Pharmacy Exam Guide

Step I

PHARMACEUTICS-I (Physical Pharmacy-I)

-1st Edition (P1C1)

PHARMACY EXAM GUIDE

STEP I

PHARMACEUTICS-I (PHYSICAL PHARMACY-I)

1ST EDITION

(PICI)

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The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication.

DEDICATED TO OUR PARENTS

AND TEACHERS

ACKNOWLEDGEMENT

The future belongs to those who believe in the beauty of their dreams.

The preparation of this book "**Pharmacy Exam Guide**" was just a dream of some students of **Doctor of Pharmacy, University of Central Punjab**, which could not be fulfill without the help and support of our teachers and parents.

We appreciate the tireless efforts of ***Our Teachers*** who encouraged us always to achieve our endeavor, no matter, how hard they can be.

We are much indebted to ***Our Parents*** for inspiring and motivating us to achieve the great goals in life.

Chapter 1 Pharmacy Orientation

1.1 Pharmacy

The art and science of preparing and dispensing drugs and medicines is called Pharmacy

1.2 Physical Pharmacy

Physical Pharmacy is associated with an area of pharmacy that deals with the quantitative and theoretic principles of science as they apply to the practice of pharmacy.

1.3 Industrial Pharmacy

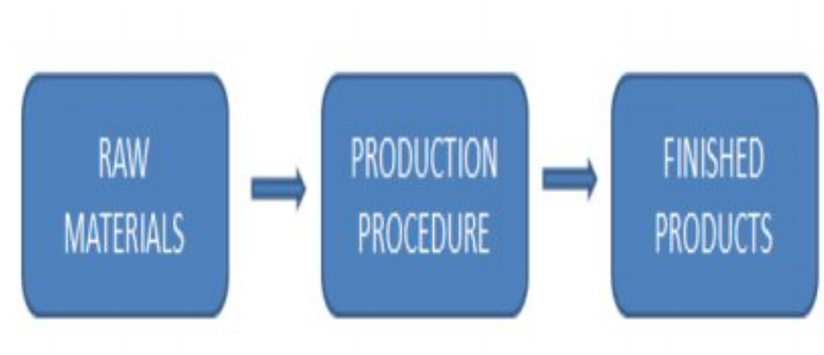
- The pharmaceutical industry is responsible for the production of drugs, ensuring that they are safe, effective and of high quality.
- Pharmacist applies all the scientific knowledge & skill during production, storage and distribution operations.
- Services provided by the pharmacist in different departments of the industry are research, medical information & monitoring products safety, regularity affairs, medical script writing, manufacturing & quality control, supplies, management and many other departments.

1.4 Research & Development (R & D)

- Formulation
- Reformulation
- Drug-excipient Compatibility Testing
- Determine proper route of administration of drug
- Product's stability including the proper packaging material
- Innovations

1.5 Production

- Conversion of raw materials to finished products.
- Supervises the operation, GMP must be observed, involved in planning production.



1.6 Quality Control

- Qualitative/quantitative checks of RM, intermediate and finished products
- Tests are performed on products
- Assay – determine the % purity of active ingredient

1.7 Drug Sales and Marketing

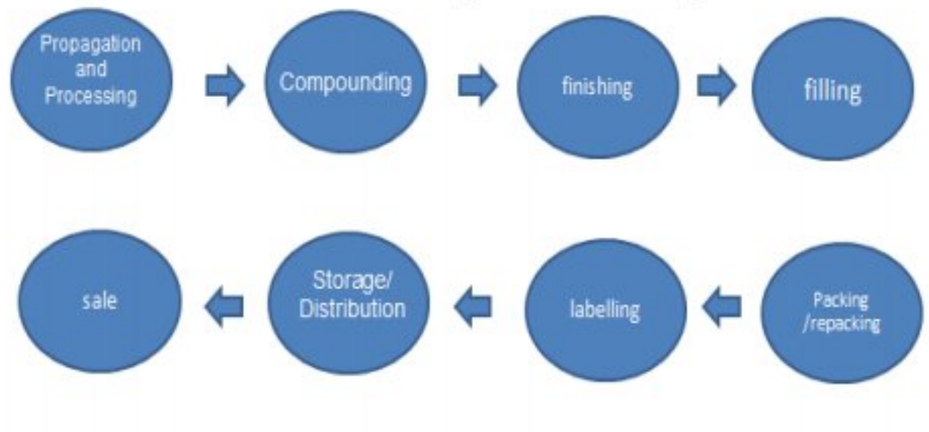
- Marketing
  1. Product managers
  2. Set policies/ targets for the sales team
- Sales
  1. Contact prescribers regarding company's products
  2. Explain products in detail

1.8 Drug Establishment

- Manufactures, imports, repacks, distributes pharmaceuticals

1.9 Drug Manufacturers

- With manufacturing facilities, engaged in production operations



1.10 Drug Trader

- Registered owner of drug product

- Procures the RM and packaging components
- Provides production monograph, QC standard, procedures
- Subcontracts a manufacturing lab

1.11 Drug Distributor/ Importer

- Imports RM, active ingredients, finished product for its own use or for wholesale distribution

1.12 Drug Distributor/ Exporter

- Exports RM, active ingredients, finished product to other countries

1.13 Drug Distributor/ Wholesale

- Procures RM, active ingredients, finished product from local establishment for local distribution on whole sale basis

1.14 Hospital Pharmacy

- A department or service in hospital under the direction of competent pharmacist
- Pharmacists work with physiscians, nurses, patient and other hospital personnel
- From which all medications are supplied to nursing units
- Part of the health care team.

1.15 Activities

- Compounding, provides stock medication, performs moderate scale manufacturing (dermatologicals, TPN)
- Responsible for Drug control system in hospital
- Responsible for the professional care of the pt regarding drug use
- Manager of hospital pharmacy
- Part of PTC, managing Drug Information Service

1.16 Hospital Pharrmacist must be knowledgeable on

- Drugs and their action
- Pharmaceutical Manufacturing Program
- Control procedure regarding
  - QC (prep of TPN/ admixtures)
  - Drug distribution through out the hospital
- Research activities both medical and pharmaceutical
- Teaching Techniques (inservice training programs)
- Pharmacy administration in hospital

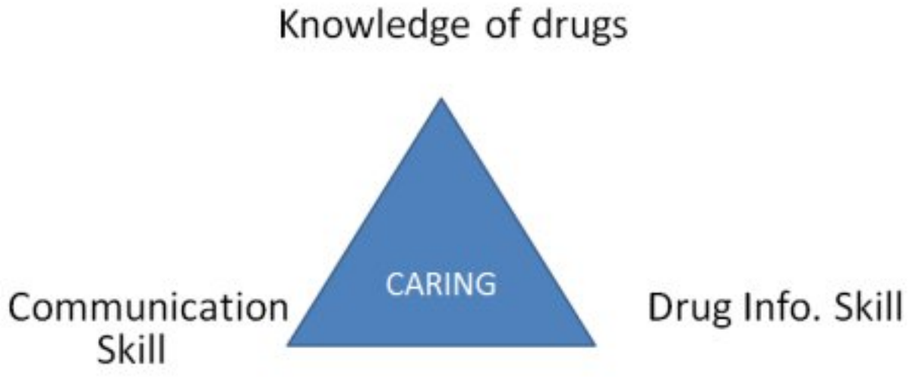
1.17 Clinical Pharmacy

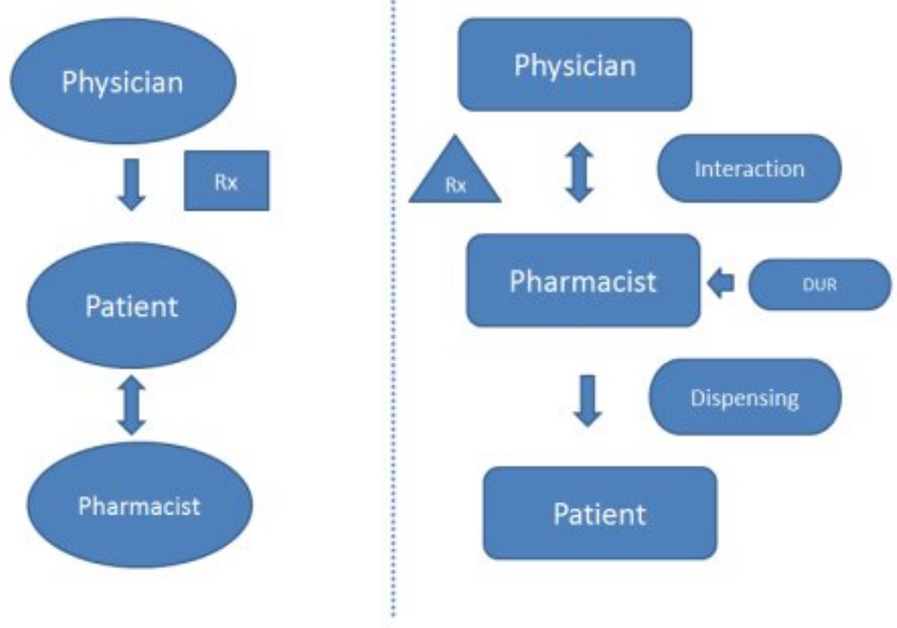
- Recent innovation in Pharmacy Practice (1970)
- Patient –oriented profession

1.18 Activities

- Makes rounds with doctor, maintains patient histories, monitors drug therapy, advises patient on drug use, side effects, and drug interactions, ADR's
- Direct pt involvement (conducting admissions, discharge, interviews)
- Drug Utilization Reviews, education to improve drug's use
- US : Doctors write Rx; pharmacists prescribe the medicine
- Important that clinical Pharmacist is familiar with different lab tests and interpretation of results
- Associated with decreased hospital mortality rates, decreased drug cost, decreased length of stay of patient
- Pharmaceutical care – optimal use of medications to achieve specific outcomes that improve a patient's quality of life

1.19 Patient-oriented pharmacist considers:





1.20 Barriers to Clinical pharmacy practice

- Lack of interest of top mgnagement
- Higher costs
- Other professionals are unhappy
- Lack of incentive for pharmacist
- Lack of training/ specializing areas to develop expertise

1.21 Drug Wholesale

1.21.1.1 Drug Wholesaling

- Important part of distributive scheme, provides mechanism to obtain various products manufactured by different labs from single agency
- Less hazards in stock handling, record keeping and bill paying for the retailer

1.22 Pharmacy Education

- Most important segment of pharmacy
- Represented by colleges of pharmacy
- Responsible for the nature and quality of pharmaceutical education
- Knowledge of diffrent physical, biological sciences qualifies a pharmacist to teach
- Masteral/ Doctoral degree

1.23 Research & Development

- Discovery/ isolation of new drugs for treating diseases
- The development of better drugs through chemical modification

Examples:

Amoxicillin	→	Co-amoxiclav
Diuretics	→	K sparing diuretics

1.24 Pharmaceutical Journalism

- Gifted with writing and editing talents
- Magazines, brochures, newsletter about different drugs for marketing purposes

1.25 Management

1.26 Oraganization Management

- Pharmacist can work as manager in differnent departments of Industry, Hospital, Pharmacy and many other Govt. or Private institutions.
- Pharmacists are working as officers of diffrent recognized associations
- Pharmacist can organize different workshops and seminars to keep pharmacists abreast with latest information in drug treatment and technology

1.27 Government Services

1.28 Pharmacist in Government Service

- Officer in Army, Navy, Air force
- Hospital pharmacist
- Ministry of Health (licensing , inspection, registration)
- Drug Regulatory Authority and drug registration
- Drug testing laboratory (analyst, microbiologist)
- Consultant (mental health, family planning, pollution, poisons, self-medication, immunization)

1.29 Forensic Pharmacy

- It is related to the pharmacist's skills used to help the medico legal problems such as DNA test, Semen test or legal emergencies.

1.30 Nuclear Pharmacy

- Nuclear pharmacy focuses on preparing radioactive isotopes for diagnostic tests & for treating certain diseases.
- Nuclear pharmacists undergo additional training specifically to handle the radioactive isotopes, unlike in community & hospital pharmacies.

1.31

1.32 Medical Communication

1.33 Medical Communications

- Newest/ rapidly developing field
- Computer handling of medical data

1.34 Community/ Retail Pharmacy

History

Community pharmacy was also named as:

- Apothecary
- Druggist
- Chemist
- Pharmaceutical Chemist
- Retail Pharmacist
- Community Pharmacist (1993)

1.35 Community Pharmacy

- Community pharmacy symbolizes the adoption of a new degree of professionalism by street pharmacist.
- This will arouse community expectations which demand care, commitment and excellence.
- It is not just a title acquired by passing the exam; it demands dedication and highest degree of professionalism.

1.36 Introduction

- Community pharmacist is the professional who would be in direct access to the public and whose duties are widely sought after by the public and patients.
- A community/retail pharmacist works according to legal and ethical guidelines to ensure the correct and safe supply of medical products to the general public
- As we are the person who will be in direct contact with the public we have to play an important role in decreasing the mortality and morbidity in the public.

1.37 Type of Pharmacy

1.37.1.1 Chain

E.g. GUARDIAN, WATSON, CLINIX, FAZAL DIN & SONS

1.37.1.2 Independent

E.g. Green Pharmacy, Decent Pharmacy etc.

1.38 Nature of Business

1.38.1.1 Retail

- sell direct to end user/customer
- Pharmacy license from Ministry of Health

1.39 Wholesale

- supply to other retailers, General Practitioners (Clinics), Hospitals etc
- Wholesale License from Ministry of Health

1.40 Layout of the Community Pharmacy

- Prescription Counter & Consulting Area
- Front Area – e.g. OTC Area
- Controlled Substances
- Store
- Refrigeration
- Computer systems – Point-Of-Sale, Inventory, Accounting etc
- Equipment-display
- Purchasing & Inventory Control

1.41 Prescription Counter & Consulting Area

- The prescription processing area → Pharmacist use to prepare prescriptions
- Consultation area → Strictly for the pharmacist's use

1.42 Front Area

- OTC drugs like Panadol, Zentel.
- Cosmetics, toiletries, rehabilitation products & other merchandises
- Vitamins and supplements

1.43 Controlled Substances

- Kept in a locked storage cabinet
  - Under supervision of pharmacist
- Psychotropic Drugs
  - Require prescriptions and must record
  - Repeated checking of the products, labeling, packaging
- Cough Mixture
  - Contain Dextromethorphan

1.44 Store/ Storage

- To keep the excess stocks
- General store or Drug store (must lock)
- Dry, cool place

1.45 Refrigeration

A refrigerator to store drugs:

- Required to be kept at temp between 2 & 8°C
- Exclusively for medications
- No food or beverages

1.46 Computer Systems

- Familiar with computer hardware & software
- Hardware
  - Monitor, CPU, keyboard, mouse, scanner, modem, printer
- Software
  - Point of Sales, Accounting, Inventory e.g. UNIX
- Most chain pharmacies are linked together
  - Facilitate the sharing of information between pharmacies

1.47 Purchasing & Inventory Control

- Must complete a purchase order (PO)
  - Product name
  - Amount & price
- Order transmitted directly to the manufacturer
- During receiving → carefully check the product against the PO
- Damaged products must be reported without delay & returned to the manufacturers
- Must check all products for expiration dates

1.48 Community Pharmacist Must Show:

- Good communication skills
  - Be able to listen carefully to what patients says
  - Be able to explain complex and sometimes sensitive information to the general public & other healthcare professionals
- Concern for the welfare of the general public
- An understanding of business principles;
- A professional and confident manner;
- The ability to inspire the trust of others;
- A willingness to take on a high level of responsibility.

1.49 Roles of Community Pharmacist

Community Pharmacist assumes 3 roles:

1.49.1.1 Retailer

Makes goods and services available

1.49.1.2 Manager

Uses limited resources efficiently and effectively

1.49.1.3 Professional

Provide valued services through trust, commitment and competence

- ❖ *Pharmacies are required to have a pharmacist on duty all the time.*
- ❖ *Most pharmacies have experienced support staff who work under the personal supervision of the pharmacist.*
- ❖ *Therefore, community pharmacists, by far the largest segment of the profession, require scientific, administrative, supervisory, counseling and pharmaceutical skills of a very high standard*

- Dispensing prescription medicines to the public on a prescription or without prescription– check dosage, ensure the medicine are correct and safe and label it
- Liaising with doctors about prescriptions;
- supervising the preparation of any medicines (not all are supplied as ready made-up by the manufacturer);
- keeping a register of controlled drugs for legal and stock control purposes;

Drugs	Example:
Antihypertensive, anticholesterol	
Sleeping pills, antidepressant, narcotics	
Cough and cold preparations	
Cough syrup containing Dextromethorphan	

- Sexually transmitted diseases
- Health promotion
- Environmental hazards

- selling over-the-counter medicines

- Counseling and advising the public on the treatment of minor ailments and any adverse side-effects of medicines or potential interactions with other medicines/ treatments;
  - Providing specialist health check services, such as monitoring blood pressure and cholesterol levels, diabetes screening and pregnancy testing.
  - Preparing dosette and cassette boxes, usually or the elderly but also for those with memory/ learning difficulties, where tablets are placed in compartments for specified days of the week;
  - Overseeing the ordering and safe storage of medical products and, in some cases, arranging the delivery of prescription medicines to patients;
  - Keeping up-to-date with current pharmacy practice, new drugs and their uses.
  - maintaining computerized records;
  - Managing, supervising and training pharmacy support staff;
  - Budgeting and financial management;
  - Promoting sales and developing the business.
  - Selling healthcare and other products, such as toiletries, cosmetics and rehabilitations product e.g. wheel chair.

1.50 Other Important Roles

- Rationale use of drugs
- Nutritional counseling
- Alcohol, drug abuse and smoking cessation
- Individualization of drug therapy
- Family planning
- Poisoning prevention
- Control of communicable diseases
- Pregnancy and infant care

Chapter 2 HISTORY OF PHARMACY

2.1 BEFORE THE DAWN OF HISTORY

- From beginnings as remote and simple as these came the proud profession of pharmacy. It's development parallels that of man.
- Among the several characteristics unique to Homo Sapiens is our propensity to treat ailments, physical and mental with medicines.
- Ancient man learned from instinct, from observation of birds and beasts. Cool water, a leaf, dirt or mud was his first soothing application.
- By trial, he learned which served him best. Eventually he applied his knowledge for the benefit of others.

