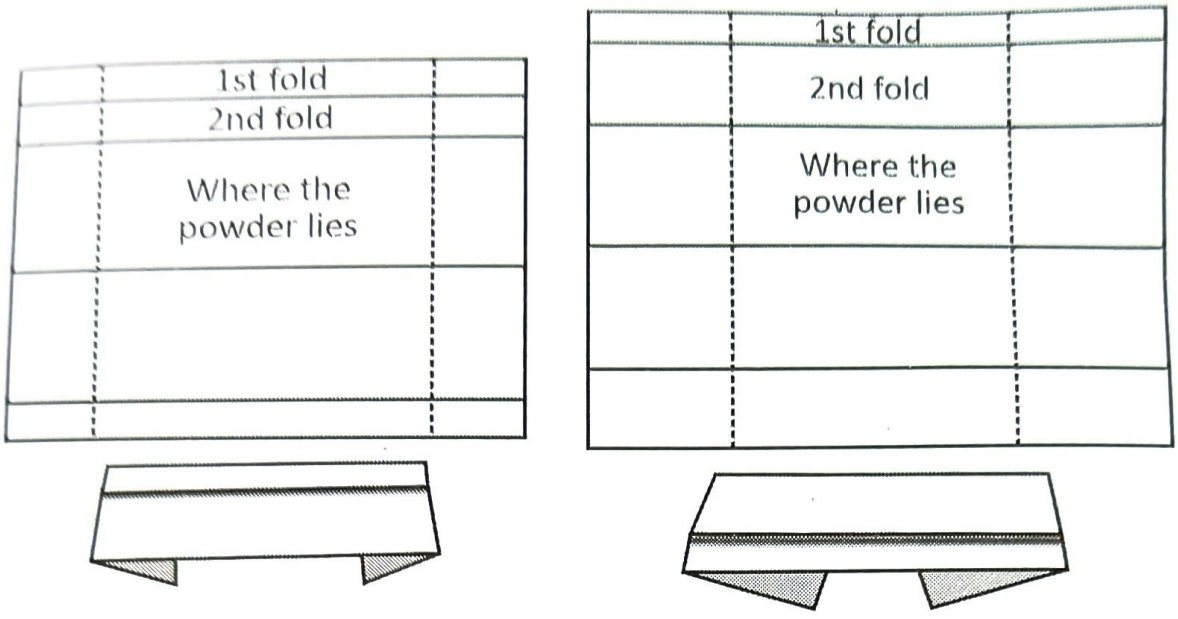


Fig. 5.29: *Steps for wrapping powder*

DIFFERENT CLASSES OF POWDER

A. Bulk powder for external use
B. Bulk powder for internal use
C. Simple and compound powder for internal use
D. Catchets
E. Compressed powders (Tablets)

A. Bulk Powder for External use

1. **Dusting powders:** They are meant for external application to the skin and generally applied in a very fine state of subdivision to avoid local irritation.

   They are of two types:

   (a) Medical: They are used for superficial skin conditions, they should not be used for application to open wounds or application on broken skin.



Fig. 5.30: *Dusting Powder*

The label should clearly specify this point. We need not sterilize the ingredients of these powders but we must be sure that they are not containing pathogens.

(b) **Surgical:** These powders must be sterile because they are used in body cavities and are applied on wounds. They are sprayed on burnt areas and are placed on the umbilical cords of infants.

These powders usually contain an antibacterial agent. The diluents are sterilizable maize starch, which is also called as absorbable dusting powder.

Functions: Lubricant, protective, adsorbents, antiseptic, astringents.

2. **Snuffs:** These are finely divided solid dosage forms of medicaments inhaled into nostrils.

   Functions: Decongestion, Antiseptic, Bronchodilator

   Packaging: Dispensed in flat metal boxes with hinged lid.



Fig. 5.31: *Marketed preparation – Snuffs*

3. **Dental Powders:** Dental powders are applied with the help of a tooth brush for cleaning the surface of the teeth.



Fig. 5.32: *Tooth powder*

Dental powder contains detergents, abrasives, antiseptics and colouring and flavouring agents incorporated in a suitable base.

Base is calcium carbonate. The detergent is in the form of soap and the abrasive action is provided by finely powdered pumice stone.

Essential oils are added to provide flavour and freshness to the mouth as well as antiseptic action.

4. **Insufflations:** Insufflations are the medicated dusting powders introduced into body cavities such as ears, nose, throat and vagina with the help of a device called insufflators.

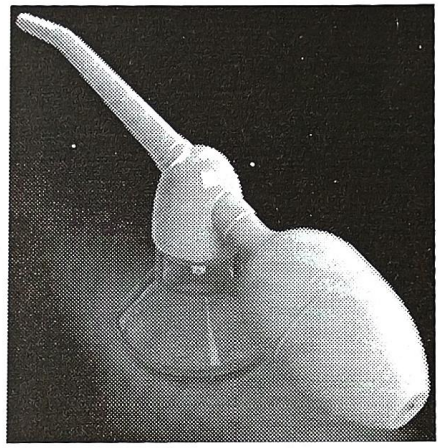


Fig. 5.33: *Insufflators*

It sprays the powder into a stream of finely divided particles all over the site of application.

D. Catches

Solid Unit dosage form of drugs called as Catches. These are molded from rice paper, used for nauseous or disagreeable powders and it dispensed powder from 0.2 to 1.5 gm.

Advantages:

1. Easily prepared, not required any complicated machines
2. Disintegrate immediately in stomach
3. Easily dispense
4. Large quantity up to 1.5 gm of drug can be swallowed by using cachets.

Disadvantages:

1. Need to be soften before swallowing
2. Easily damaged
3. They cannot protect drug from light and moisture
4. The shell is very brittle
5. Not suitable for large scale manufacturing

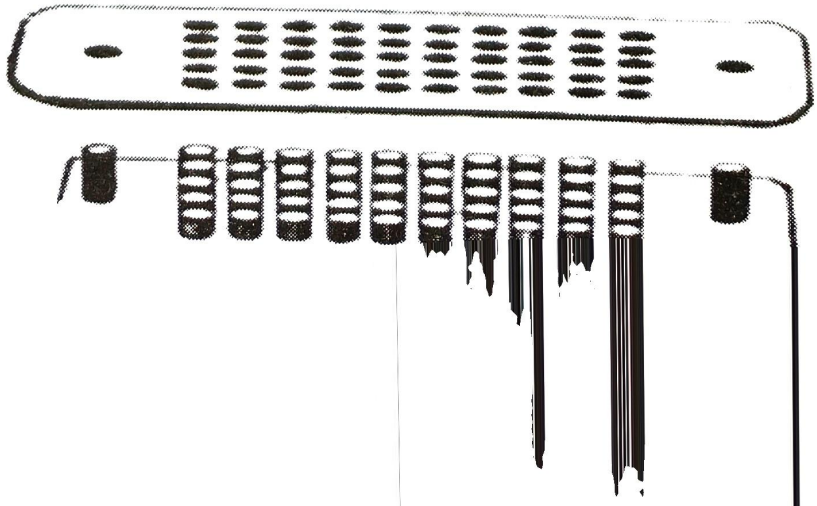
Catches are of Two Types

1. **Wet seal:** A wet seal cachet consist of two similar convex halves, which are having flat edges. The powdered drug is placed in one half, the edges of the other half are moistened with water and placed on the first half in which drug is placed. The flat edges of both the halves are pressed to seal it perfectly.
2. **Dry seal:** Dry seal cachets consists of the upper half and the lower half. The diameter of the upper half is slightly bigger than the lower half. The powdered drug is filled in lower half and upper half is fitted over it. The filled cachets are then placed in in a machine and press the two halves to sealed, then removed and packed in boxes.

E. Compressed Powders (Tablets)

Small, usually cylindrical molded or compressed tablets:

The drug used were potent and mixed with lactose and a binder such as powdered acacia, after which the mixture was moistened to produce a moldable, compatible mass. This mass was forced into holes of a mold board wood or plastic, after which tablet where ejected using a peg board, whole pegs matched the hole in the mold, dried and dispensed.



DISPENSING OF POWDER

Dispensing of powders involve special problems:

A number of problem arise while dispensing a powder containing volatile substances, hygroscopic and deliquescent powders, eutectic mixtures, efflorescent powders, liquids, explosive substances and potent drugs. So special considerations are done while dispensing such powders.

1. **Volatile substances:** Certain vegetable powders contain volatile oils. To prevent the loss of volatile oils, these vegetable drugs must be powdered lightly in mortar .Similarly the volatilization of substances like menthol; camphor and essential oils may take place on incorporation in powders. This is prevented or at least minimized by the use of double wrapping. The inner wrapper should be of wax paper and outer wrapper may be of any thick paper.
2. **Hygroscopic and deliquescent powders:** The powders which absorb moisture from the atmosphere are called hygroscopic powders. But certain powders absorb moisture to such a great extent that they go into solution and are called deliquescent powders. Example of such substances include ammonium chloride, iron and ammonium citrate, pepsin, phenobarbitone, sodium bromide, sodium iodide, potassium citrate, zinc chloride etc.

   Such substances are usually supplied in granular form in order to expose less surface area to the atmosphere. These powders should not be finely powdered. Such powders should be double wrapped. In humid weather or when dealing with very deliquescent substances, further wrapping in aluminium foil or plastic cover is advisable.
3. **Efflorescent powders:** Some crystalline substances liberate water of crystallization wholly or partly on exposure to humid atmosphere or during trituration and thus, become wet or liquefy. Example of such substances include caffeine, citric acid, ferrous sulphate etc. This difficulty may be overcome by using either corresponding anhydrous salt or an inert substance may be mixed with efflorescent substance before incorporating with other ingredients.

4. **Eutectic mixtures:** When two or more substances are mixed together they liquefy due to the formation of a new compound which has a lower melting point than room temperature .Such substances are called eutectic substances. Example of such substances include menthol, thymol, camphor, phenol, salol, aspirin, phenacetin, chloral hydrate etc.

These substances can be dispensed by two methods:

(i) Dispense as separate set of powders with directions that one set of each kind shall be taken as a dose.

(ii) An equal amount of any of inert absorbent like magnesium carbonate, light magnesium oxide, kaolin, starch, lactose, calcium phosphate etc., may be mixed with eutectic substance and then blended together lightly with a spatula on a sheet of paper. When in addition to liquefying substances, other ingredients are also present, the liquefiable substances should first be triturated together to form the eutectic mixture. Then the remaining ingredients of the prescription are incorporated and mixed together.

Effervescent granules are prepared for:

1. To incorporate large quantity of drug.
2. To increase the surface area.
3. To mask the taste of drug.
4. To increase the rate of absorption.
5. To change the pH.
6. To prevent from moisture.

When these are added to water produce effervescence which releases the carbon dioxide which change the taste of the drug and makes it more palatable.