2.2 PRE-HISTORIC PHARMACY

- Since humanities earliest past, Pharmacy has been a part of everyday life. Some of mankind's oldest settlements such as Shanidar support the contention that pre historic people gathered plants for medicinal purposes. By trial and error, the knowledge of the healing properties of certain natural substances grew.
- When healers at shanidar or other prehistoric settlements approached disease, they placed it within the context of their general understanding of the world around them, which was alive with good and evil spirits. The magical portions for curing were part of the duty of the Shaman (usually in-charge of all or most things supernatural in tribe)
- The Shaman diagnosed and treated most serious illnesses. He compounded the remedies needed to keep away the influences of evil spells or spirits.

2.3 ANTIQUITY (ANCIENT TIMES)

2.4 EGYPTIAN TIMES

When organized settlements aroused in the great fertile valley of Nile and the Indus River, changes occurred that gradually influenced the concepts of disease and healing.

2.5 BABYLONIANS

- For the Babylonians, medical care was provided by two classes of practioners:
  - The asipu (magical healer)
  - The asu (empirical healer)
- The asipu relied more heavily on spells and magical stones far more than plant materials.
- The asu drew upon a large collection of drugs and manipulated them into several dosage forms that are still basic today such as suppositories, pills and ointments.
- The asipu and asu were not in direct competition and sometimes cooperated on difficult cases.

2.6 DAYS OF PAPYRUS EBERS

- Though Egyptian medicine dates from about 2900 B.C, best known and most important Pharmaceutical record is the "Papyrus Ebers" (1600 B.C), a collection of 800 prescriptions mentioning 700 drugs. The drugs are chiefly botanical although mineral and animal drugs are also noted.
- Such botanical substances as acacia, castor bean and fennel are mentioned along with apparent references to such minerals as iron oxide, sodium carbonate, sodium chloride and sulfur.

2.7 GREEK CIVILIZATION

During the millennium that followed the roots of modern medical profession in the west arouse from Greek civilization.

2.8 ASKLEPIOUS (GOD OF HEALING)

- Beginning in the 7th century BC, the wise and kind Asklepios gradually superseded Apollo as the greatest of the healing gods.
- At the touch of his hands or of the tongue of his sacred serpent, miraculous things happened.
- The staff of Asklepios entwined by a Sacred serpent gradually emerged as the official symbol of medicine around the world.
- On the right hand of Asklepious stood Hygeia, one of his daughter.
- Her arm entwined by a serpent and holding a bowl thought to have contained a healing poison.
- And in the earliest records one finds a similar mixed concept of drug or Pharmakon , a Greek word that meant "magic spells'' or "poison".

2.9 HIPPOCRATES

- From another period in Greek history the greatest name

- That is still with us today is that of Physician Hippocrates known as the "father of medicine".
- He is one of the most important name in the development of Pharmacy as a profession based on scientific knowledge rather than a mixture of medicine and spiritual acts.
- During this period the word Pharmakon came to mean "a purifying remedy".
- He mentioned around 200-400 drugs as well as methods of carrying out various Pharmaceutical processes.

2.10 Dioscorides

- He was a Greek Physician and botanist (first century A.D). He was the first scientist to deal botany as an applied science of Pharmacy .
- His work "De Materia Medica", is considered a milestone in the development of Pharmaceutical botany and in the study of naturally occurring medicinal materials. This area of study is today known as "Pharmacognosy"
- He explained methods of preparing crude drugs from opium and many other botanical drugs. He developed the art of identification, collection, purification and proper storage of botanical drugs.

2.11 Claudius Galen

- He was a renowned Greek Pharmacist and Physician. He practiced and taught both medicine and pharmacy in Rome, his Principles of Preparing and compounding medicines ruled in the western world for 1500 years.
- He aimed to create a perfect system of Physiology, Pathology and treatment of illness.
- He wrote 500 books on medicine including numerous drugs of natural origin, formulae and methods of compounding.
- It was his tremendous work in the field of crude natural origin drugs that still today his name is associated with that class of pharmaceuticals compounded by mechanical means –"Galenical Preparations".
- The most famous of his formulas is one for a cold cream called Galen's cerate, essentially similar to that known today.

2.12 Middle Ages

2.13 Saints Cosmas and Damian

- Twinship of health professions, Pharmacy and medicine is nowhere more strikingly portrayed than by
  - Damian, the apothecary and
  - Cosmas, the Physician
- They were the twin brothers of Arabian descent .Their twin careers were cut short in the year 303 by martyrdom.
- They were the pattern saints of Pharmacy and medicine and many miracles are attributed to them

2.14 Muslim Era (Golden Era of Pharmaceutical Progress)

As Western Europe struggled, a new civilization arouse among those who followed the teachings of Muhammad (P.B.U.H).The formerly nomadic people who united into the nations of Islam conquered huge areas of middle east and Africa and eventually expanding into Spain and eastern Europe.

2.14.1.1 Abbasid Caliphate

In Baghdad, the first Pharmacy was established in 754 under the Abbasid caliphate during the Islamic golden age.

The clear-cut separation of the two professions, physicians and Pharmacist was done in 800 A.D in Abbasid caliphate.

2.14.1.2 Yahanna Bin Masawayh

He was one of the contributors to Arabic Pharmacy. He Wrote a book "Ibn-e-Masawayh" which includes 30 aromatics, their Physical properties, method of detecting adulteration (spoil) and Pharmacological effects.

Ibn-e-Masawayh recommended saffron for liver and stomach ailments.

2.14.1.3 Abu- Hassan Ali Bin Sahl Rabban at Tabari

He wrote a famous book " paradise of wisdom". It contains discussions on the nature of man, cosmology (study of stars), embryology, diet and diseases.

2.14.1.4 Sabur Bin Sahl

The first medical formulary to be written in Arabic is "al-Aqrabadin". In it, he gave medical recipes stating the methods and techniques of compounding these remedies, their Pharmacological actions, the dosages and the means of administration.

2.14.1.5 Abu bakr Muhammad Ar Razi

He was one of the greatest Physician in Islam But at the same time he was supporter of the art of Al-Chemy.

To a great extent, he influenced the development of Pharmacy and medical therapy throughout the middle ages. He wrote two books named Ar-Asrar and Sirr Al Asrar.

2.14.1.6 Al Ghafiqi

He was the highly respected Physician in cordova (muslim spain) an that he was also interested in Pharmacy as well

2.14.1.7 Abu Al Qasim Al Zahrawi

He was Pioneer in the preparation of medicines by sublimation and distillation. Also he worked on the extraction or urinary bladder stones.

2.14.1.8 Ibn-e-Sina

Among the brilliant contributors to the sciences of Pharmacy and Medicine during the Arabian era was one genius who seems to stand for his time - the Persian, Ibn-e-Sina (about 980-1037 A.D.), called Avicenna by the Western world. Pharmacist, poet, physician, philosopher and diplomat. Avicenna was an intellectual giant, a favorite of Persian princes and rulers.

He wrote in Arabic. He wrote the famous book " Kitab Al Shifa (the book of healing). He also described 700 preparations, their properties, mode of action and their indications.

2.14.1.9 Al –Beruni

He wrote one of the most valuable Islamic works entitled "Kitab-ul-Saydalah" (the book of drugs) where he gave detailed knowledge of the properties of drugs and outlined the role of Pharmacy and the functions and duties of the Pharmacist.

He was known as father of Arabic Pharmacy.

2.15 Modern Age & Early Research

Upon this time, Pharmacy remained a function of medicine. But with increasing variety and complexity of compounding, forced physicians to quit pharmacy and focus more on healing.

2.16 Frederick-II - Separation of Pharmacy and Medicine

In European countries exposed to Arabian Influence, public pharmacies began to
Appear in the 17th century.
However, it was not until about 1240 A.D.
That, in southern Italy, Pharmacy was separated from Medicine.

Frederick II, was Emperor of Germany. At his palace, he presented subject Pharmacists with the first European edict completely separating their responsibilities from those of Medicine, and prescribing regulations for their professional practice

2.17 Paracelsus - Bornbastus Von Hohenheim (1493-1541)

Perhaps no person in history exercised such a revolutionary influence on Pharmacy and
Medicine as did Aureolus Theophrastus. Bornbastus Von Hohenheim (1493-1541),

A Swiss Physician and chemist who called himself Paracelsus. He influenced the transformation of Pharmacy from a profession based primarily on botanical science to one based on chemical science.

2.18 Swede Karl Wilhelm Scheele

He was a Swedish Pharmacist and extracted several plant acids like lactic acid , citric acid ,tartaric acid, benzoic acid etc

2.19 Edward Jenner

Remarkable advance in medicine and Pharmacy took place in the year 1796 when edward jenner performed the first vaccination on a human patient

2.20 Friedrick serturner

He was a german Pharmacist and isolated Morphine from opium

2.21 Joseph Pelletier & Joseph Caventou

They were French and isolated several alkaloids like strychnine and brucine from nux vomica and quinine and cinchonine from cinchona. Pelletier together with Pierre Robiquet isolated caffeine and Robiquet independently separated codeine from opium.

Chapter 3 Official Books of Pharmacy

3.1 Origin and Development of Pharmacopoeias

The word Pharmacopoeia is derived from Greek, Pharmakon and poieo. It indicates a book issued by a recognized body or authority containing a list of drugs and formulas for medicinal preparations, together with description of these substances and standards to which they must conform.

3.2 Origin

Prior to Pharmacopoeias apothecary have to look for guidance and knowledge to books written by individuals who have achieved fame in medicines.
These books may be divided into 2 classes:

- The Herbal
- The Formularies

3.3 The Herbal

- ✓ These books contain information about medicinal plants, their properties and recipes for preparing remedies. The most important book was "The Meteria Medica" by Dioscorides. It contains more than 600 plants and herbs having medicinal value and also animal and mineral substances.
- ✓ This book remained authority for more than 1500 years. Its complete edition was printed in 1529.
- ✓ Another important name is "Pliny the Elder" 23-79 A.D. reported 1000 plants of medicinal value.

3.4 The Formularies

- ✓ These were the more authoritative books for physicians and consists chiefly of recipes and list of medicinal substances and were variously styled as "Compendium, Dispensatorium or Antidotarium"
- ✓ These books based on ancient Greek, Roman and Arabian writers.
- ✓ The most widely known book was Antidotarium of Nicholas describing the preparation of confectioneries, lozenges, ointments, pills, syrups and many other classes of preparations and also prescribed apothecaries weight and measure system i.e., the grain and drachms still employed in present day pharmacy.

3.5 Development of Pharmacopoeia

- ✓ The development of Pharmacopoeia must be credited to the discovery of printing techniques in the15th century. It was felt that there should be some authoritative formulary, at least for some particular community.
- ✓ 1st book published by College of Florence in1498. It contains the important work of Nicholas.
- ✓ The city of Nuremberg was 1st community to process a Pharmacopoeia who was legally binding on the apothecaries of that city in 1529. They adopted 100 year old book "Luminare Majus" published in 1406.
- ✓ In 1546 it was replaced by Dispensatorium of Valerius Cordus.
- ✓ This action of Nuremberg stimulated others to publish their own pharmacopoeias.
- ✓ In 16th century, pharmacopoeias of London, Augsburg, Antwerp, Lyons, Basle, Valencia, Cologne, Paris and Amsterdam emerged.

3.6 London Pharmacopoeia

- ✓ It was published in 1618 by College of Physicians and contains more than 2000 drugs and preparations. Mostly old work was gathered. It remained English pharmacopoeia for 3 centuries.
- ✓ Numerous editions were published.

3.7 Fusion of National Pharmacopoeias

- ✓ Medical Act of 1858 ordered the fusion of London, Edinburgh and Dublin pharmacopoeias to form British Pharmacopoeia.
- ✓ The General Council of Medical Education and Registration of UK was given exclusive rights of publishing, printing and selling the book.
- ✓ 1st edition with the collaboration of Pharmaceutical Society appeared in 1864. Subsequent editions in 1867, 1885, 1898, 1914 and sixth in 1932.
- ✓ A pharmacopoeia commission was established in 1914 to revive and make amendments in official books.

3.8 Formularies

- ✓ These are supplementary to Pharmacopoeias.

- ✓ The scope of Pharmacopoeia is mainly restricted to drugs and preparations which at the time of publication are of sufficient importance.
- ✓ Information regarding drugs and preparations which are widely used but are not official and also the recently introduced substances which have not yet proved sufficiently important for inclusion in pharmacopoeia must be sought elsewhere.
- ✓ Various books of this kind appeared from time to time, but the most important were.
  a) British Pharmaceutical Codex (B.P.C.)
  b) Extra Pharmacopoeia (E.P.)
- ✓ B.P.C. is published by Pharmaceutical Society. 1st edition was published in 1907, 2nd in 1911 than in 1915, 1922 and 1923.
- ✓ E.P. was published in 1883 by W.. Martindale and W. W. Westcott. In 1933 after the death of W. H. Martindale (son of W. Martindale) the rights of this book were purchased by society.

3.9 USP & NF

- ✓ Pharmacopoeia and Formulary are published by some recognized authority and this is in most cases is Government.
- ✓ But in US both the National Pharmacopoeia and NF have been published by private organizations.
- ✓ In US legal recognition of drug standard occurred in 1906, when First Food and Drug Act was enacted.
- ✓ Under this act both the USP (originally published in 1820 by the United States Pharmacopoeial Convention) and NF (established in 1888 by American Pharmaceutical Association) received full recognition by US Govt.
- ✓ Both USP and NF were published by private initiatives but have had the impact of Law.
- ✓ In 1974 United States Pharmacopoeial Convention purchased the NF from American Pharmaceutical Association.
- ✓ USP was originally published and revived by Physicians, the NF always remained a project of Pharmacists.
- ✓ USP published revisions while NF publishes editions every 5th year.
- ✓ Both USP AND NF cooperated to fulfill the common objective i.e., to provide standards which serve as the basic measures of strength, quality, purity, packaging and labeling of drugs to ensure that the American Public receives pharmaceutical products of uniform and consistent quality and strength.

3.10 International Pharmacopoeia

- ✓ In 1951, WHO published the Pharmacopoeia Internationalis, a compilation in two volumes (volume 2 in 1955).
- ✓ It designed a collection of standards which could serve as reference for the establishment of international standards.
- ✓ Its 2nd edition was published in 1963 and 3rd edition comprising 5 volumes in 1979.

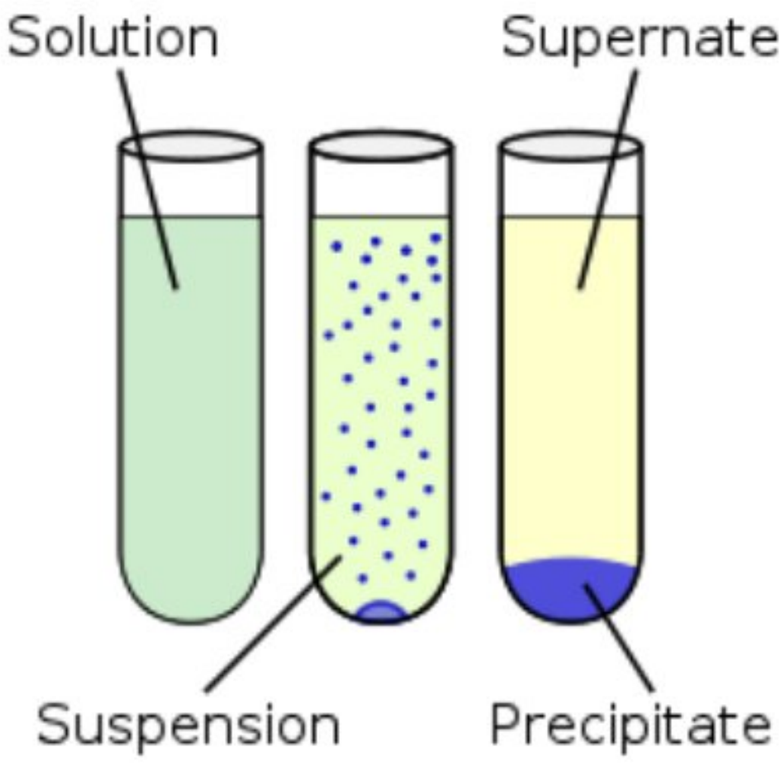
3.11 European Pharmacopoeia

- ✓ In 1964 a council of Europe was established and included **7** countries, whose council of ministers adopted a resolution to establish an European Pharmacopoeia.
- ✓ The 7 countries were Belgium, France, Germany, Italy, Luxemburg, the Netherlands and UK. Latter on Switzerland was accepted as 8th member.
- ✓ These countries signed a document by which this Pharmacopoeia was made legal and binding for all.
  1st volume published in 1969
  2nd volume in 1971 and
  3rd volume in 1975

Chapter 4 PRECIPITATION

4.1 PRECIPITATION

- ✓ It is a process of separating solid particles from a previously clear liquid i.e., a solution, by physical or chemical changes.
- ✓ Precipitates can form when two soluble salts react in solution to form one or more insoluble products.
- ✓ Precipitates can also form when the temperature of a solution is lowered. The lower temperature reduces the solubility of a salt, resulting in its precipitation as a solid.
- ✓ The separated solid is called "Precipitate", the cause of precipitation is called the "precipitant" and liquid which remains in the vessel above the precipitate is called the "Supernatant liquid".



4.2 APPLICATIONS

It has many applications:

4.3 OBTAINING SOLID SUBSTANCES

It provides a convenient method of obtaining solid substances in the form of fine particles e.g., precipitate of $CaCO_3$ (precipitated chalk).

4.4 PURIFICATION OF SOLIDS

One of the most important uses of precipitation is in the purification of solids. Process as applied to purification is termed recrystallization. The impure solid is dissolved in a suitable solvent at elevated temperature. On cooling the bulk of the impurities remain solubilized while the purified solid product precipitates.

4.5 CLARIFICATION OF LIQUIDS THROUGH PRECIPITATION

In many cases, part of the matter to be removed in order to ensure a clear product is formed by precipitation as a result of physical or chemical change. The important methods are:

i) Precipitate due to change of solvent
ii) Precipitate of proteins
iii) Precipitate by proteins (Adsorption)

4.5.1.1 PRECIPITATION DUE TO CHANGE OF SOLVENTS

Whenever precipitate by change of solvent is done, sufficient time of 12-24 hours is given for solid particles to settle down and then separated by filtration. Tinctures are usually clarified in this way, alternate solvent be water and alcohol.

4.5.1.2 PRECIPITATION OF PROTEINS

The conversion of proteins into an insoluble form and then removal by filtration may be considered as a preliminary to clarification. For example, Liquid extract of Liquorices, Pituitary Extract, Purified Ox bile.