Reactions:

1. $3NaHCO_3 + C_6H_8O_7.H_2O \rightarrow C_6H_5Na_3O_7 + 3CO_2 + 3H_2O$

   Sodium Bicarbonate + Citric Acid → Sodium citrate + Carbon dioxide + Water

2. $3NaHCO_3 + C_4H_6O_6 \rightarrow C_4H_4Na_2O_6 + 2CO_2 + 2H_2O$

WEIGHING TECHNIQUES

Weighing of ingredient is an important step in formulation of all pharmaceutical preparation. Dispensing balance is used for compounding and dispensing of medicine. A dispensing balance consist of horizontal beam with knife edges on both the side on which two pans are suspended and knife edge at the center. The left pan is used for placing the weights and right pan is used for placing the material.

Steps in Weighing the Material

1. Place the balance in a clean and plain platform.
2. Adjust the level of the balance and clean the pan using cotton.
3. Take two equal size butter paper and each paper will be placed in both the pan.
4. Using forceps place the weight in left hand side pan, to avoid sweat from the hand.
5. Take the bottle of powder medicament and check the label for the correct ingredients and then by using spatula only remove the medicaments and place it on right hand side balance until the pointer come exactly on null position.
6. Transfer the weighed material on paper or container.
7. Return the weights in drawer using forceps only and clean the pan and spatula.
8. Close the bottle and return to its place. Then next bottle should be removed and weigh the material. This will avoid mixing of two ingredients.

Possible Errors in Weighing

1. The balance is not properly kept.
2. The null point is not adjusted properly.
3. The two pans are unequal.
4. The pan surface is not uniform.
5. The butter papers are not kept in pan.
6. Weights are handled without forceps.

Minimum Weighable Amount

The dispensing balance is used for weighing; a minimum weighable quantity should be not less than 100 mg or 2 grains with maintaining error ± 5%. Means error in dispensing should not be more than ± 5%. It means that any preparation if we are dispensing 100 mg than it should not be less than 95 mg and not more than 105 mg.

Care and usage of Dispensing Balance

1. It should be kept in a dust free and moisture or humidity control room.
2. It is to be kept in a plane area and Standard operating procedure should be displayed at the place where balance is kept.
3. Before and after weighing each ingredient, balance should be cleaned with cotton.
4. Drawer of balance should be closed during weighing.
5. Always use spatula to transfer any material.
6. Use forceps for transferring the weights.
7. When the balance is not in use, it should be clean and cover it properly.

EFFERVESCENT GRANULES

Effervescent granules are the specially prepared solid dosage form of medicament, meant for internal use. They contain a medicament mixed with citric acid, tartaric acid and sodium bicarbonate. Sometime saccharin or sucrose may be added as a sweetening agent. Before administration, the desired quantity is dissolved in water, the acid and bicarbonate react together producing effervescence. The carbonated water produced from the release of carbon dioxide serves to mask the bitter and saline taste of drugs. Moreover, carbon dioxide stimulates the flow of gastric juice and helps in the absorption of medicament.

Additives used in the formulation of effervescent granules:

1. Sodium bicarbonate

2. Citric acid
3. Tartaric acid
4. Sodium saccharine

Functions:

1. **Sodium bicarbonate:** It reacts with citric and tartaric acid in presence of water. Evolved carbon dioxide gas and effervescence are evolved
2. **Citric acid:** It is used to release water of crystallization & to create conditions for release of more water. It also used to neutralize bicarbonate.
3. **Tartaric acid:** Used for neutralization
4. **Sodium saccharine:** Sweetening agent.

Method of Preparation

There are two methods of preparation of effervescent granules:

1. Heat method
2. Wet method

Heat Method

A large porcelain dish is placed on a water bath, with as much of the dish as possible exposed to the water or steam. The dish must be hot to ensure rapid liberation of water of crystallization from citric acid. If heating of the dish is delayed, the powder which is added to it, will heat up slowly and the liberated water of crystallization will go on evaporating simultaneously. As a result sufficient water will not be available to make **Coherent mass.**

The water needed for granulation is provided from two sources:

(i) From water of crystallization of citric acid. The citric acid contains one molecule of water of crystallization which is liberated during heating.

$$3NaHCO_3 + C_6H_8O_7.H_2O \rightarrow C_6H_5Na_3O_7 + 3CO_2 + 3H_2O$$

Sodium Bicarbonate — Citric acid — Sodium citrate — Carbon dioxide — Water

(ii) The water produced from the reactions of citric acid & tartaric acid with sodium bicarbonate.

$$2NaHCO_3 + C_4H_6O_6 \rightarrow C_4H_4Na_2O_6 + 2CO_2 + 2H_2O$$

Sodium bicarbonate Tartaric acid Sodium tartrate Carbon dioxide Water

(iii) Generally heating takes 1 to 5 minutes. The damp mass is then passed through sieve

Dried in an oven temperature not exceeding 60°C.

Wet Method

In this method,the mixed ingredients are moistened with a non-aqueous liquid (e.g., alcohol) to prepare a coherent mass which is then passed through a number 8 sieve and dried in an oven at a temperature not exceeding 60°C. The dried granules are again passed through the sieve to break the lumps which may be formed during drying. The dried granules are packed in air tight containers.

STERILE FORMULATIONS

Sterile dosage forms are those which are free from any microorganisms, dust, fibres and foreign particles and should be isotonic.

PARENTERAL DOSAGE FORMS

The word parenteral arises for Greek word "Para" meaning outside and "Enteron" that is intestine. Parenteral are sterile solutions/ suspensions in aqueous or oily vehicle.