4.5.1.3 PRECIPITATION BY PROTEINS (ADSORPTION)

It has a limited application in Pharmacy. It is used to remove tannins from wine and the proteins being used are gelatin or isinglass. These substances swell in cold water but are insoluble, and form with tannins, an adsorption compound which is also insoluble.

4.6 PURIFICATION OF ORGANIC COMPOUNDS

The organic compounds derived from natural sources are seldom pure. They are often mixed with other substances which also occur with them. Similarly the compounds prepared in the laboratory are generally mixed with the products which may also have been formed during the course of reaction, in order to study its properties and to determine its formula. A given substance must be free of all impurities and obtained in a state of purity. The methods employed for purification depend on the nature of the organic compound and the impurities present in it.

The process commonly used for purification of organic substances is;

i) Precipitation/ Crystallization

ii) Sublimation
iii) Distillation
iv) Fractional distillation
v) Steam distillation
vi) Distillation under reduced pressure

4.7 Precipitation Reactions Can Be Used For Making Pigments

4.8 Removing Salts from Water in Water Treatment

4.9 In Classical Qualitative Inorganic Analysis

4.10 Method of Precipitation

- Precipitation is usually carried out in resistant-glass beakers, and the solution of the precipitant is added slowly and with efficient stirring of the suitably diluted solution. The addition must always be made without splashing; this is best achieved by allowing the solution of the reagent to flow down the side of the beaker. Only a moderate excess of reagents are added to complete the precipitation.
- As a general rule, precipitations are not filtered off immediately after they have been formed. In most cases it is allowed to stand for 12-24 hours so that particles achieve the size which can be easily filtered.

4.11 Filtration

- Filtration is the process of separating the precipitate from the mother liquor, the object is to get the precipitate and the filtering medium quantitatively free from the solution. The system employed for filtration are;
  i) Filter paper
  ii) Porous filtered plates made of resistant glass, silica or porcelain.
- The choice of filtering media depends upon the nature of precipitate and cost.

4.12 Washing Precipitate

- Most precipitates are produced in the presence of one or more soluble compounds. Since the soluble compounds are frequently not volatile at the drying temperature of the precipitate, so it is necessary to wash the precipitate to remove impurities as completely as possible.
- Washing is done with minimum portion of liquid. It is better to wash with a number of small portions of the washing liquid, which are well drained between each washing.
- Following factors must be kept in mind before washing;
  i) It should have no solvent action on precipitate.
  ii) It should not disperse the precipitate.
  iii) It should not form volatile or insoluble product with precipitate.
  iv) It should be easily volatile at the drying temperature of precipitate.
- In general pure water should not be used unless it is certain that it will not dissolve precipitate. To overcome this problem ion is usually added. For this Ammonium Salts are usually selected.

4.13 Drying and Igniting Precipitate

- After a precipitate has been filtered and washed, it must be brought to a constant composition before it can be weighed. The further drying and igniting the precipitate will depend on the nature of the precipitate, and the nature of the filtering medium. The choice of drying or igniting depends on the temperature to which the precipitate is heated.
- In general drying is applied when temperature is below 250°C.
  (For maximum temperature ovens and ignition is applied up to a temperature of 1200°C.)

Chapter 5 CRYSTALLIZATION

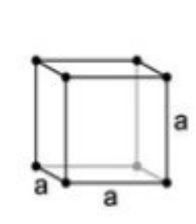
5.1 CRYSTALLIZATION

- ✓ The process of crystallization is reversal of dissolution changes, in which solid melts.
- ✓ A typical crystal has regular geometric form with sharp straight edges and plane surfaces. When fractured it breaks into pieces with plane faces meeting in sharp edges.
- ✓ This crystalline nature of powders and metals is revealed only by microscopic examination.
- ✓ The regular external form of crystal is formed by a regular assembly of atoms or ions arranged in a space lattice having a uniform geometrical form.
- ✓ The arrangement of these units is the most important characteristic of a crystal, even if external form is destroyed by powdering, the internal structure remains.
- ✓ Crystals may vary in size and shapes owing to the conditions under which they are formed.

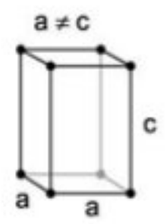
5.2 CLASSIFICATION

For classification all crystals are referred to 7 groups.

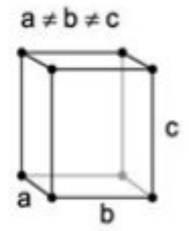
i) Cubic
ii) Tetragonal
iii) Orthorhombic
iv) Hexagonal
v) Monoclinic
vi) Triclinic
vii) Rhombohedral



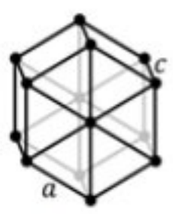
Cubic



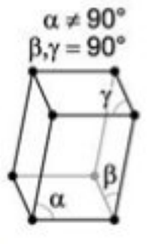
Tetragonal



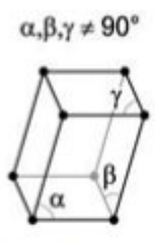
Orthorhombic



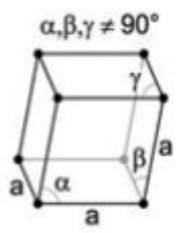
Hexagonal



Monoclinic



Triclinic



Rhombohedral

5.3 CRYSTALS GROUPED BY PROPERTIES

There are four main categories of crystals, as grouped by their chemical and physical properties:

5.4 COVALENT CRYSTALS

A covalent crystals has true covalent bonds between all of the atoms in the crystal. You can think of a covalent crystal as one big molecule. Many covalent crystals have extremely high melting points. Examples of covalent crystals include diamond and zinc sulfide crystals.

5.5 METALLIC CRYSTALS

Individual metal atoms of metallic crystals sit on lattice sites. This leaves the outer electrons of these atoms free to float around the lattice. Metallic crystals tend to be very dense and have high melting points.

5.6 IONIC CRYSTALS

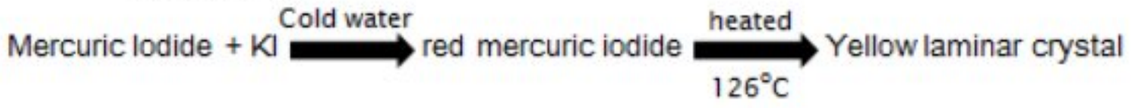
The atoms of ionic crystals are held together by electrostatic forces (ionic bonds). Ionic crystals are hard and have relatively high melting points. Table salt (NaCl) is an example of this type of crystal.

5.7 MOLECULAR CRYSTALS

These crystals contain recognizable molecules within their structures. A molecular crystal is held together by non-covalent interactions, like Vander-Waals-Forces or hydrogen bonding. Molecular crystals tend to be soft with relatively low melting points. Rock candy, the crystalline form of table sugar or sucrose, is an example of a molecular crystal.

5.8 POLYMORPHISM

- Many substances exist in two or more crystalline forms called "Polymorphs".
- The differences are due to difference in crystalline structure which give rise to difference in physical properties e.g. solubility.



- This variety of polymorphism exhibited by elements is termed "Allotropy".
- Reversible is called enantiotropic and irreversible monotropic.
- Polymorphism is known to occur in many steroids, sulphonamides and barbiturates.
- Detection of different polymorphic forms has been achieved by X-ray Diffraction and infrared adsorption of crystalline solid.
- When crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show same absorption spectra in solution.

5.9 EXAMPLES

- Sulphathiazole exits in two polymorphic forms. Form-I undergoes a change in crystal structure at 174°C to Form-II.

- Cortisone acetate exists in several forms but only one is stable in aq. suspension.
- Biological activity of Chloromphenicol palmitate has been correlated with polymorphic behavior.
- Four different polymorphic forms of theobroma oil have different melting points. It is used in making suppositories which melts at room temperature. By melting the oil of theobroma at the lowest possible temperature (about 33°C) the stable beta form is not lost and suppository stable at room temperature is produced.
- In the formulation of drugs known to exist as polymorphs, it is essential that the form present in the final preparation should be stable.

5.10 Isomorphism

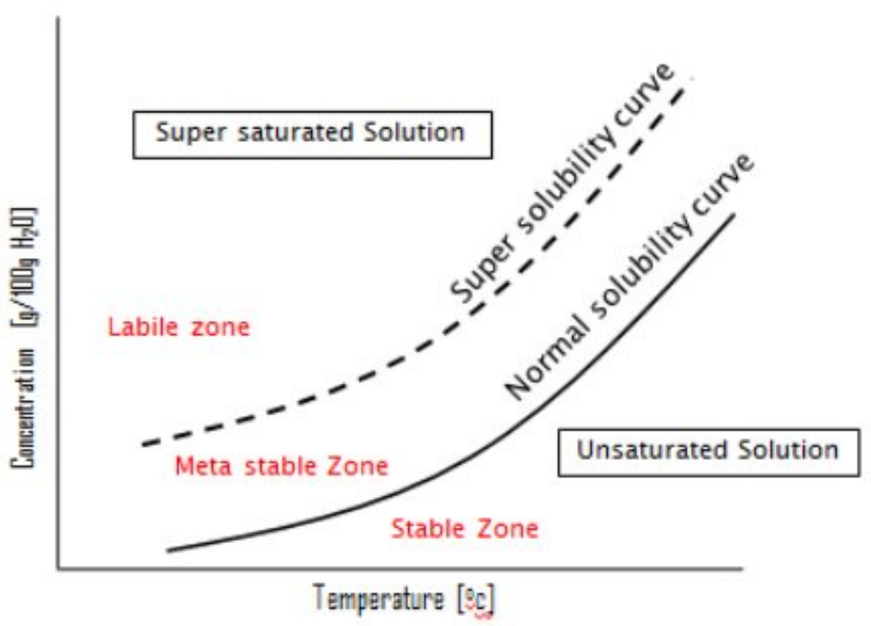
- Many chemical substances of similar chemical constitution form crystals of similar shape and are said to be isomorphous (the same shape).
- e.g. $MgSO_4.7H_2O$ and $ZnSO_4.7H_2O$
- $Na_2HPO_4.12H_2O$ and $Na_2HSO_4.12H_2O$
- Another property of isomorphous substances is the formation of mixed crystals e.g., solutions of Potash alum and Chrome alum are mixed and allowed to crystallize, a homogenous mixture of two double salts is obtained (pale violet crystals)

5.11 Mechanism of Crystallization

- The solution must be saturated before any solid matter can be crystallized.
- If the temperature of saturated solution is lowered or solvent is allowed to evaporate, then the excess of solid material separates out.
- Super saturation can be achieved by lowering the temperature carefully without separation of crystals.
- Formation of crystals from solution involves two steps;
  - Creation of crystalline nuclei.
  - Growth of these nuclei into crystals.
- Nuclei may arise spontaneously (rare) or by seeding (seeding is introduction of a minute crystal of solute).
- The driving force for this nucleation and subsequent growth of crystal is the super saturation of solution.

5.12 Theory of Miers

- This theory postulates that a definite relationship exists between the concentration and the temperature at which crystals will spontaneously form in an initially unseeded solution.
- The form of that relationship is "super solubility curve" roughly parallel to and above the normal solubility curve.



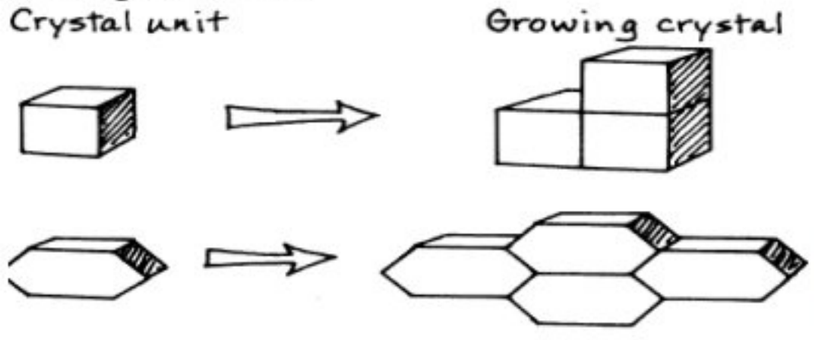
Ostwald–Miers diagram for a solute/solvent system

- The Theory states that between the two curves (meta stable zone) there will be no spontaneous nucleation, but above the super solubility curve there is spontaneous nucleation.
- In crystallization process the nuclei formation should be under control since the number of nuclei will control the size of crystals. Slow cooling yields large crystals due to reduction in number of nuclei formed and rapid cooling results in small crystals due to increased number of nuclei formed.

5.13 Formation of Nuclei

Nuclei may originate in the following ways:

- Spontaneously due to cooling of a super saturated solution in labile zone.
- Deliberate seeding with minute crystals.
- Crystals left from previous batch.
- Attrition of existing crystals giving rise to fragments that act as seeds. The degree of stirring will affect.



5.14 Size of Crystals

The size of crystals usually depends upon the conditions of crystallization.

Very small crystals are obtained by rapid cooling with frequent stirring. It is generally avoided because of difficulty in washing and less purity.

Medium size crystals are obtained when hot solution is allowed to cool slowly without mechanical disturbance in a warm room.

On large scale from refrigerating plant tubes lines are circulated around the tank in outer jacket or in coiled tubes within the solution.

Very large crystals are obtained by setting aside a large volume of solution and allowing it to evaporate spontaneously. The liquid should be rendered perfectly clear by filtration and guarded against dust. Seeding is done.

5.15 Mother Liquor

Mother liquor is the liquid remaining after crystallization. It is usually not discarded, but is subjected to further concentration and again set aside to crystallize. This process is repeated until whole dissolved solute is crystallized.

5.16 Crystallization Techniques

5.17 Slow Evaporation

This is the simplest way to grow crystals and works best for compounds which are not sensitive to ambient conditions in the laboratory. Prepare a solution of the compound in a suitable solvent. The solution should be saturated or nearly saturated. Transfer the solution to a CLEAN crystal growing dish and cover. The covering for the container should not be air tight. Aluminium foil with some holes poked in it works well, or a flat piece of glass with microscope slides used as a spacer also will do the trick. Place the container in a quiet out of the way place and let it evaporate. This method works best where there is enough material to saturate at least a few milliliters of solvent.

5.18 Slow Cooling

This is good for solute-solvent systems which are less than moderately soluble and the solvent's boiling point is less than 100°C. Prepare a saturated solution of the compound where the solvent is heated to just it's boiling point or just below it. Transfer the solution to a CLEAN large test tube and stopper. Transfer the test tube to a Dewar flask in which hot water (heated to a temperature of a couple of degrees below the solvent boiling point). The water level should exceed the solvent level in the test tube, but should not exceed the height of the test tube. Stopper the Dewar flask with a cork stopper and let the vessel sit for a week. A more elaborate version of this involves a thermostatic oven rather than a Dewar flask.

5.19 Vapor Diffusion

This method is good for milligram amounts of material. A solution of the substance is prepared using solvent S1 and placed in test tube-T. A second solvent-S2 is placed in a closed beaker-B. S2 is chosen such that when mixed with S1 the solute will become less soluble. The test tube containing S1 is then placed in the beaker and the beaker is sealed. Slow diffusion of S2 into T and S1 out of T will cause crystals to form. If S2 is more volatile than S1 the solvent level will increase and prevent microcrystalline crusts from forming on the sides of T.

5.20 Solvent Diffusion (Layering Technique)

This method also is good for milligram amounts of materials which are sensitive to ambient laboratory conditions (air, moisture). Dissolve the solute in S1 and place in a test tube. Slowly dribble S2 into the tube so that S1 and S2 form discreet layers. This will only be successful if, (1) The density of S2 < S1 and, (2) Care is exercised in creating the solvent layer. Using a syringe is the best way to add the second solvent. The narrower the tube , the easier it is to build up the layer. Five millimeter NMR tubes are excellent vessels to use for this crystal growing technique. CH_2Cl_2/C_2H_5OH is a good solvent combination to try this method (if your compound is insoluble in ether).

5.21 Reactant diffusion

This is similar to the other diffusion methods except that solutions of the reactants are allowed to diffuse into one another. If the product of the reaction is insoluble, crystals of the product will form where the reactants mix. It is mentioned in literature of this technique being used with diffusion in silica gels.

5.22 Sublimation

Simply seal a sample under vacuum in a glass tube and place the tube in an oven for a few days or weeks. Larger crystals tend to grow at the expense of smaller ones. If it doesn't work raise the temperature of the oven or move to another hotter one. In some cases a tube furnace can be used. Vacuum sublimation is ideal for very air sensitive compounds as the tubes can be loaded in dry boxes.

5.23 Convection

One may attempt to grow crystals by convection by creating a thermal gradient in the crystal growing vessel. The idea behind this method is that the solution becomes more saturated in the warm part of the vessel and is transferred to the cooler region where nucleation and crystal growth occur. To create the convection one may use either local heating or local cooling. The velocity of the convection current is proportional to the thermal gradient across the vessel. Care must be taken to not make the gradient too large, or the convection will be too rapid and inhibit crystal growth.

5.24 Crystal growth in suspensions

Crystal growth in suspensions is undesirable because crystals have a tendency to bind together forming a hard cake which is difficult to redisperse.
Crystal growth may lead to other undesirable changes e.g., large crystals tend to produce gritty texture for topical or ophthalmic use.
The causes of crystal growth in suspensions are:

1. Temperature fluctuations
   Rise in temperature causes increased solubility and a fall causes super saturation and hence crystallization.
2. Solid present in the meta stable zone where, they have greater solubility than stable state, so that solution is supersaturated with respect to latter.
3. Small crystals have a greater solubility than large crystals so that solution is supersaturated with respect to latter.
4. Change of crystal structure due to presence of dispersing solvent.

5.25 Methods of Preventing

It includes;

1. Use of narrow size range.
2. Grinding the solid in the presence of dispersing fluid.
3. Use of surface active agents which are adsorbed on the surface of crystals.

e.g., a simple suspensions of cortisone acetate powder for use as eye drop is liable to crystal growth. It can be avoided by grinding with hydrated Aluminium hydroxide and inclusion of methyl cellulose.

5.26 Fractional Crystallization

A process by which a chemical compound is separated into components by crystallization. In fractional crystallization the compound is mixed with a solvent, heated, and then gradually cooled so that, as each of its constituent components crystallizes, it can be removed in its pure form from the solution.
This technique is often used in chemical engineering to obtain very pure substances, or to recover saleable products from waste solutions, e.g., Benzoic acid, Paraffin, Naphthalene, Nitrochlorobenzene, Xylene etc.

Chapter 6 DISTILLATION

6.1 DISTILLATION

- ***Distillation*** is a method of separating mixtures based on differences in volatility of components in a boiling liquid mixture.
- Distillation differs from evaporation in two important respects:
  - The liquid from which the vapour arises is usually heated to boiling point and maintained there during the process. While in evaporation the temperature is kept usually below the boiling point of the liquid to be removed.
  - The vapour which arises is made to pass through an apparatus called a condenser which cools the vapour, thereby reforming the liquid.

6.2 DISTILLATE

- A liquid product condensed from vapor during ***distillation***

6.3 RECEIVER

- ***Receiver*** adapters are used to allow collection of distillates emerging from a condenser.

6.4 STILL

- A still is the apparatus used for distillation.

6.5 CONDENSER

- The selection of the condenser is essential to success in many distillation processes.
- The quantity of water need for the condensation of a vapour to the liquid state is partly dependent upon the boiling point of the liquid and partly upon the latent heat of the vapour.
- The efficiency of a condenser dependent upon
  - The area of the cooling surface – cooling capacity is directly proportional to area
  - The heat conducting qualities of the cooling surface.
  - Metal is better conductor of heat than glass.
- The usefulness of a condenser is enhanced by its construction:
  - Enables to be cleaned readily so as to remove all the traces of previous product.
  - Enables a broken part to be replaced without the expense of an entirely new condenser.
- Condensers are used in an upright or oblique position in order to:
  - The film of condensed liquid which act as a bad conductor of heat drains away as rapidly as possible
  - The cooling water flows in a direction which is reverse of that of the condensed liquid
- There are three principal classes of condensers:
  - Single surface condenser
  - Double surface condenser
  - Multi tubular condensers

6.6 SINGLE SURFACE CONDENSER

The commonest form is the Liebig condenser of which the spiral or worm condenser and the ball condenser may be regarded as modification.

(*Baird and Tatlock*)

FIG. 18. SPIRAL CONDENSER

(*Baird and Tatlock*)

FIG. 19. BALL CONDENSER

6.7 DOUBLE SURFACE CONDENSER

In these, the vapour passes through an annular space cooled on its inner and outer surface by cold water.

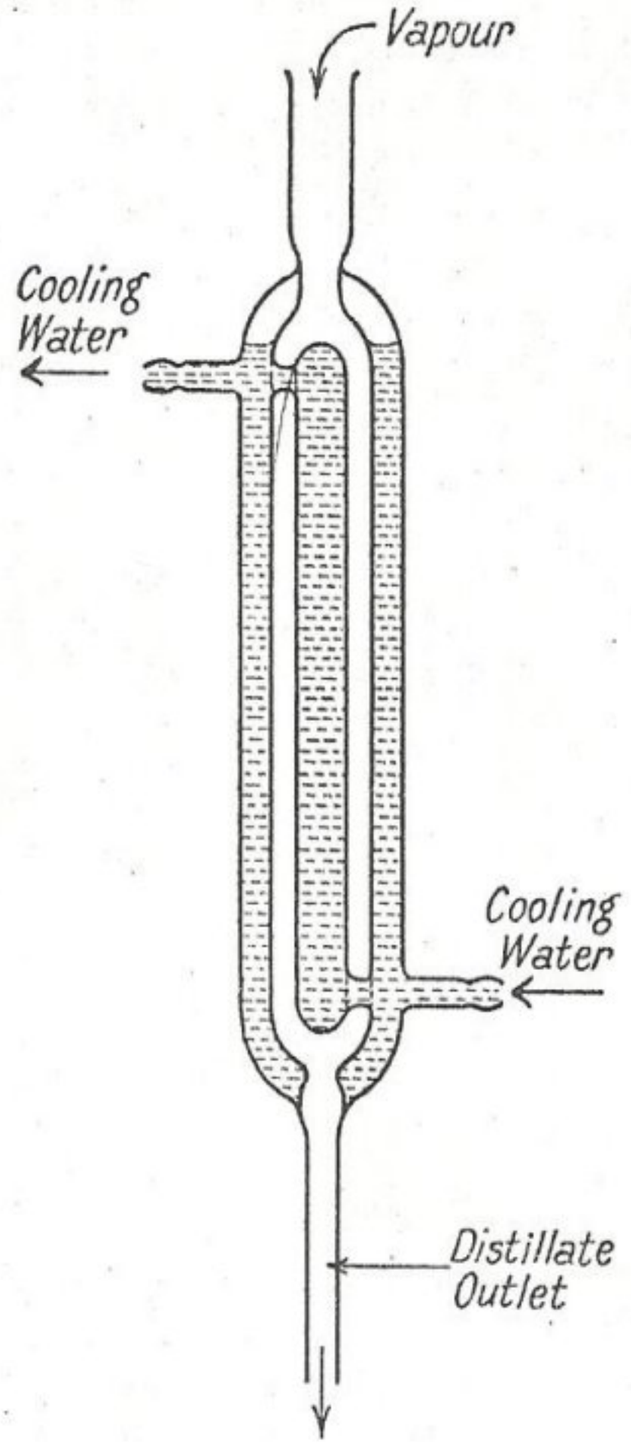


Fig. 20. Double Surface Condenser

6.8 Multi Tubular Condenser

These resemble the Liebig's condenser but have several tubules instead of one. They are usually made up of metal and are used in large scale work.

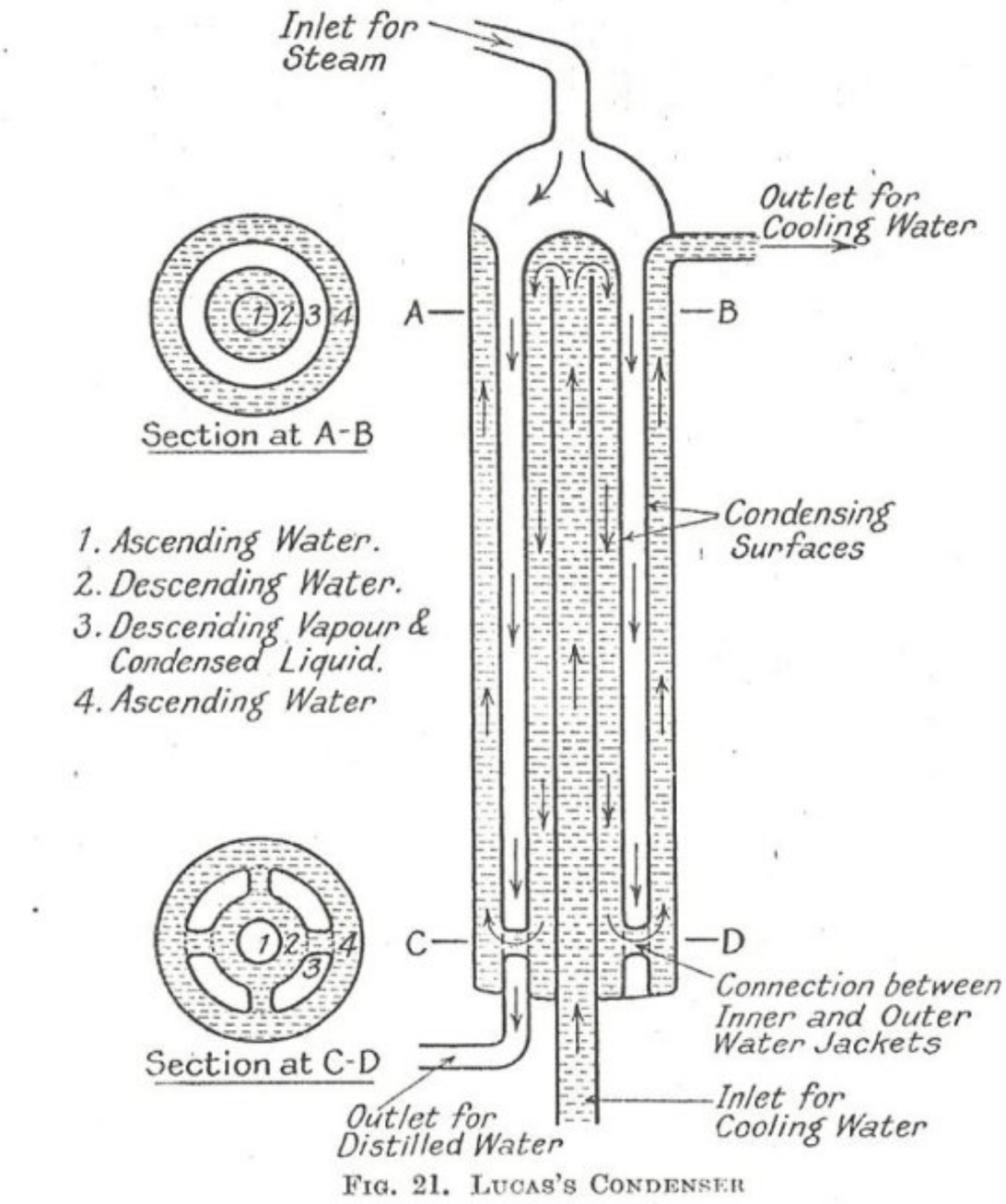


Fig. 21. Lucas's Condenser

6.9 Reflux Condenser

It is not a particular form of condenser; it describes any condenser use for preventing the volatilization of liquid or liquids undergoing heating. ***Condensers*** are often used in ***reflux***, where the hot solvent vapors of a liquid being heated are cooled and allowed to drip back.

6.10 Water Cooled Condenser

In systems involving heat transfer, a ***condenser*** is a device or unit used to condense a substance from its gaseous to its ***liquid*** state, typically by ***cooling*** it.

6.11 Air Condenser

An air condenser is the simplest sort of condenser. There is only one tube, and the heat of the fluid is conducted to the glass, which is cooled by air.

6.12 Application of Simple Distillation

- The process of simple distillation is widely used in the preparation of many official compounds, e.g. Ethers, Amyl Nitrite, and Spirit of Nitrous Ether
- Distillation is also used to concentrate liquids and to separate solids from liquids when liquids to be separated is valuable e.g. alcohol, ether.

- Steam under pressure is the usual source of heat for large stills
- Distilled water is an important product of distillation.

6.13 Distilled Water

Distilled water is used in all official preparations in which water is required. Ordinary drinking water usually contains traces of calcium and magnesium salts derived from the soil through which it has passed. Distilled water is prepared by the distillation of drinking water.

The solid impurities are not volatile and therefore can be removed by distillation while the gaseous impurities are volatile so they pass over with the steam and contaminate the distillate. The gaseous impurities (Importantly ammonia) are removed in two ways.

6.14 Removal of Gases Impurities

6.14.1.1 By Fractional Collection of the Distillate

In this method, advantage is taken of the fact that gases are more volatile than water and therefore pass over in the first portion of the distillate which may be rejected.

6.14.1.2 By Pre-heating the Water to be Distillate

The same fact is used but applied differently. The water to be distillated is heated to 90°C, or higher, before admission to the still and thus the most of the gaseous impurities are volatilized before distillation commences.

6.15 Removal of Solid Impurities

6.15.1.1 By Fractional Collection – a Discontinuous Process

About 80% of the distillation is collected, this being the product.

About 10% of the water undergoing distillation still remains in the still when distillation is stopped. Distillation to dryness or nearly so, may decomposition of solids with formation of volatile substances which would contaminate the distillate.

6.15.1.2 By Pre-Heating – a Continuous Process

Distillate is collected continuously because the water in the still is maintained at a constant level; hence decomposition of solid impurities cannot occur.

Continuous process has more advantage over discontinuous economically as it saves heat, labour and time.

A few broken pieces of clean unglazed porcelain may be placed in the distillation flask to prevent "bumping".

6.16 Automatic Still for Water Distillation

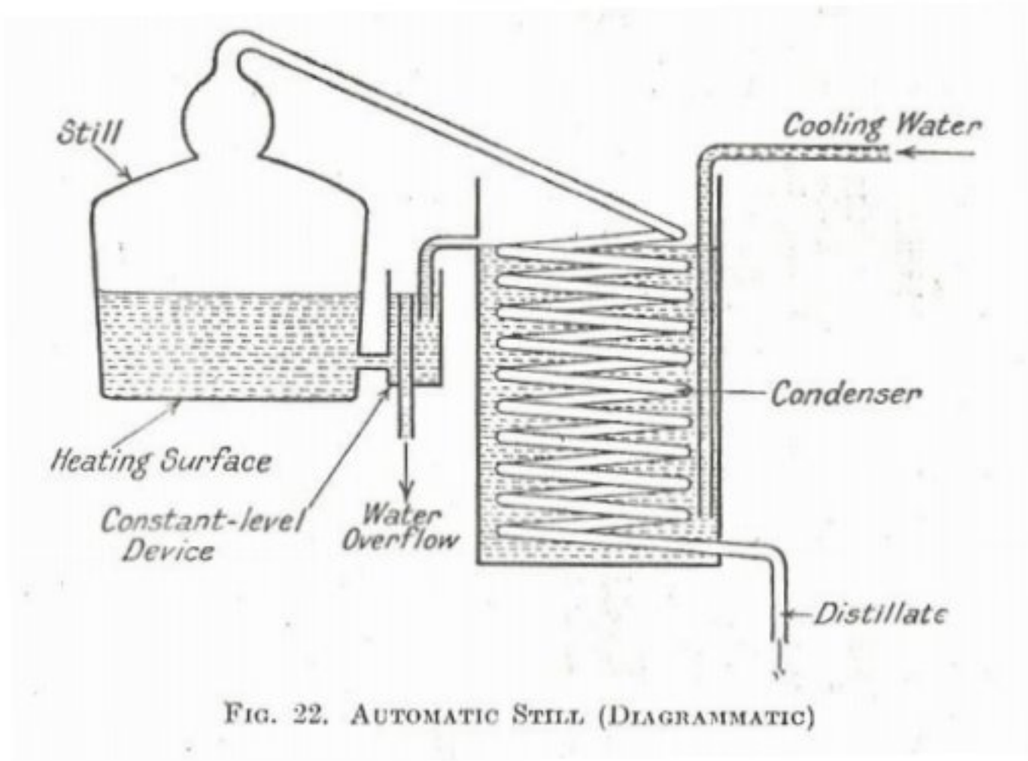


Fig. 22. Automatic Still (Diagrammatic)

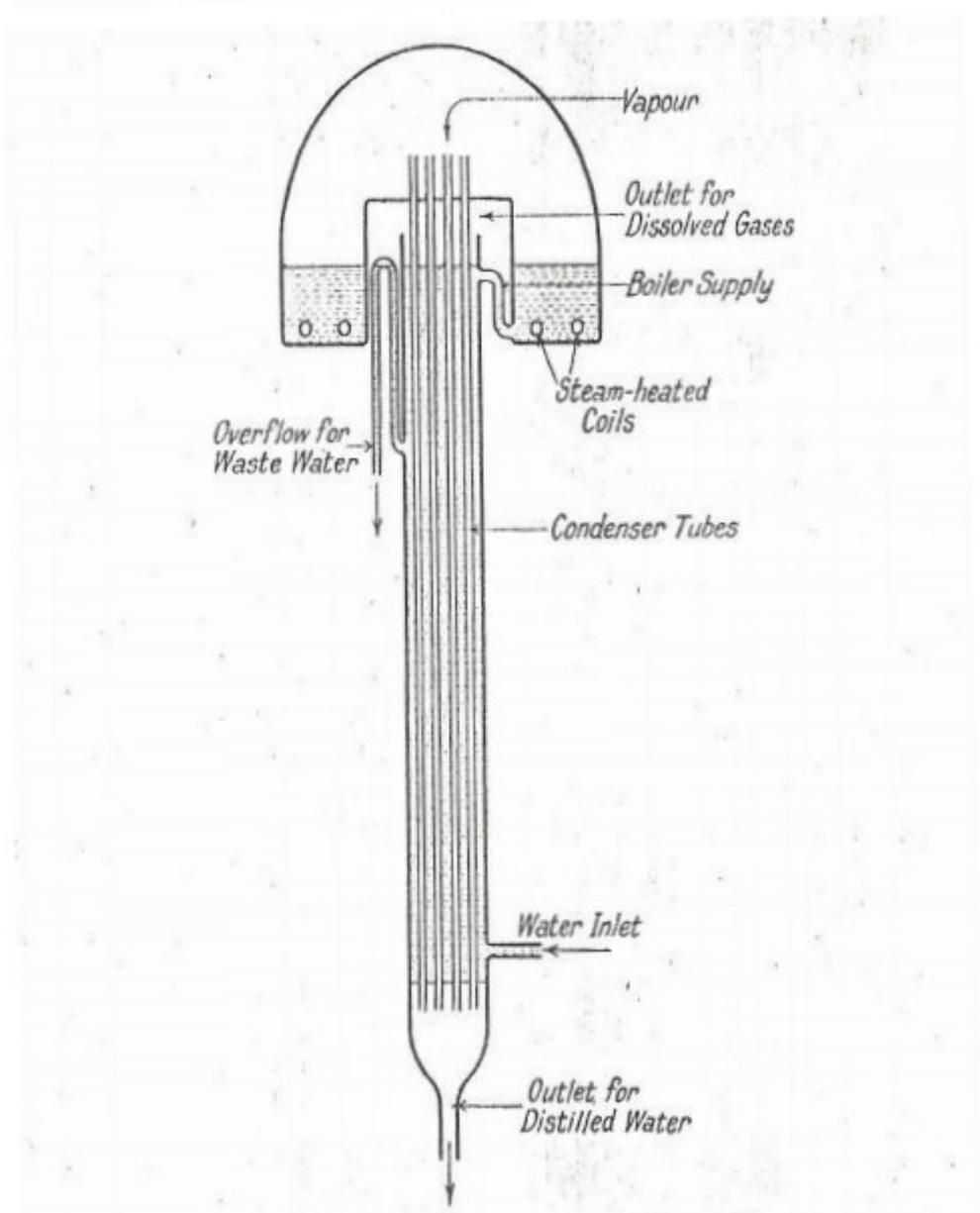


Fig. 23b. Stokes' Still, Multi-tubular Form (Diagrammatic)