Definition

Parenterals are sterile dosages that are used for injection through skin of other tissues.

General Requirements for Parenteral Dosage Forms

- **Sterility:** Parenterals should be free from microorganisms. Aseptic conditions should be maintained during their preparations and administration.
- **Stability:** The physical and chemical stability of Parenterals must be maintained during storage.

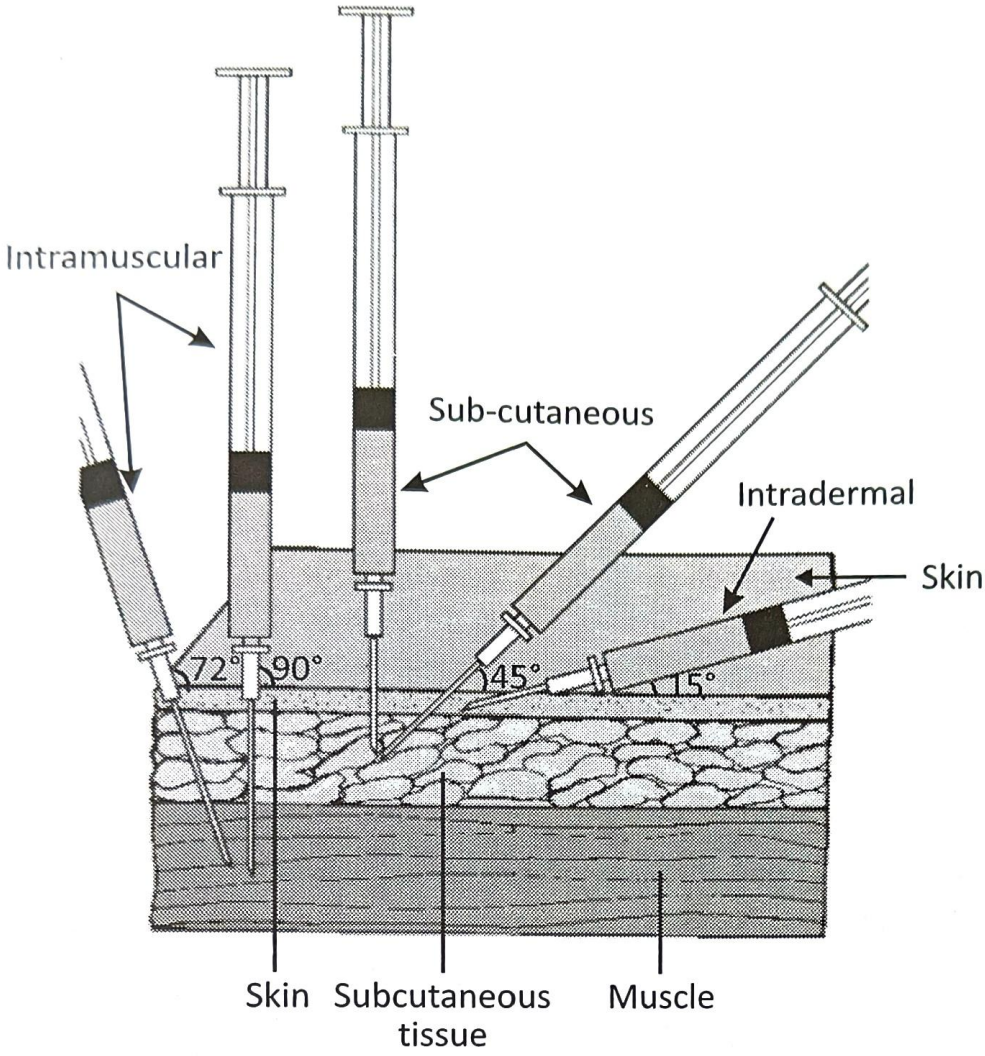


Fig. 5.35: *Parenteral dosage forms*

- **Isotonicity:** The parenterals should be isotonic with the blood plasma and body fluids.

  Free from pyrogens. The parenterals should be free from toxin and pyrogens. It should pass the test for pyrogen, as its presence causes rise in temperature after administration.
- **Free from foreign particles:** The parenterals should be free from foreign particles like dust and fibres and pass the clarity test.
- **Chemical purity:** The parenterals should be free from chemical impurities and if possible must be within limits.

Injectable Formulation

These contain sterile solutions, are prepared by dissolution of active ingredient/ substances in Water for Injection or suitable non-

aqueous base or mixture of both. The solution may contain sediments that can be redispersed by shaking the container. The suspension should be stable to deliver a homogenous dose from the container.



Fig. 5.36: ***Injection Formulation***

OPHTHALMIC DOSAGE FORMS

Ophthalmic dosage forms are preparations designed for application to the eye:

1. For the treatment of diseases
2. For symptomatic relief of symptoms
3. As an aid to surgical procedures

Eye Drops

Eye drops are the sterile solutions or suspensions or emulsions intended for instillation in the Eye.

Formulation of Eye Drop

1. **Vehicle:** Aqueous that is purified water and oily vehicles used for preparation.
2. **Preservatives:** Aqueous vehicle may support the bacterial and fungal growth, so preservatives must be added to avoid bacterial growth. Bactericides which are used, e.g.,
   - Benzalkonium Chloride
   - Phenyl Mercuric nitrite/Acetate
   - Chlorobutanol

3. **Sterilization:** Eye drops are sterilized by Autoclave sterilization at 121°C temperature for 15 min. Bacterial filters are used for heat labile drugs.
4. **Surfactant:** The order of surfactant toxicity

   Anionic > cationic > nonionic

   For example, Tween 20, 80 and polysorbate
6. **Label:** Not for injection, "For external use only"
7. **Container:** Eye drops are packed in a neutral glass container or in a suitable plastic container. Neutral glass bottle with a capacity of 4 ml to 8 ml capacity is used.