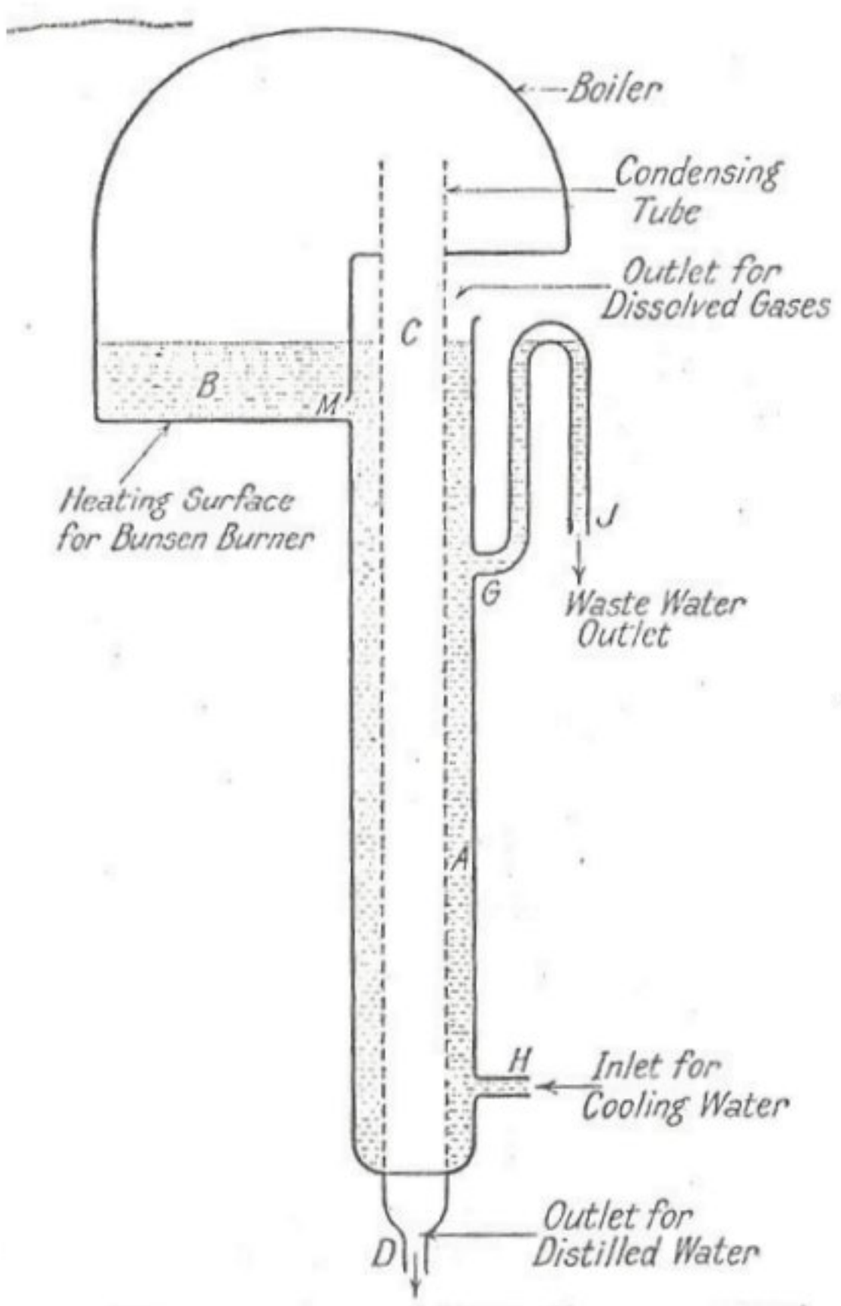


FIG. 23A. STOKES' STILL (DIAGRAMMATIC)

6.17 WATER FOR INJECTION

- Water for injection is prepared by distillation from a glass or metal still fitted with an entrainment separator to prevent pyrogens being carried out over to the distillate in the spray. It must comply with the limit test prescribed officially for distilled water an in addition test for sterility ant the absence of pyrogens must be satisfied.
- Sterile Water for Injection USP is a clear, colorless, odorless liquid. It is sterile, hypotonic, non-pyrogenic, and contains no bacteriostatic or antimicrobial agents. Sterile Water for Injection USP is a diluent or solvent suitable for intravascular injection after first having been made approximately isotonic by the addition of suitable solute.

6.18 DISTILLATION UNDER REDUCED PRESSURE

- Liquid boils when its vapour pressure is equal to the hydro-statistic pressure (Surface Pressure).
- Mass of vapour formed is proportional to vapour- pressure of evaporating liquid and inversely proportional to external pressure.

- If after reducing pressure of a liquid equals to external pressure on its surface, the process becomes distillation under reduced pressure, but if the maximum vapour-pressure of the liquid is lower than the pressure on its surface evaporation is lower than the pressure on its surface, evaporation only occurs and the process is correctly described as evaporation under reduced pressure. In practice, both processes are referred to as evaporation under reduced pressure.

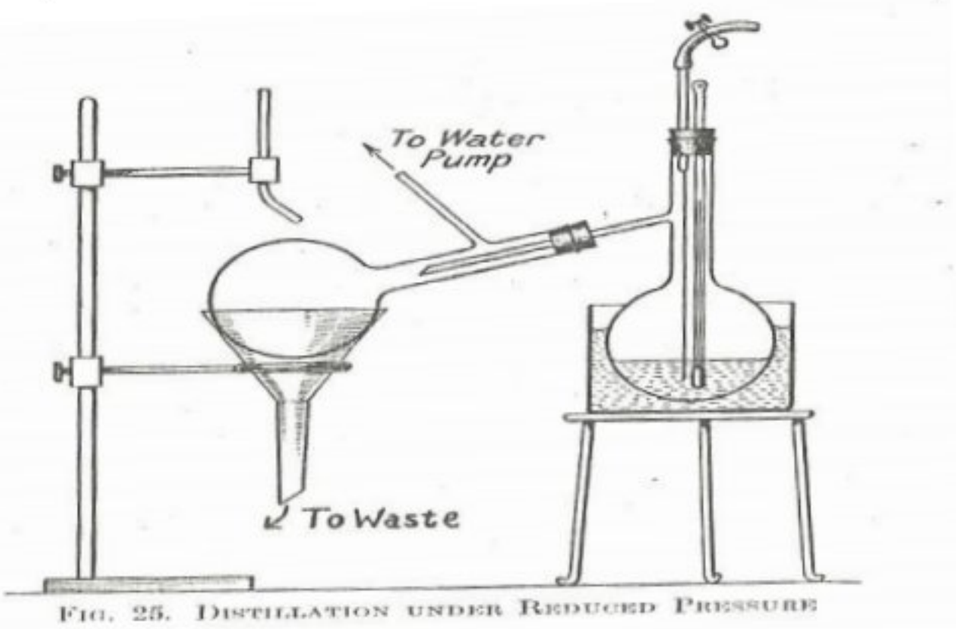


FIG. 25. DISTILLATION UNDER REDUCED PRESSURE

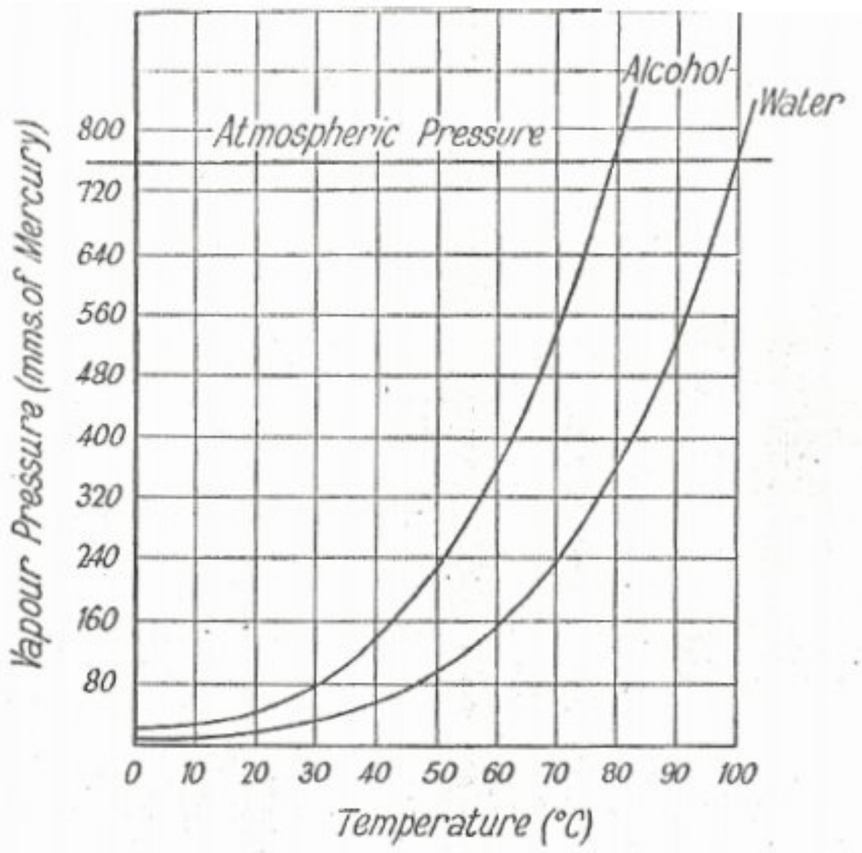


FIG. 1. TEMPERATURE: VAPOUR-PRESSURE CURVES

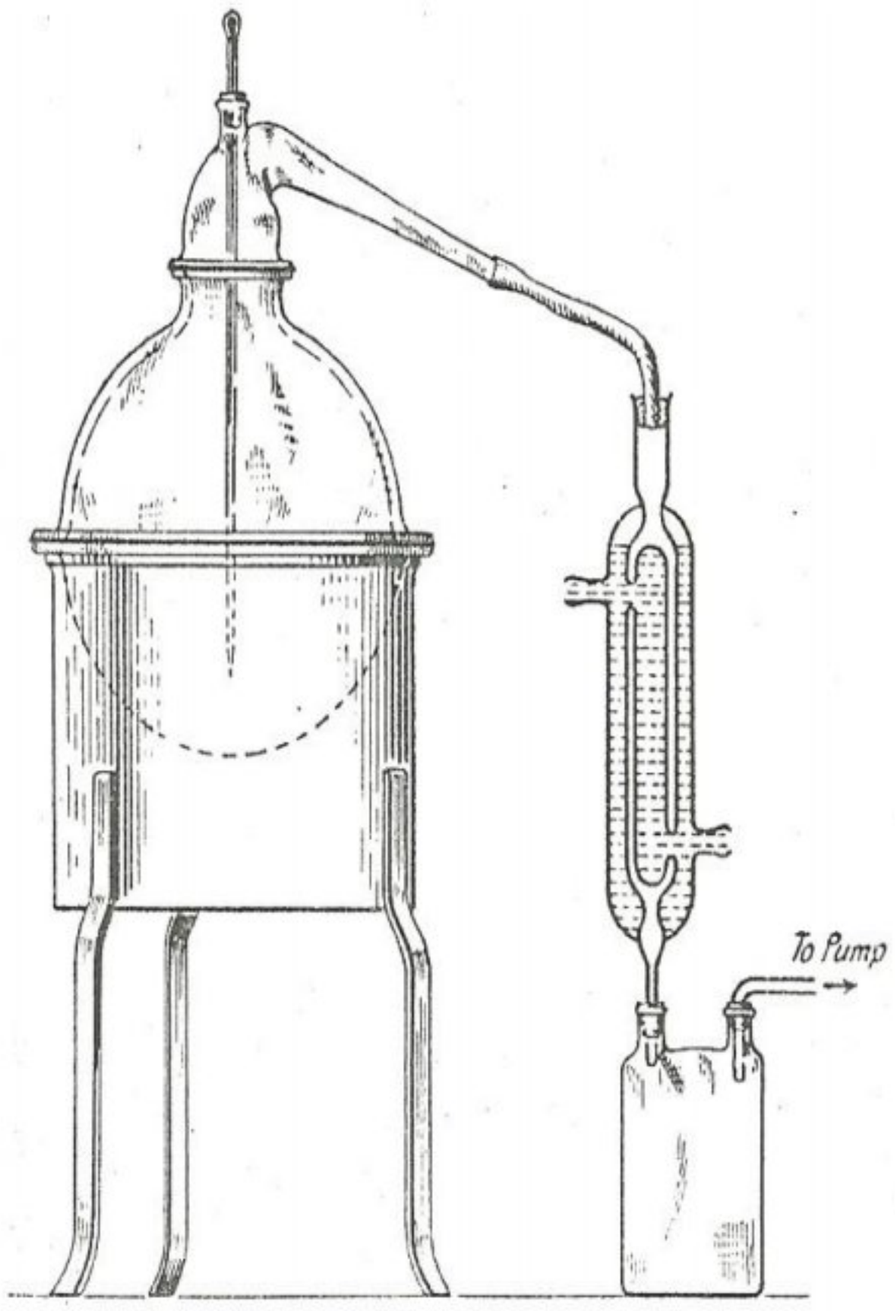
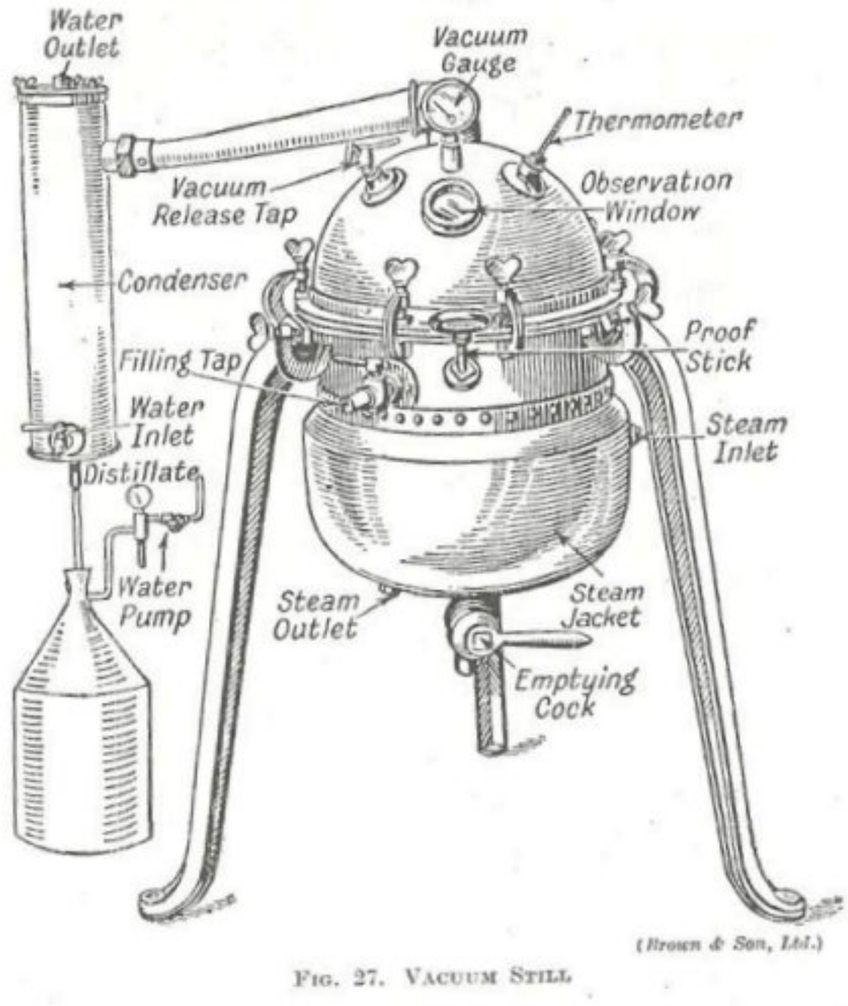


FIG. 26



(Brown & Son, Ltd.)

FIG. 27. VACUUM STILL

6.19 APPLICATION

- Distillation under reduced pressure is used for purposes of concentration when
- The constituents of the extraction liquids are thermo-labile i.e. to minimize chemical change
- To Prevent Destruction of Enzymes
- To Prevent Racemization
- To Prevent Hydrolysis of Glycosides and Alkaloids
- A light friable product is desired i.e. to influence physical form

6.20 DISTILLATION OF IMMISCIBLE LIQUID – DISTILLATION IN STEAM

- Distillation of two immiscible liquids is called distillation in steam when one of the immiscible liquids is water.
- Theory
  - Mixture boils when VP1+VP2= External pressure
  - Mixture boiling point < either of the constituent
  - Boiling point of mixture remains stationary until one of the constituent is completely removed.
  - Composition of vapours distilling over remains constant unless one of the constituent is completely removed.
  - The composition of vapours distilling over, by volume, is directly proportional to the vapour pressure pressures of the liqud.

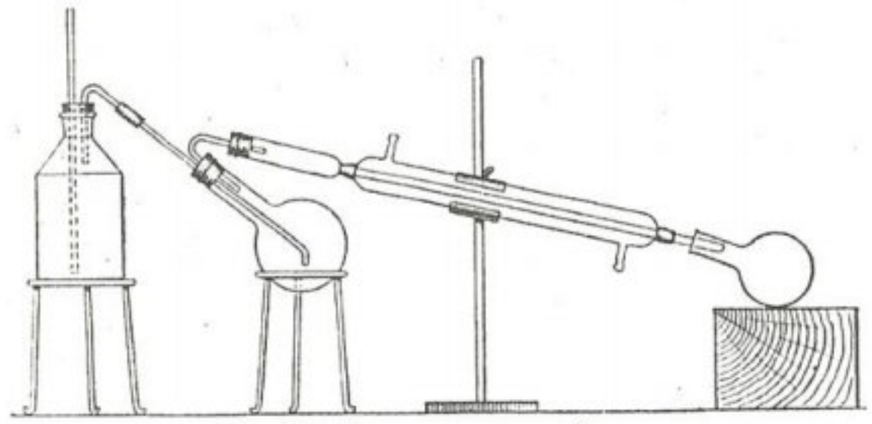


FIG. 28. DISTILLATION IN STEAM

Applications in Pharmaceutics

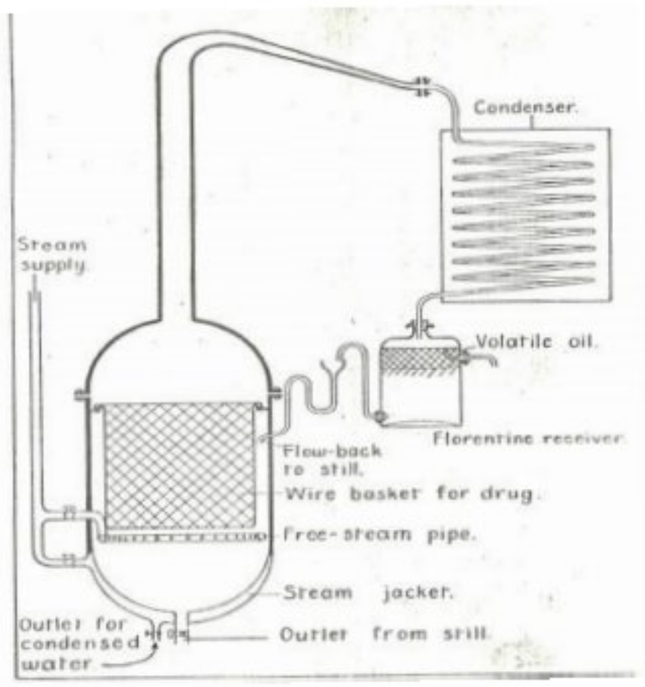
6.21 APPLICATION IN PHARMACEUTICS

6.22 PREPARATION OF VOLATILE OILS

- The Boiling Point of many volatile oils is above 200 °C and at these high temperature chemical changes e.g. oxidation would in some instances take place.
- Distillation of volatile oil with water follows the law governing the distillation immiscible liquids namely that distillation of immiscible liquids, namely that distillation takes place when the sum of the vapour pressure equal to atmospheric pressure. Hence the boiling point of such a mixture would be lower than

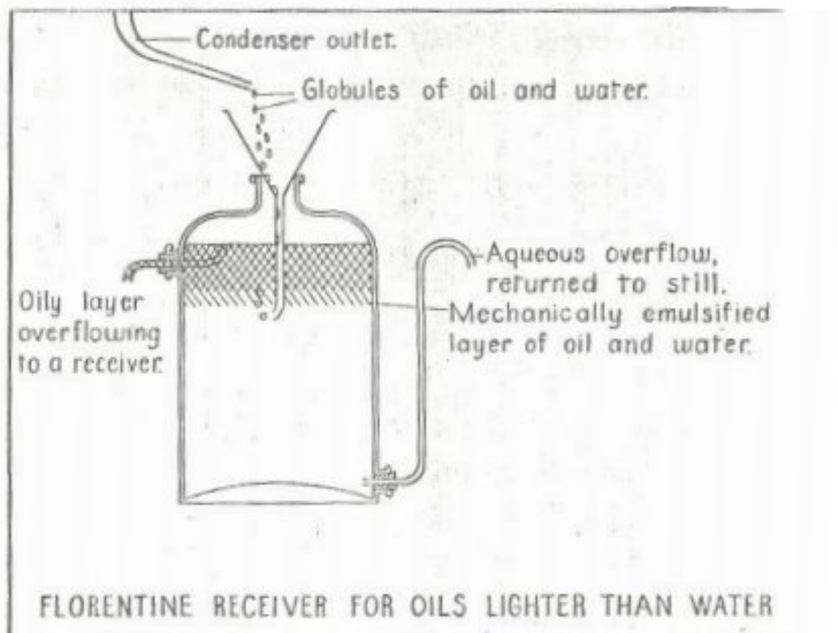
that of the constituent with lower boiling point of water (100 °C).

- It helps in:
  - Separation of volatile oil at lower temperature
  - Preventing carbonization of the drug
  - Direct heating of a mixture of a drug and water by a naked flame would similarly cause partial carbonization of the layer of drug resting on the bottom of the still and again volatile decomposition product would give an empyreumatic odour to the volatile oil, impair its value.
  - Perforated heat is applied, upon heating steam rises through the perforations, passes through the drug ad on to the condenser carrying with it the volatile oil.
  - A layer of water is run into the still and the drug suitably comminuted, is placed in the wire basket. Steam is admitted to jacket of the still and the water therein raised to boiling. At this point, steam is admitted into the still itself by the free-stream pipe, thus heating the drug and reducing the condensation of steam therein. The oil vapour and steam are condensed in the worm condenser, and drip into the Florentine receiver. In this most of the oil is mechanically separated from the water.

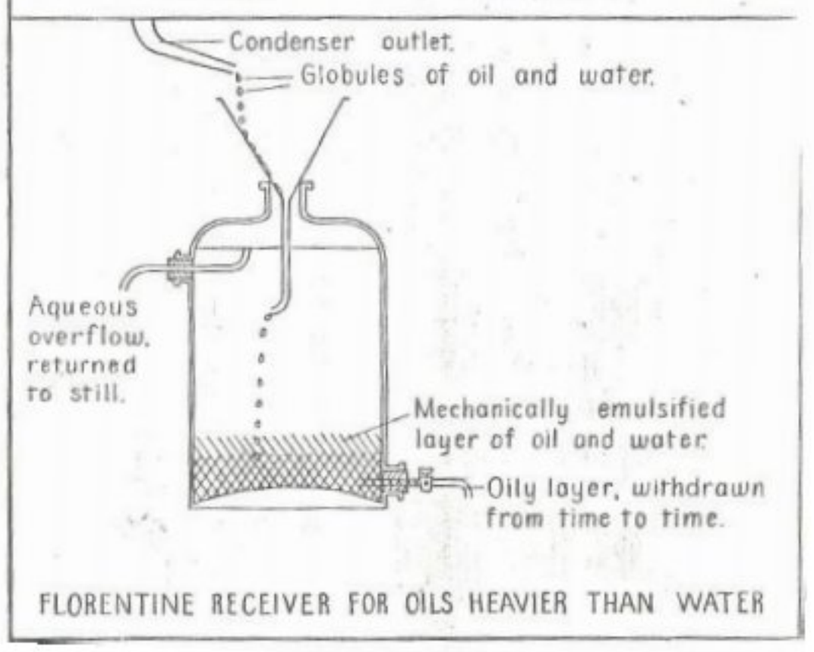


6.22.1.1 Separation of Oil and Water

- The distillate is usually collected in a vessel called Florentine receiver. It is separated into upper oily layer and lower water layer. As the receiver fills the liquid also passes into the spout whence it overflows upon reaching the upper bend. Because the spout leads from the bottom of the receiver only water can overflow and in this manner the bulk of the water is automatically separated from the oil.



FLORENTINE RECEIVER FOR OILS LIGHTER THAN WATER



FLORENTINE RECEIVER FOR OILS HEAVIER THAN WATER

6.23 2. Distillated Aromatic Waters

6.24 Distillation of Miscible Liquids - Fractional Distillation

- Fractional distillation is the separation of a mixture into its component parts, or fractions, such as in separating chemical compounds by their boiling point by heating them to a temperature at which one or more fractions of the compound will vaporize. It is a special type of distillation.
- The total pressure is the sum of the partial pressures; thus if A and B are two miscible liquids, and P1 and P2 represents their respective partial pressure, the mixture boils when

  P1 + P2 =External Pressure (normally 1 atmosphere)
- With certain expectations noted later, the vapour arising from two miscible liquids at boiling point

- Is richer in the component exerting the greater partial pressure – as would be expected from the facts noted for immiscible liquids and
- Is therefore different in composition from the liquid yielding it.
- A boiling-point curve for mixture of A and B may be obtained by preparing a graded series of mixtures, determining the boiling point of each and plotting against composition. Similarly, the vapour yielded by each member of the series at its boiling point may be yielded by each member of the series at its boiling point may be analyzed and its composition plotted against the boiling point of the liquid giving rise to it. Provided with such curves, the composition of the vapour which any mixture of A and B yields at its boiling point may be found by drawing a line from this point, parallel with the abscissa-axis, to cut the other curve (thus connecting liquid and vapour at the same temperature), and drawing lines from these points to the abscissa-axis.
- Assume a mixture of the two miscible liquids A and B containing 20 % of A and 80 % of B, A having lower boiling point than B. When the boiling point of the mixture is reached, the liquid gives rise to a vapour richer in A than the liquid which gave rise to it, the vapour containing 60 % of A. If this vapour is condensed the resulting liquid when heated to boiling point give rise to a vapour containing more than 60 % of A, the proportion of A present, as shown in the diagram, being now 90 %. If this vapour is condensed and the resulting liquid is heated to boiling, the vapour formed now contains 98 % of A. If this vapour is condensed and re-heated, it produces a vapour containing 100 % of A.

6.25 Discontinuous Fractional Distillation

- The above forms the basis of the discontinuous method of fractional distillation, which may be carried out as shown in the following example, in which A is a liquid with a boiling point 70°C, B is water, the mixture consisting of equal parts of A and B, As the difference in the boiling point is 30°C, it would be convenient to collect the distillate in 10 fractions, changing the receiver for each rise of 3°C, in the temperature, the receivers being labeled, No. 1 (70°C up to 73°C), No. 2 (73°C up to

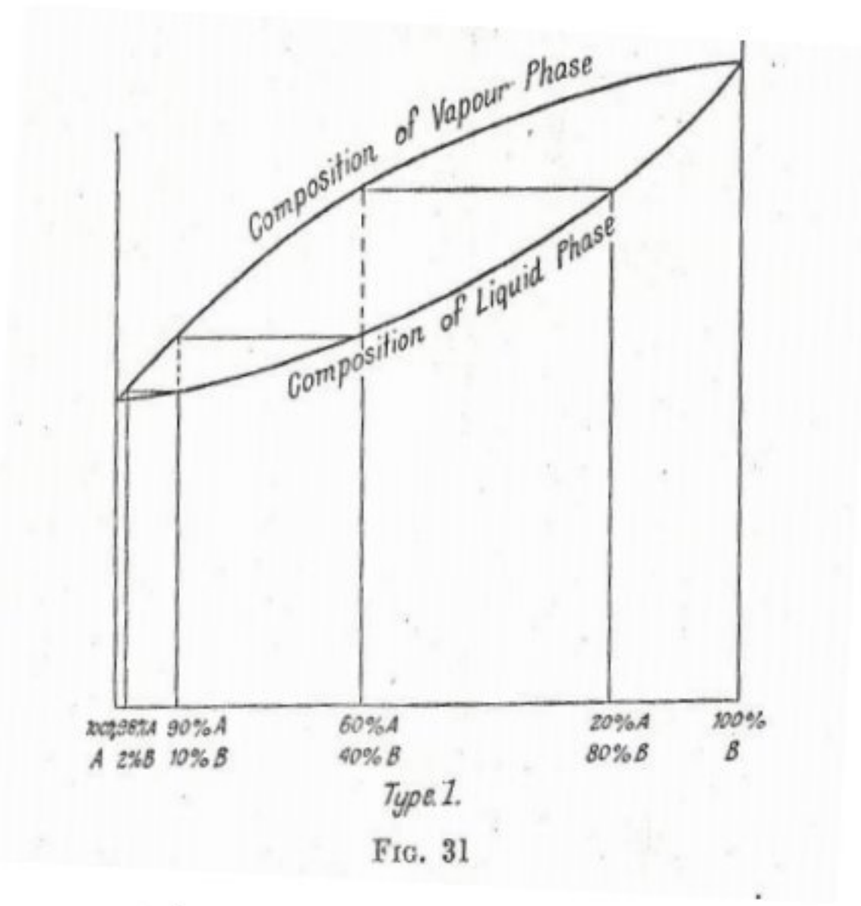


Fig. 31

76°C) etc.

- The mixture will properly commence to boil at about 70 – 77 °C, and the distillate would therefore be collected in receiver No.3 (76° up to 79°C), receiver No. 4 taking its place at 79°C, and so on until the temperature reached 100°C, indicating that only water remained in the distillation flask, at which point distillation would be stopped.
- The contents of receiver No.3 (i.e. the first collected) would then be placed in a clean distillation flask and heated to boiling. Distillation would probably commence at 70° to 71°C, and the distillate would therefore be collected in receiver No.1, receiver No.2 taking its plave at 73°C, and at 76°C. Distillation would be stopped. The flask allowed to cool and te contents of receiver No.4 added. Upon resumption of distillation the liquid would probably commence to boil between 73°C and 76°C, and the distillate would therefore be collected in receiver No.2, receiver No. 3 taking its place at 76°C, and at 79°C. Distillation would again be stopped the flask allowed to cool, and the contents of receiver No.5 added. The first distillate from this would go into the appropriate receiver probably No.3 and the fractions up to 84°C, (receiver No.5), collected at which point the contents of receiver No. 6 would be placed in the distillation flask and so on.
- The whole process would then be repeated, starting with the contents of receiver No.2 and collecting from it this distillate passing over from 70°C to 73°C (i.e. collecting in receiver No.1) stopping distillation , adding the contents of receiver No.3 and proceeding

as before. Ultimately the "middle fraction" (i.e. those from 73°C up to 100°C) would be reduced almost to zero. The contents of receiver No.1 would be then be redistilled and the fraction boiling at 70°C collected this being pure A.

6.26 Continuous Fractional Distillation

- The tedium of the discontinuous method led to the introduction of simpler methods of effecting fractionation, the principle of which is shown in the figure below. Assume again a mixture of A 20 % with B 80 %, heated to boiling in a distillation flask and as shown in the lowest pair of curves, giving rise to a vapour containing 60 %A. The latter impinges on a cool surface (at the second pair of curves), condenses there and is partially re-vaporized (i.e. heated to its boiling point) by more hot vapour arising from the distillation flask. As shown (first condensation and partial re-vaporization in figure), the vapoir which arises will contain 90 % A. the latter impinges on a higher cool surface (at the third pair of curves), condenses there and is again re-vaporized by the succeeding upward flow of hot vapour. Again a vapour richer in A rises, now containing 98 % A; a repetition of the process at a still higher cooling surface (third condensation and partial re-vaporization in figure), yield pure A.
- The above forms the basis of the continuous method of fractional distillation and necessarily involves the use of special still-head in which condensation and re-vaporization is effected continuously. These special still-heads are called fractionating column.

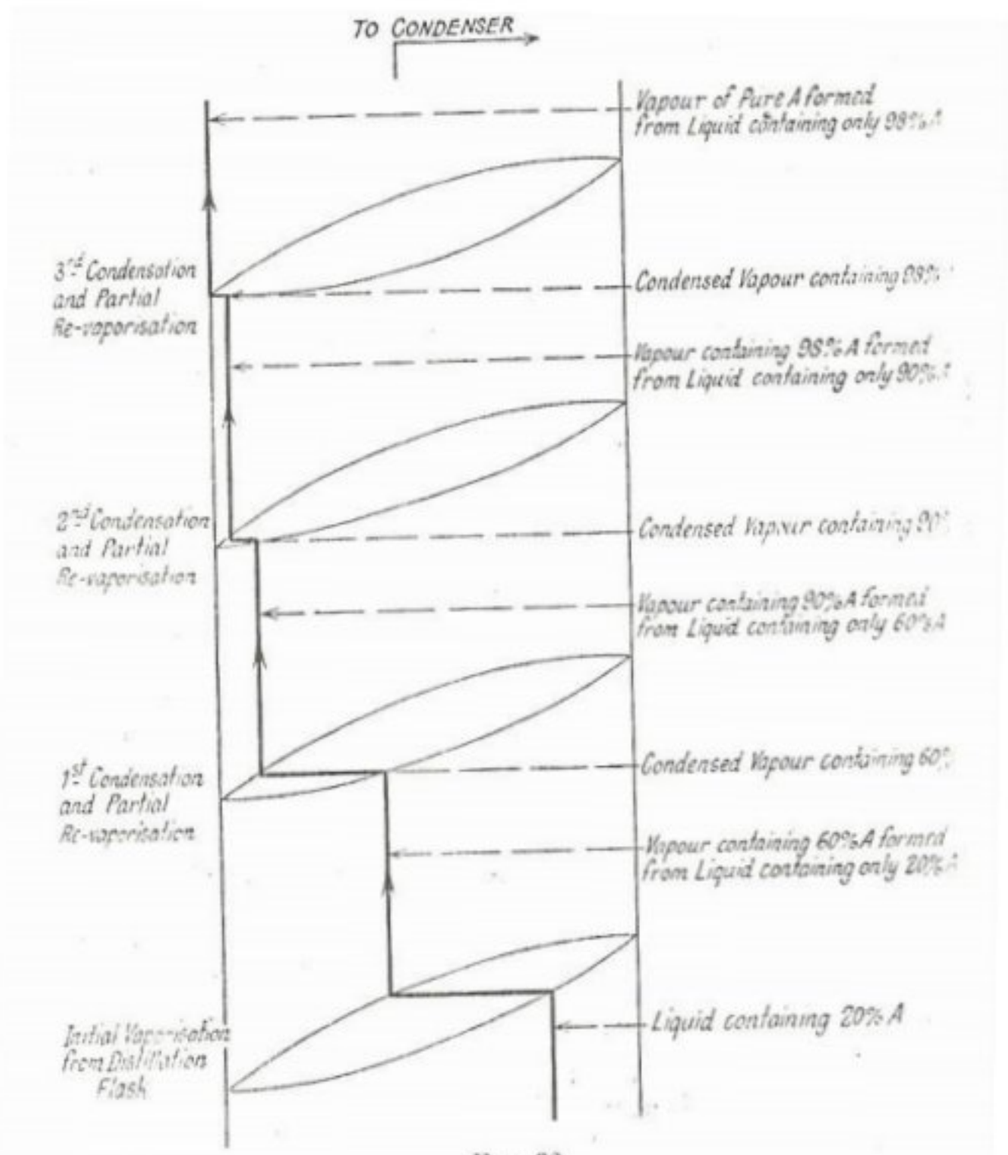


Fig. 32

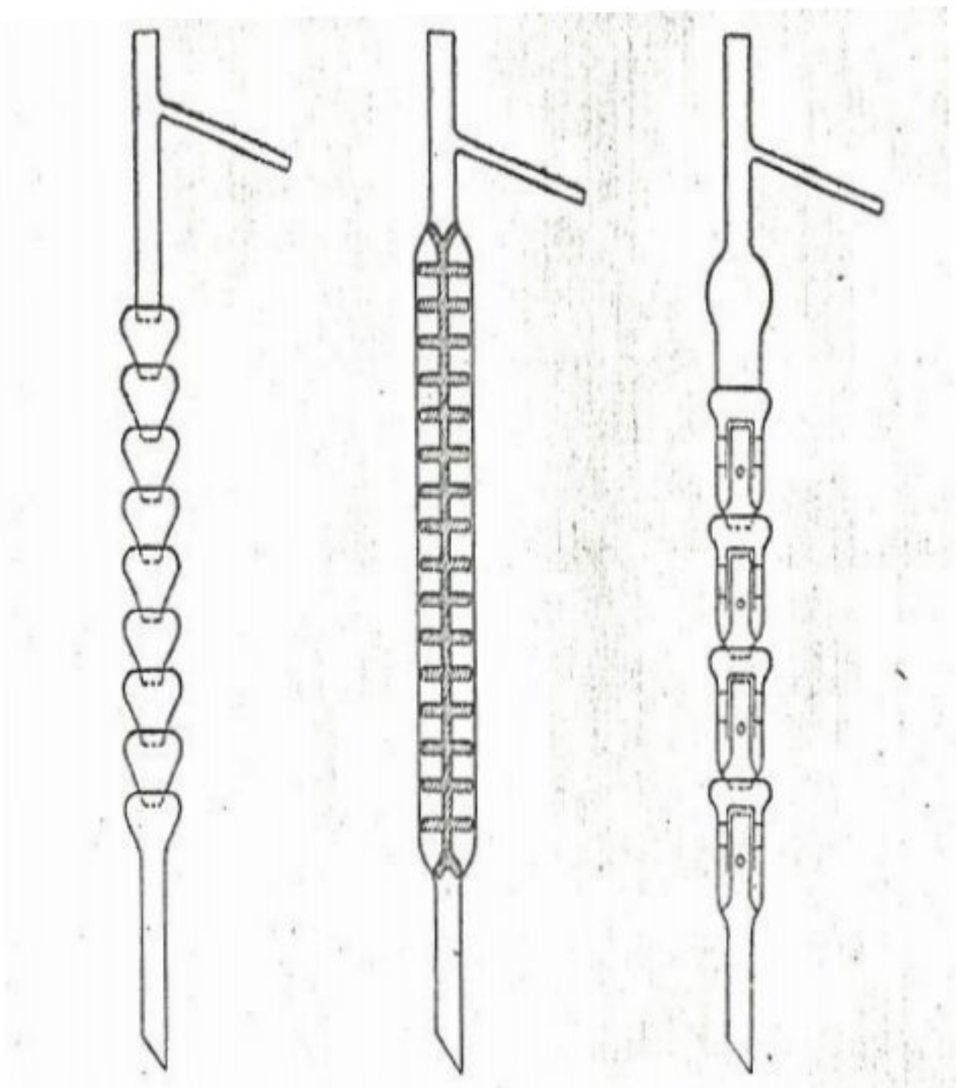


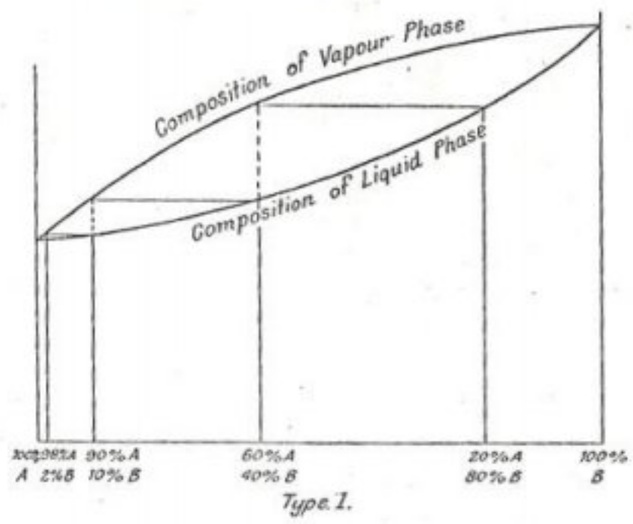
Fig. 33. Fractionating Columns

6.27 Constant Boiling Temperatures (Azeotropic Mixture)

Type 1.