Eye Ointment

Ointments are semi-solid dosage forms for external use, usually consisting of solid or semi-solid hydrocarbon base of melting or softening point close to human body temperature. Prepared from non aqueous bases, e.g., soft paraffin, liquid paraffin and bees wax. It contains tresses of bleaching agents which may cause irritation. They may contain antimicrobial agents, antioxidants and stabilizing agent.

Eye applicaps are used which contains only one application of the eye-ointment preparation so the sterility is maintained.

Examples:

(a) Chloramphenicol ointment

(b) Tetrasycline ointment

(c) Hydrocortisone ointment.

Containers: Packed in collapsible tubes for to maintained sterility, capacity of 1 mg to 5 mg.

IMMUNOLOGICAL PRODUCTS

Immunology is the study of the immune system. The immune system is a host defence system comprising many biological structures and processes within an organism that protects us from infection and disease causes bacteria. If the immune system is not functioning, it can result in disease, such as autoimmunity, allergy and cancer.

Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine.

SERA

The clear, pale-yellow liquid that separates from the clot in the coagulation of blood. Sera does not contain bacteria or toxins. It contains anti-formed in another animal. Sera acquired immune immediately and remain a short time. Specific animal by immunization, whole blood collected in, but the serum is a nonspecific mixture obtained after centrifugation.

Antotoxic SERA Sera may be Anti-toxic, Anti-viral, Anti-bacterial. Anti-toxic sera more effective than Anti-viral, Anti-bacterial.

VACCINE

Vaccine is an antigenic substance prepared from the causative agent of a disease or a synthetic substitute, used to provide immunity against one or several diseases. It contains dead bacteria or weak bacteria or toxins. Vaccine stimulates the body to make antioxidants.

Vaccines are preparations of antigenic materials, which are administered with the objective of inducing in the recipient specific and active immunity against infectious microorganisms or toxins produced by them. They contain living or killed microorganisms, bacterial toxoids or antigenic material from the particular parts of bacterium, rickettsia or virus.

Classification of Vaccines

1. **Active Immunization:**
   - Live Attenuated Vaccines, e.g., Measles, Mumps, Rubella, Rotavirus, Tuberculosis (BCG).
   - Inactivated or whole killed vaccines, e.g., Hepatitis A and some influenza vaccines.

- Toxoids, e.g., Diphtheria, tetanus
- Cellular fractions

2. **Passive Immunization:**
   - Immunoglobulins
   - Antisera

TOXOIDS

In some bacterial infections (e.g., diphtheria, tetanus), the clinical manifestations of disease are caused not by the bacteria themselves but by the toxins they secrete. Toxoid vaccines are produced by harvesting a toxin and altering it chemically (usually with formaldehyde) to convert the toxin to a toxoid. The toxoid is then purified. Toxoid vaccines induce antibodies that neutralise the harmful exotoxins released from these bacteria.

Toxoids are inactivated toxins, are vaccines directed at the toxins produced by a pathogen. The tetanus and diphtheria toxoids have long been part of the standard childhood immunization series. They require a series of injections for full immunity, followed by boosters every 10 years.



CHAPTER

6

Pharmaceutical Plant Layout

First we have to find appropriate location of the pharmaceutical company. Once it is decided, nest step is to plan a suitable layout for the pharmaceutical plant. We need to follow basic regulatory requirements for constructing pharmaceutical plant.

According to National Agency for Food and Drug Administration (NAFDAC), your proposed layout and design should aim at minimizing the risk of errors and permit effective cleaning and maintenance in other to avoid cross-contamination, build-up of dust or dirt and in general, any adverse effect on the products.

The best way to achieve this goal is to design the layout in such a way that it follows a logical order corresponding to the steps of the operation.

FEATURES OF A GOOD PHARMACEUTICAL PLANT LAYOUT

A good pharmaceutical plant layout should possess the following characteristics:

- Adequate floor space must be available for installation and utilization of machines.

- The machines should be properly arranged to facilitate minimum material handling is necessary for low-cost processing.
- There should be smooth and continuous flow of production process at every step without any kind of delay.
- There should be arrangement of adequate safety and security features such as first aid, fire extinguisher, emergency exit.
- A good layout should allow effective supervision, coordination and control of the production processes
- There should be room for adjustment and modifications whenever the need arises.

ADVANTAGES OF A GOOD PHARMACEUTICAL PLANT LAYOUT

The advantages **of a good pharmaceutical plant layout include** but are not **limited to:**

- Optimum use of available floor space for production operations.
- Quality of product should be best in order to minimise chances of contamination.
- Efficient arrangement for receipt, transportation, storage, and delivery of raw material and finished goods.
- Low cost of material handling.
- Minimum wastage and spoilage.
- Conducive working conditions resulting in improved efficiency.
- Reduced risk of human error to increase productivity.
- Risks of occupational hazards should be minimized.
- Minimized cost and efforts in supervision of production processes.
- Provision of control and supervision operations at appropriate points.

QUALITY CONTROL

"Quality control may be defined as that industrial management technique or group of techniques by means of which products of uniform acceptable quality are manufactured. It is indeed the mechanism by which products are made to measure up to specifications determined from customer's demand and transformed into sales, engineering and manufacturing requirements. It is concerned with making things right rather than the discovering and rejecting those made wrong".