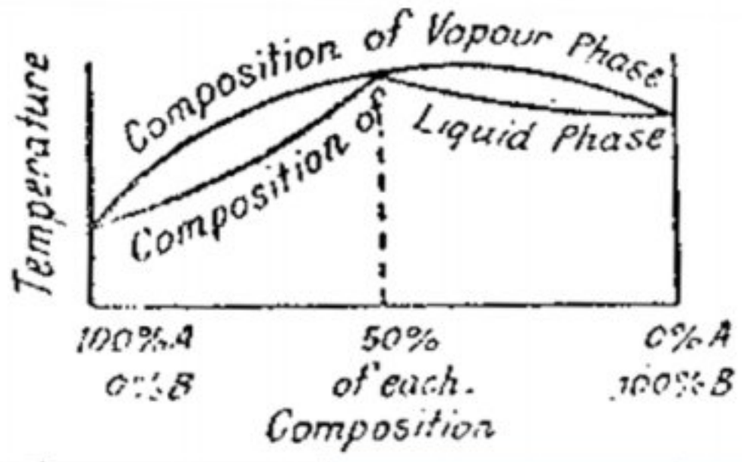
The two liquids do not form any mixture with a higher or lower boiling point than either of the two pure components.

For example Methyl Alcohol and water



Type 2.

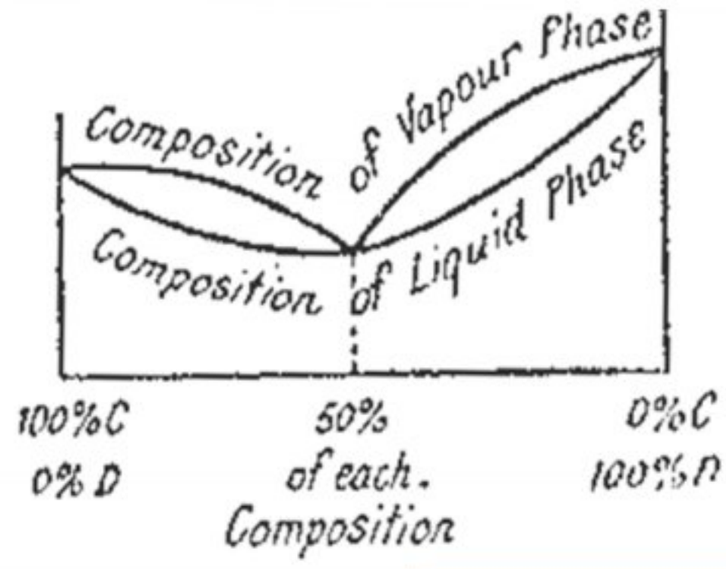
The two liquids form a mixture with a higher boiling point than that of the component with the higher boiling point. For example HCl and water



		DISTILLATE	RESIDUE
Type 2	More component of lower boiling point than the constant boiling point mixture	Pure component of lower boiling point	Constant boiling point mixture
	More component of higher boiling point than the constant boiling point mixture	Pure component of higher boiling point	

Type 3.

The two liquids form a mixture with a lower boiling point than that of the component with the lower boiling point. For example C_2H_5OH and water



		DISTILLATE	RESIDUE
Type 3	More component of lower boiling point than constant boiling point mixture	Constant boiling point mixture	Pure component of lower boiling point
	More component of higher boiling point than the constant boiling point mixture		Pure component of higher boiling point

6.28 COMPARISON

		FACTIONAL DISTILLATION	
		Produces a distillate of	**Leaves a residue in still**
Type 1	Mixture of any proportions	Component of lower boiling point	Component of higher boiling point
Type 2	More component of lower boiling point than the constant boiling point mixture	Pure component of lower boiling point	Constant boiling point mixture
	More component of higher boiling point than the constant boiling point mixture	Pure component of higher boiling point	
Type 3	More component of lower boiling point than constant boiling point mixture	Constant boiling point mixture	Pure component of lower boiling point
	More component of higher boiling point than the constant boiling point mixture		Pure component of higher boiling point

6.29 APPLICATION OF FRACTIONAL DISTILLATION

6.30 PREPARATION OF ALCOHOL

Alcohol is one of the important pharmaceutical substances in the preparation of which fractional distillation is employed. The important stages in the preparation of alcohol are:

- The preparation of a sugar solution from suitable material
- Malt is usually employed in conjunction with cheap materials, e.g. maize and rice, which contain starch, which is converted to sugars by the action of diastase contained in the malt.
- Fermentation of this sugar solution by the action of yeast
- This converts the bulk of the sugar into alcohol and carbon dioxide, but numerous other substances are formed in small amount of which the more important are glycerin, succinic acid and higher homologues of ethyl alcohol which are known as fuel oil. The fermentation liquid, called the wort, usually contains only 10 to 14 % of alcohol.
- Fractional Distillation of this fermented liquid in a special form of still called Coffey's still, which is quite different in construction from the apparatus described above. The principal structure as shown in the diagram is two towers, one called the analyzer, the other the rectifier. The weak alcoholic liquid, previously heated, passes down the analyzer through a series of perforated copper plates and in its downward passage meets an ascending current of superheated steam. At each plate the weak alcoholic liquid is heated, some of the alcohol vaporized and carried along in the steam so that upon reaching the bottom of the tower. The weak alcoholic liquid has been completely deprived of alcohol.
- The steam and alcoholic vapour then pass up the rectifier, which acts in much the same way as a fractionating column, allowing the alcohol vapour to pass on to a condenser, but condensing the steam and a small proportion of the alcohol vapour. This condensed liquid is returned to the analyser. The rectifier is cooled by the weak alcoholic liquid which passes downward through a coiled pipe in the rectifier. In this way, the weak alcoholic liquid is heated is ready for entry into the analyzer.
- The distillate obtained from the Coffey still may contain as much as 95 % of alcohol. This alcohol is not pure. It is purified by the distillation with water which precipitates the fused oil, filtration through animal charcoal followed by redistillation in a still called a rectifying still.

- Dehydrated Alcohol may be prepared from 95 % alcohol by taking advantage of the fact that alcohol, water and benzene from a ternary constant of boiling point mixture. If therefore, sufficient benzene is added to form this mixture with all the water present and some of the alcohol, distillation will result this ternary mixture volatilizing first when it can be rejected. Subsequently the remaining anhydrous alcohol is distilled.

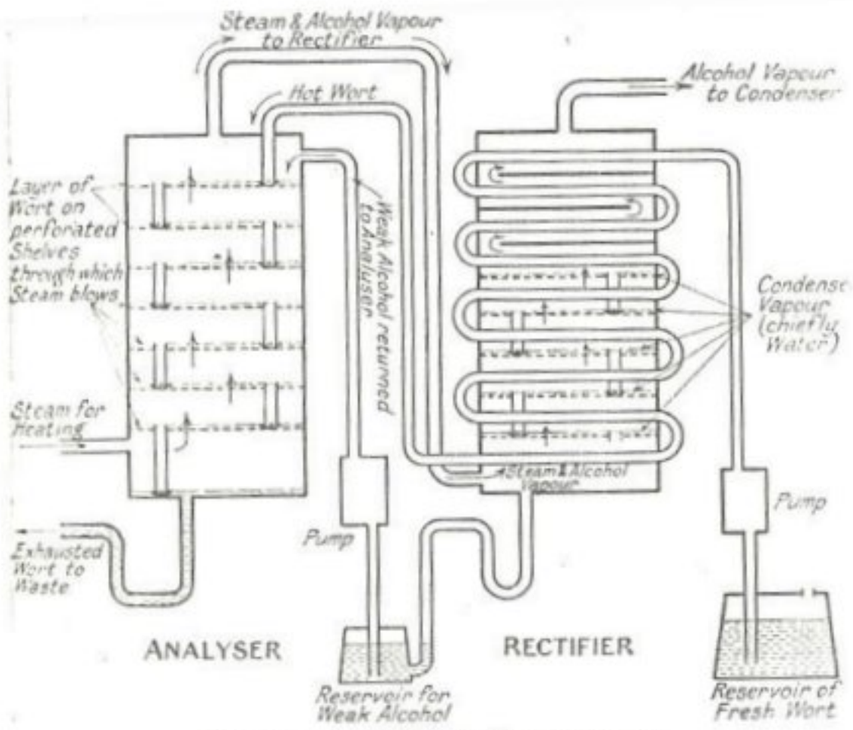


FIG. 35. COFFEY'S STILL (DIAGRAMMATIC)

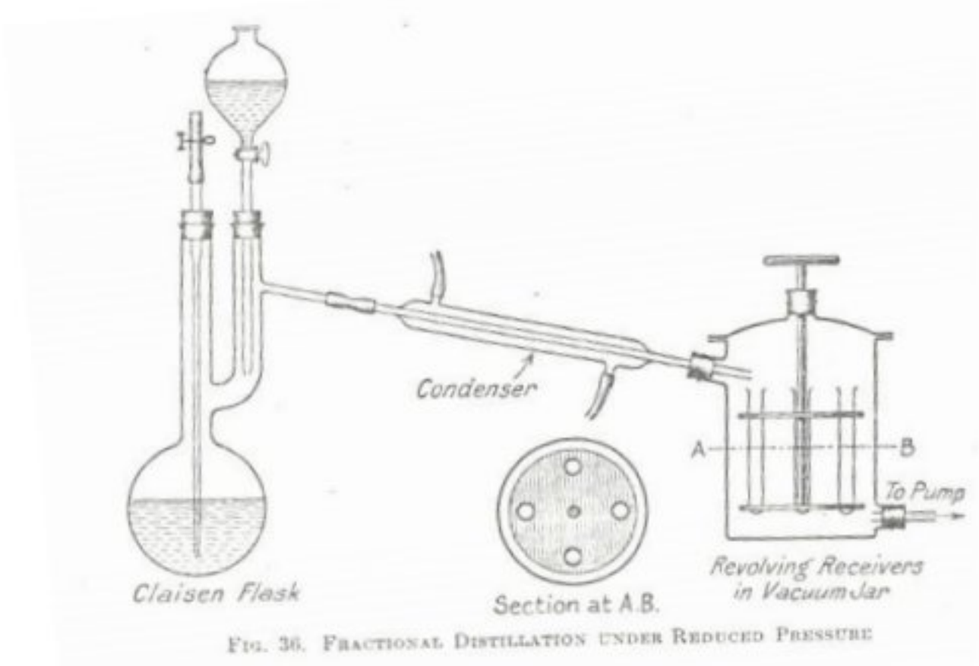


FIG. 36. FRACTIONAL DISTILLATION UNDER REDUCED PRESSURE

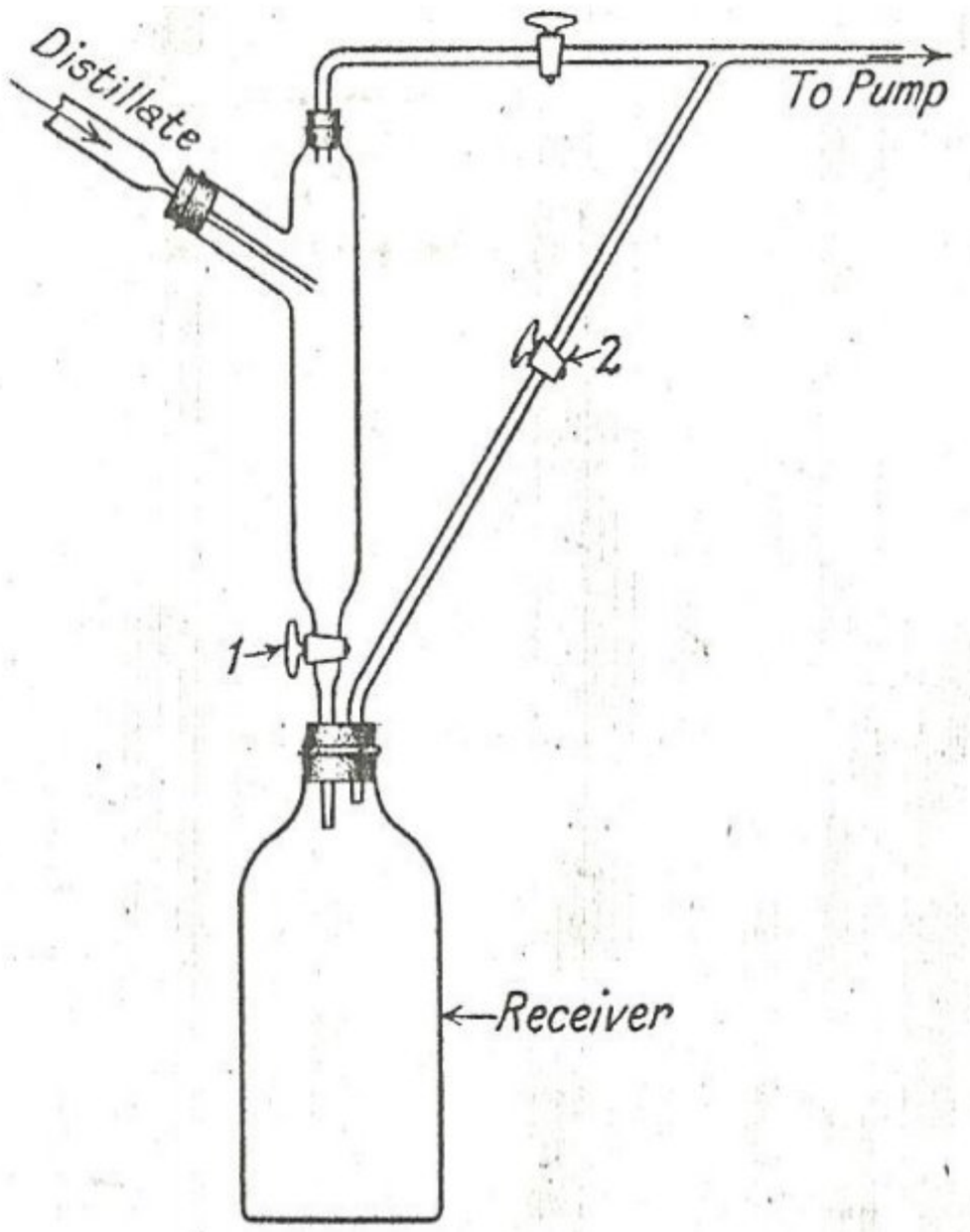


FIG. 37. APPARATUS FOR FRACTIONAL COLLECTION OF DISTILLATES

6.31 DESTRUCTIVE DISTILLATION

Destructive or dry distillation is the process of effecting decomposition of organic substances by heating them strongly without access of air.

- Destructive distillation of Wood
- Destructive distillation of Coal
- Destructive distillation of Shale.

6.32 DESTRUCTIVE DISTILLATION OF WOOD

The wood of Pinus sylvestris and other species of Pinus are used for distillation;

This distillation yields the following products;

- Gases (methane, ethane, ethylene, CO and hydrogen.
- A liquid distillate called pyroligneous acid.
- Charcoal or impure carbon left in the klin.

The wood yields 40-50% of its own weight of crude pyroligneous acid, the principal constituents of which are;

- Methyl of Wood Alcohol 3 - 4%
- Acetic Acid 6 - 8%
- Acetone 0.1-0.5%

- Water
  80%
- Tar (in solution and suspension)
  7%

6.33 Creosole (Oil of Tar)

From the destructive distillation of beech-wood which is richer in guaiacol. The Tar is distilled and the fraction of distillate obtained between 200° and 220°C is collected and separated and it consists principally of

- Guaiacol
- Creosole

6.34 Wood Charcoal

Material left in the retorts or kilns and consists of carbon with inorganic substances (ash) about 7%.