"Quality control means the recognition and removal of identifiable causes and defects, and variables from the set standards".



Fig. 6.1: *Objectives of quality control*

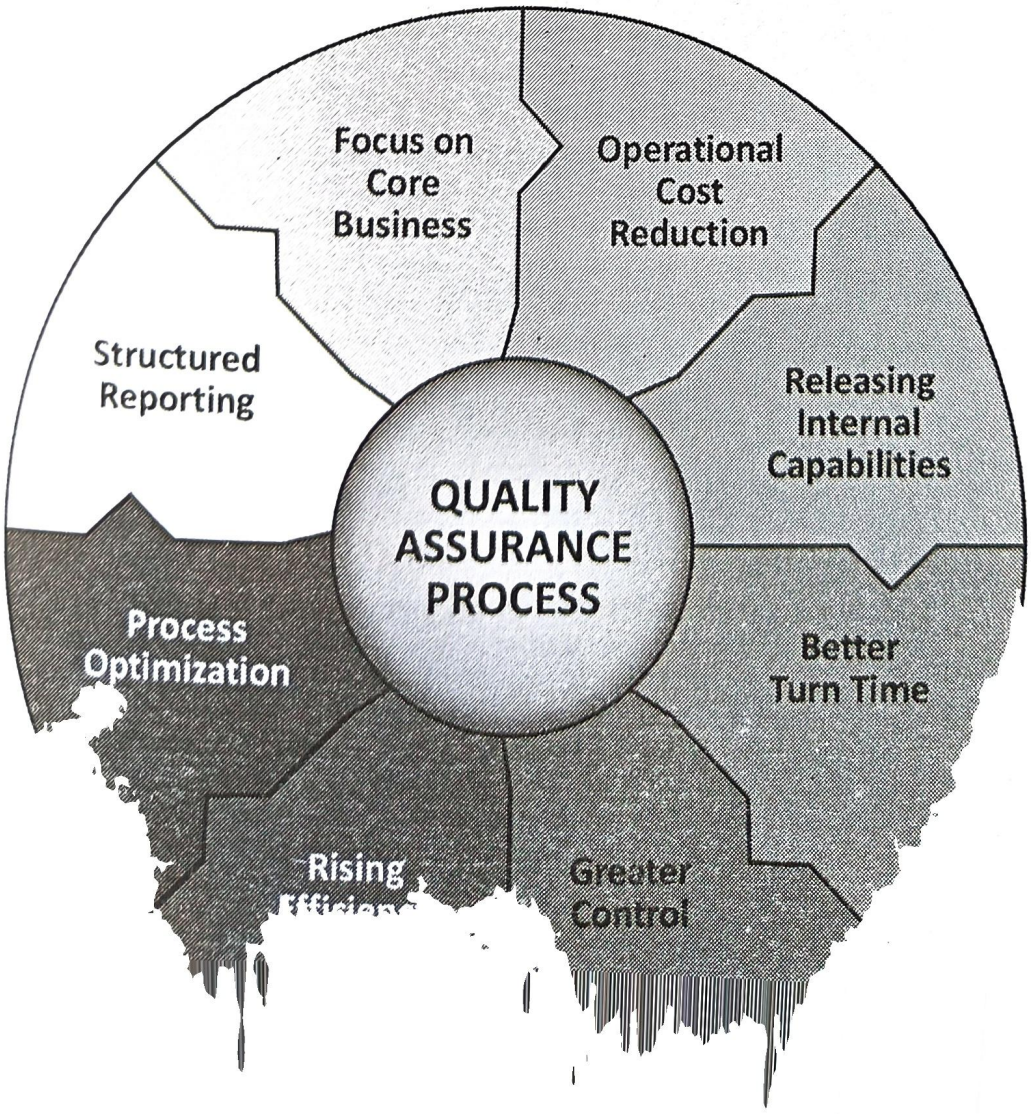
Important Objectives of Quality Control

- To establish the desired quality standards which are acceptable to the customers.
- To discover flaws or variations in the raw materials and the manufacturing processes in order to ensure smooth and uninterrupted production.

- To evaluate the methods and processes of production and suggest further improvements in their functioning.
- To study and determine the extent of quality deviation in a product during the manufacturing process.
- To analyse in detail the causes responsible for such deviation.
- To undertake such steps which are helpful in achieving the desired quality of the product.

QUALITY ASSURANCE

Quality assurance can be defined as "part of *quality management* focused on providing confidence that *quality requirements* will be fulfilled." The confidence provided by quality assurance is twofold—internally to management and externally to customers, government agencies, regulators, certifiers, and third parties. An alternate



definition is "all the planned and systematic activities implemented within the quality system that can be demonstrated to provide confidence that a product or service will fulfil requirements for quality."

Objectives of Quality Assurance

The objectives of Quality Assurance system in the pharmaceutical industry are to ensure that:

- Product design and development is by requirements of cGMP, Good Laboratory Practices (for non-clinical developmental studies), and Good Clinical Practices (for clinical studies).
- The operations and control steps in production should be very well and clearly written.
- Managerial responsibility is specified clearly in each job description.
- Adequate raw materials and packaging materials should be used for manufacturing drug products.
- Calibrations and validations must be done to ensure quality of raw materials, intermediate and finished products.
- Finished products are appropriately checked by pre-determined procedures.
- Authorized persons should certify every production batch before releasing it outside for sale and supply.
- There are satisfactory measures adopted to ensure the quality of the product is maintained throughout its shelf life.
- Procedures exist for regular self-inspection or quality audits to assess the effectiveness of the QA system.
- Any deviation should be reported and then adequately investigated by the authorized persons. The results should be recorded.

- Changes having an impact on product quality are adopted through a system that calls for approval from management.
- There should be regular evaluation of products to ensure production of consistent quality products.

CURRENT GOOD MANUFACTURING PRACTICE (CGMP)

FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.

The approval process for new and generic drug marketing applications includes a review of the manufacturer's compliance with the CGMPs. FDA assessors and investigators determine whether the firm has the necessary facilities, equipment, and ability to manufacture the drug it intends to market.

Code of Federal Regulations (CFR): FDA's portion of the *CFR* is in Title 21, which interprets the *Federal Food, Drug and Cosmetic Act* and related statutes, including the Public Health Service Act. The pharmaceutical or drug quality-related regulations appear in several parts of Title 21, including sections in parts 1-99, 200-299, 300-499, 600-799, and 800-1299.

The regulations enable a common understanding of the regulatory process by describing the requirements to be followed by drug manufacturers, applicants, and FDA.

- 21 CFR Part 314 For FDA approval to market a new drug.
- 21 CFR Part 210. Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
- 21 CFR Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals.

- 21 CFR Part 212. Current Good Manufacturing Practice for Positron Emission Tomography Drugs.
- 21 CFR Part 600. Biological Products: General.

Following are the basic GMP facility requirements that have to be followed by the pharmaceutical manufactures:



- Manufacturing process should be properly defined and controlled. All critical process should be validated to ensure the consistency of the process. Results of the validation of the process should comply with specifications.
- Any changes made in the process should be evaluated and the records of batch manufacturing should be controlled.

  Changes that can have any impact on the quality of the product must be validated.
- Procedures and any instructions should be written in clear language to understand them properly.
- Training should be provided in production, quality control and in carrying out documentation.
- At the time of production and testing of final products, the records made manually or by instruments that provide the evidence that all the steps defined in procedures and

instructions were done properly. Any deviation from the written procedure should be investigated and documented.

- Documents of manufacturing including distribution with a complete history of a batch should be retained till the expiry of the batch.
- A well-defined procedure should be examined and the root causes of the defects should be investigated and appropriate preventive action should be taken to prevent recurrence of the defect.

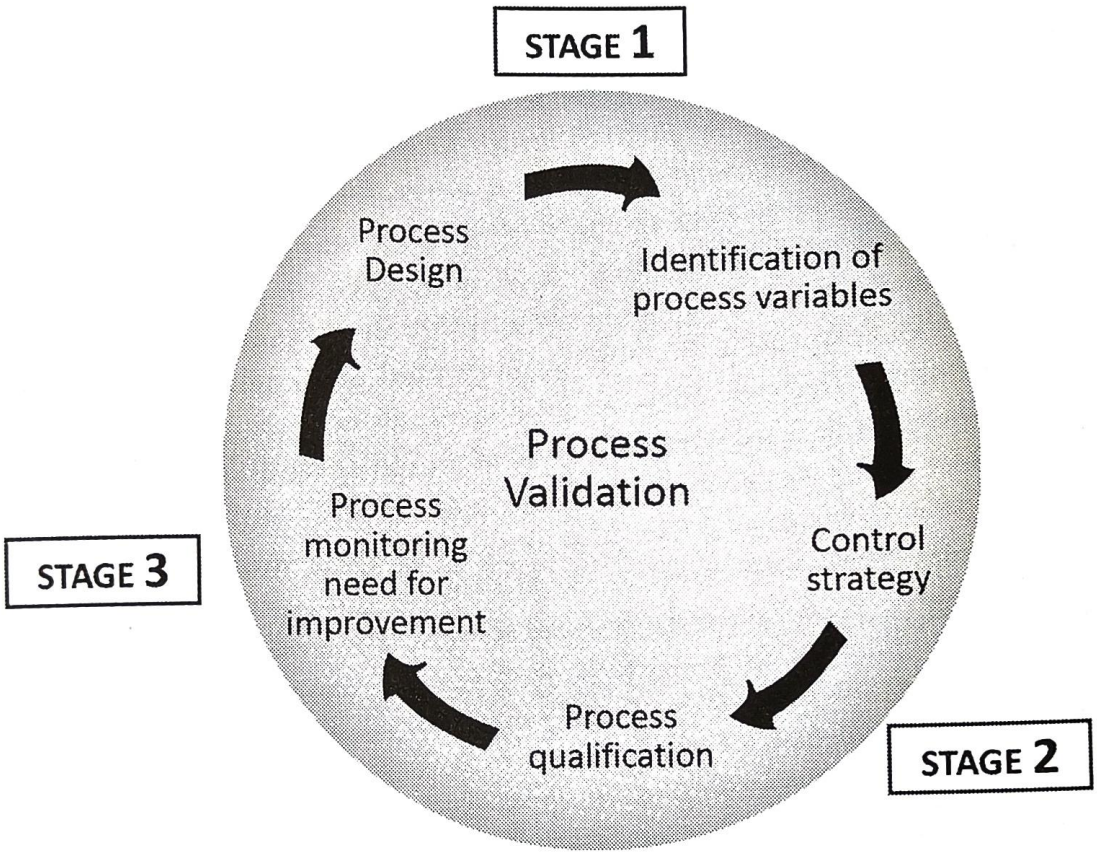
CALIBRATION

- Calibration is defined as the process of ensuring accuracy and quality of measurements produced by equipment.
- Calibration performance of any equipment is compared against a reference standard
- Calibration assures accuracy of measurements
- Instruments must be calibrated from time-to-time.
- Calibration should be done as per guidelines of SOP.

VALIDATION

- Validation is the process by which it is ensured that the quality, safety and efficacy are maintained as per acceptable criteria.
- Usually, process validation is done by a third party to make sure that the buyer is given a product that meets the specifications, requirements, and accepted standards. Documented results must be produced at the end of the process.
- Validation is a documented process that provides assurance that a service will consistently produce a product meeting its pre determined acceptable criteria.

- There are no reference standards used in validation
- Validation provides proof of consistence across all the processes; bathes of products or methods being used.
- Validation is done when the change is made in existing system or when the revalidation period has reached.
- It should be performed as per the validation protocol.





CHAPTER

7

Novel Drug Delivery System

INTRODUCTION

A novel drug delivery system can be defined as a new approach that combines innovative developments, formulations, new technologies, novel methodologies for delivering pharmaceutical compounds in the body as needed to safely achieve its desired pharmacological effect.

It may include scientific site-targeting within the body, improves drug potency, control drug release with prolonged pharmacological effect.

It involves the development of novel, better and safer drugs with long half-life and large therapeutic indices.

CLASSIFICATION OF NOVEL DRUG DELIVERY SYSTEMS

1. **Lipoidal Drug Delivery System**

   Example: Liposomes, Cubosomes, Transferosomes, Solid lipid Nanoparticles (SLN)

2. **Non-Lipoidal Drug Delivery System**

   Example: Niosomes, Bilosomes

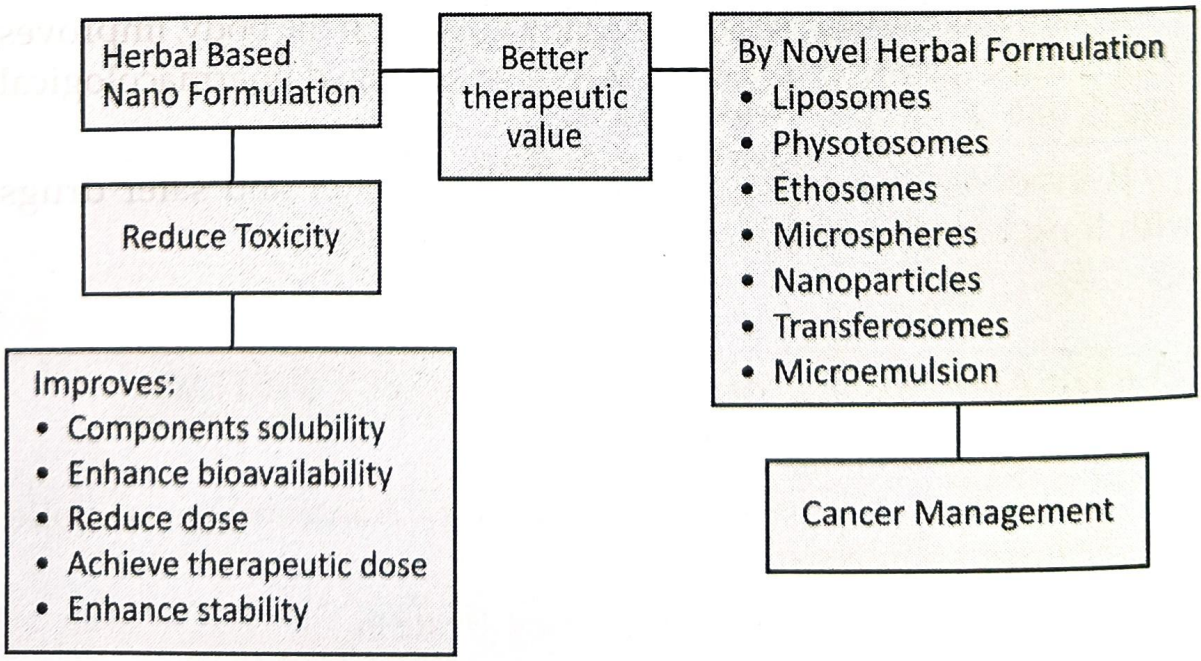
3. **Emulsified Drug Delivery System**

   Example: Nanosuspension, Nanoemulsions

4. **Polymer based Drug Delivery System**
   Example: Polymeric nanoparticles, Dendrimer nanocarriers
5. **Metal based Drug Delivery System**
   Example: Silica materials, Carbon nanomaterials
6. **Biological Drug Delivery System**
   Example: Cyclodextrins, Phytosome

ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM

- Due to maintenance in desired drug concentration, there occurs no problem in delivery.
- Accurate dosing.
- Efficiency and safety are enhanced.
- Site or target specific delivery of drug with optimum dose.
- Toxicity or side effects are minimum.
- Beneficial to patients with improved comfort and standard of living.



CHALLENGES OF NOVEL DRUG DELIVERY SYSTEM

- Major challenge is to deliver the right concentration of drug at right place on right time.
- Physical handling of liquid and dry nano particles is difficult.
- Aggregation may result due to small size and large surface area.
- Problems are evolved in delivering poorly soluble drugs.
- Novel approaches in the delivery of poorly soluble drugs.
- Overcoming bioavailability hurdles for poorly soluble clinical candidates.
- Rationale formulation design for poorly soluble compounds.
- There also occur challenges while delivery of protein drug.
- Challenges in Paediatric and geriatric drug delivery.
- Overcoming addictive nature of drugs.
- Advances in Self-Emulsifying Drug Delivery Systems (SEDDS).