6.35 Destructive Distillation of Coal

Destructive distillation of Coal yields two layers:

- Aqueous layer (ammonium hydrogen carbonate, ammonium hydrosulphide and other compounds
- Tarry layer (crude coal tar)

Prepared coal tar contains phenols, basic compounds (e.g. aniline, pyridine, acridine), sulphur compounds (notably thiophene) and hydrocarbons (e.g. benzene, zylene, anthracene and naphthalene)

6.36 Destructive Distillation of Shale.

Principle compound is Ichthammol obtained from the tar obtained by destructive distillation of Shale.
Each ton of Shale yields 12-15 gallons of tarry oily distillate. This is redistilled and the fraction obtained between 100°-300°C is used in the manufacture of ichthammol.
This is subjected to following three processes:

- Sulphonation
- Washing
- Neutralization

Ichthammol contains:

- Ammonium Ichthosulphonate (>10.5%)
- Ammonium Sulphate (<1/4th)

Chapter 7 Miscellaneous Pharmaceutical Processes

7.1 Efflorescence

A large number of crystals exist in hydrated form i.e. molecules of water combine with their own molecules. This attached water is called water of crystallization. It should be noted that the presence of water of crystallization is not essential to the crystal structure e.g.; NaCl, KNO_3, tartaric acid and many other inorganic or organic substances have definite crystalline structure without water of crystallization. They are called anhydrous substances.

Hydrated substances under normal condition generate a small but definite aqueous vapor pressure due to their water of crystallization. The vapor pressure due to water in atmosphere is approximately 10 mm of Hg at 15°C. If the vapor pressure of hydrated substance exceeds atmospheric pressure, then the substance tends to give up its water to form substances with less water molecules or anhydrous substances. This phenomenon is known as "Efflorescence".

7.2 Deliquescence

If a substance has lower aqueous vapor pressure than the surrounding atmosphere, then it may take up water forming a definite hydrate containing a higher proportion of combined water and a solution of substance in water is formed. This property is known as deliquescence. It may take place in case of anhydrous substances. Substances liable to this change are called deliquescent or hygroscopic.

7.3 Exsiccation

Process of removing water of crystallization i.e. combined water from a substance is called exsiccation i.e. **a process of efflorescence controlled and accelerated**. The temperature needed to remove water of crystallization varies widely, e.g. $CuSO_4.5H_2O$ loses 2 molecules of water at 30°C, 2 more at 100°C and last one at 200°C. It is important to note that prolong heating at low temperature will not be effective, only desired temperature will remove water of crystallization. Heating is carried out on a water bath or in an oven. If definite hydrated substance is required, temperature is carefully controlled.

Salts containing large proportion of water of crystallization (e.g. $Na_2CO_3.10H_2O$) usually liquefy in its own water when heated. Certain salts cannot be completely exsiccated without decomposition e.g. $FeSO_4.7H_2O$, contains 7 molecules of water, loses 6 molecules on water bath but decomposes before losing the last one.

7.4 Desiccation

Desiccation or drying is a process of removing mechanically admixed water from substances (different from exsiccation).

Strictly speaking the term desiccation refers to the complete removal of water and term desiccated substance is used for those substances from which water has been completely removed. The term "dry" is frequently used to explain substances which still contain mechanically admixed water, provided this water is not noticeable to the touch e.g. majority of dry vegetable drugs such as senna leaves contains about 12% moisture. In pharmacy many processes are used for separation of liquid. The process used in drying may be classified to the degree of dryness needed.

7.5 Gravitational drying

It includes:

- Decantation
- Filtration
- Drainage
- Absorption

First two are methods of separation rather than drying. These methods constitute the processes by which the desired solid is separated from the greater portion of the liquid i.e. they are processes of drying preliminary to drying by evaporation.

7.6 Trituration

Trituration is the name of the process for reducing the particle size of a substance by grinding, as by grinding of powders in a mortar with a pestle. Trituration additionally refers to the production of a homogeneous material through mixing.

7.7 Levigation

It is the process of wet grinding. The material to be grounded is made into a paste with water. On the small scale grinding of paste may be effected in a mortar using a flat headed pestle. On the large scale, a mill like edge runner mill is used. The materials subjected to wet grinding include Kaolin B.P., prepared chalk, and calamine. The process of levigation on small scale has almost

ceased because now manufacturers supply levigated powders. At the end of levigation process, the paste contains fine particles with a small proportion of coarse particles which have escaped grinding. The fine particles are separated from the coarse particles by the process of elutriation.

7.8 Elutriation

It is the process of separation depending upon the low density of fine particles and high density of coarse particles. The paste prepared by levigation is mixed with a large volume of water and the mixture is allowed to stand for some time, during which the heavy coarse particles settled to the bottom of the vessel. The upper layer of liquid still contains the fine particles in suspension. The upper liquid is poured of or decanted and the fine particles are allowed to settle to the bottom. The wet paste consisting of fine particles, is then dried. On small scale, process can be carried out in a conical measure (flask) by simply pouring out the upper liquid containing fine particles. On large scale, elutriation tanks are used. They have stirring gear and a number of taps at regular intervals from top to bottom. This saves time.

7.9 Vaporization

Matter exists in three states:

- ✓ Liquid
- ✓ Solid
- ✓ Gas

The Kinetic energy postulates that molecules of matter are in a state of constant motion. The molecules at the surface of substance may leave if they have a free path and their velocity is sufficiently great. In other words some of the molecules pass into and become intermingled with the atmosphere. This is called vaporization. Rise in temperature increases the velocity of the molecules, hence more molecules escape from a hot substance. The vapors form in this way exerts a pressure called vapor pressure which varies with temperature.

7.10 Cooling effect of evaporation:

The molecules escapes from the surface are those possessing sufficiently high velocity, such molecules have the greatest kinetic energy. This explains why a liquid which is evaporating becomes cool because the molecules with the greatest heat content escape.

7.11 Latent heat of vaporization:

To maintain a liquid at the same temperature during evaporation, it is necessary to supply heat. This heat which doesn't make itself evident by a rise in temperature is called latent heat of vaporization. It is important to remember that more heat is required to evaporate water that to rise its temperature

7.12 Evaporation

Vaporization in which molecules or vapors escaping from a liquid aren't collected but allowed to diffuse into atmosphere is called evaporation.

It is one of the most important process in the manufacture of pharmaceutical preparation e.g. preparation of liquids, soft and dry extracts, extraction of enzymes, hormones, antibiotics and many other substances. There are many factors which influence evaporation e.g. physical factors, Pharmaceutical and technical factors.

7.13 Physical factors include:

a. Surface area of liquid exposed to atmosphere.
b. Difference between maximum and actual vapor pressure of atmosphere.
c. Ratio between pressure on the liquid and its vapor pressure.

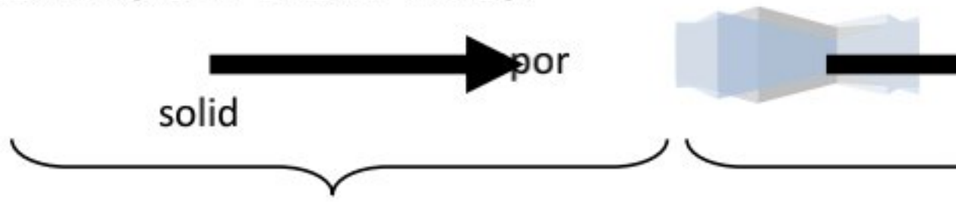
7.14 Pharmaceutical and technical factors:

a. Temperature.
b. Temperature and time of evaporation.
c. Temperature and moisture content .
d. Type of product require.
e. Films and deposits.
f. Cost and convenience.

7.15 Sublimation

Solids with higher vapor pressure can pass directly from the solid to the gaseous state without melting. This process is known as sublimation. The reserve process is i.e. recondensation to solid phase may be referred as deposition.

7.16 Process of sublimation can be classified into different types:

Type 1: Solid 

Vaporization

Condensation

Type 2: Solid → liquid → vapor → liquid → solid

Type 1 is true sublimation which occurs in very few compounds.

Type 2 is really distillation process because vapors arise from liquid but in pharmacy the process is common though erroneously described as sublimation.

The difference between the types is chiefly due to pressure. If a solid can, at some special temperature exert a vapor pressure equal to the external pressure, it will on heating to this point, pass directly to vapors and the reverse changes will occur on cooling vapors i.e. the sublimation will occur.

If a solid cannot, at any temperature, exert a vapor pressure equal to its external vapor pressure, on heating, it will first liquefy and when vapor pressure of the liquid equals to the external pressure, the liquid will boil and vaporizes and reverse will occur on cooling the vapors i.e. sublimation of type 2 will occur.

EXAMPLES OF TYPE 1: arsenic trioxide

EXAMPLES OF TYPE 2: iodine and camphor.

Triple point pressure of iodine is 91 mm of Hg and it melts at 114°C. Whereas the triple point pressure of camphor is 380 mm of Hg and it melts at 180°C.

7.16.1.1 TYPE 3 SUBLIMATION:

Solid→liquid→vapors → solid

7.17 ADSORPTION

It may be defined as concentration of a substance at the interphase or boundary between two heterogeneous phases e.g. solid or gas, two insoluble liquids, a solid and a liquid, a solid and a solution.

When charcoal is shaken with Strychnine Hydrochloride solution, the strychnine-HCl concentrates in a very thin layer which wets the charcoal. If the free liquid is filtered off, the thin layer of concentrated strychnine-HCl remains at the surface of charcoal and is said to be adsorbed by charcoal.

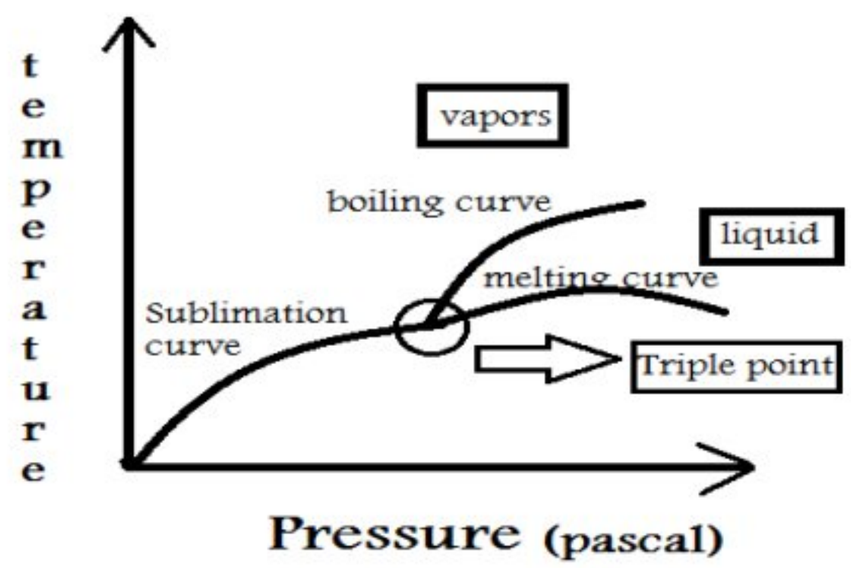
The essential feature of adsorption is therefore the occurrence of a difference between volume concentration and surface concentration and adsorption is said to be positive when volume concentration diminishes while surface concentration increased and negative when volume concentration increases and surface concentration diminishes.

7.18 ACTIVATION OF ADSORPTIVE AGENT:

It's a treatment whereby the surface of particles is freed from impurities, thereby ensuring maximum adsorption, or treatment leading to the formation of very small colloidal size particles, thus increasing the surface area.

For example, activated charcoal prepared from coconut shells is subjected to the action of steam and air at high temperature whereby impurities are removed. Activated charcoal is used in removing coloring materials from solvent used in dry cleaning, from sugar juices in the preparation of sucrose. It is also used in gas masks to adsorb poisonous gases.

Gr Lloyds's agent is a special hydrated aluminum silicate which is superior to Fuller's earth which chiefly consists of aluminum silicate, used as adsorptive in the preparation for Vitamin B1 B.P.



7.19 FUSION

Fusion or liquefaction is the process of heating a solid until it melts. Melting occurs sharply at a fix point or solid may pass gradually through a soft stage to form a liquid. The process is widely used in pharmaceutical works specially for melting fats, waxes and resins for the preparation of ointments, suppositories and plasters.

7.20 CALCINATION

It is the process whereby an inorganic substance is strongly heated so that any volatile component is driven off. It is used in gravimetric analysis and in the preparation of Calcii hydroxidum (Calcium Hydroxide), magneneii oxidum leve (light calcinated magnesia), zinc oxidum (zinc white).

7.21 Ignition

Organic matter when strongly heated in air, first carbonizes and then upon further heating, the carbon oxidizes to form carbon dioxide and an ash remains. This process is called as ignition or incineration or ashing. The process is applied in the official estimation of several organic salts of the alkali metals.

7.22 Centrifugation

It is the process whereby a substance or a liquid is rotated at a very high speed either to remove the liquid from the substance (for drying) or to separate suspended particles in a liquid.

Drying by centrifugal force is used in some industries and the machines used are called "hydro extractors". The process consist in placing the materials to be dried in a drum containing numerous holes and rotating at a very high speed. The water is thrown off from the material.

The process is also used in laboratory work for draining and drying crystals.

7.23 Centrifugal separation

The speed of sedimentation of a solid suspended in a liquid suspension depends upon the size of the particles, the viscosity of liquid and difference in densities between the solid and liquid. The speed of sedimentation is also governed by force of gravity.

By means of centrifugal apparatus, the suspended particles maybe subjected to a force many times greater than the force of gravity and sedimentation is speeded up to a remarkable extent.

The suspension is contained in a rotating container called bowl. The heavy solid particles are forced to the periphery of the bowl, the lighter liquid remains in the center. Large scale centrifugal separators work continuously, the suspension being fed upwards into the rotating bowl where the solid is collected on the walls and the clear liquid passes out at the top center.

Centrifugal separators play a considerable role in pharmaceutical clarification processes. One great advantage is absence of filtering media. They are used for varnishes, lacquers (sealing coat after polishing), oils of all kinds, animal fats and also used in the preparation of Insulin and Penicillin.

7.24 Freeze drying (lyophillization)

This term is used to describe drying by sublimation from the frozen condition and has become well known process in recent years because of its use for the drying of blood plasma, blood serum and different antibiotics.

The process involves freezing the solution of the materials in a suitable container connected to a high vacuum system. A partial pressure of water vapors less than that of material being dried is attained. Under these conditions, the water sublimes from the frozen mass until the material is desiccated. There are mainly three stages:

- Freezing
- Removal of vapors
- Aseptic transfer to the final container.

According to the USP and BP, less than 2% moisture in penicillin injection is required.

7.25 Freezing:

This is done by external cooling with mechanical refrigeration. The freezing temperature varies with different materials; important thing is that the material should remain frozen throughout drying process.

7.26 Water removal:

This is affected by ejector pumps or by rotary pumps. Sometimes, desiccants have been used additionally to remove the last traces of moisture.

7.27 Drying in bulk of final container:

The biological materials dried by sublimation are usually intended to be in sterile condition especially for injections. Drying in an ampule or bottle is satisfactory and reduces contamination risks.

Aseptic transfer of liquid is simpler than of a dry powder. Similarly a sterility test on a sample of concentrated liquid is satisfactory than one on dry powder.

Chapter 8 SOLUTION

A solution is a homogeneous mixture of two or more substances. A solution may exist in any phase.

8.1 SYSTEM

System is the bounded space which is under consideration.

8.2 PHASE

Phase is a distinct homogeneous part of a system separated by definite boundaries from other parts of the system.

8.3 DISPERSION

Dispersion consists of at least two phases with one or more dispersed (internal) phase contained in a single continuous (external) phase.

8.4 TYPE OF DISPERSION

- True solution
- Colloidal dispersion
- Coarse dispersion

8.5 TRUE SOLUTION

A true solution is defined as a mixture of two or more components that form a homogeneous molecular dispersion, Or a one phase system. The particle size in true solution is less than 1nm. A true solution cannot scatter light and cannot be visualized by microscopy.

8.6 COLLOIDAL DISPERSION

The colloidal dispersion can be heterogeneous or homogeneous (one-phase system). The particle size in colloidal dispersion is greater than true solution but less than coarse dispersion i.e. 1 to 500 nm.

8.7 COARSE DISPERSION

The particle size in coarse dispersion is greater than 500nm (0.5µm). There are two common type of coarse dispersion in pharmaceutics

1. Emulsions (liquid-liquid dispersion)
2. Suspension (solid-liquid dispersion)

8.8 BINARY SOLUTION

A solution consisting of only two substances is known as binary solution.

8.9 SOLUTE & SOLVENT

A solution consists of two or more substances; the substance which is greater in amount is called the solvent while the substance which is lesser in amount is referred as solute.

Generally in liquid and solid solution the liquid is taken as solvent while the solid substance is the solute irrespective of material quantity. Similarly in case of a solution consisting of water and any other solid or liquid substance, the water is taken as solvent while the other substance is the solute irrespective of the material quantity.

8.10 TYPES OF SOLUTIONS ACCORDING TO STATES

Solute	Solvent	Types of solutions	Examples
Solid	Solid	Solid in solid	Alloys
Liquid	Solid	Liquid in solid	Hydrated salts
Gas	Solid	Gas in solid	Dissolved gases in minerals
Solid	Liquid	Solid in liquid	Salt solution in water
Liquid	Liquid	Liquid in liquid	Alcohol in water
Gas	Liquid	Gas in liquid	Aerated drinks
Solid	Gas	Solid in gas	Iodine vapours in air
Liquid	Gas	Liquid in gas	Humidity in air
Gas	Gas	Gas in gas	Air

8.11 TYPES OF SOLUTE

8.12 NON-ELECTROLYTE

The substances that do not ionize when dissolved in water and do not conduct electric current is called non-electrolyte, e.g. solution of sucrose, urea and glycerin.

8.13 ELECTROLYTE

The substances that ionize when dissolved in water and conduct electric current is called electrolyte. There are further divided into

1. Strong Electrolyte: Substance that completely ionized in water, e.g. HCl and Sodim Sulphate.
2. Weak Electrolyte: Substances that partly ionized in water, e.g. Ephedrine and Phenobarbital.

8.14 PHYSICAL PROPERTIES OF SUBSTANCES

- EXTENSIVE PROPERTIES: Properties which depend on the quantity of the matter in the system, e.g. mass and volume.
- INTENSIVE PROPERTIES: Properties which are independent of the amount of the substances in the system, e.g. temperature,

pressure, density, surface tension, and viscosity of pure liquid.

The physical properties of the substance can be classified into following:

1. ADDITIVE PROPERTIES: depend on the total contribution of the atoms in the molecule or the sum of properties of the constituents in a solution, e.g. molecular weight.
2. CONSTITUTIVE PROPERTIES: depend on the arrangement and number or kind of atoms within a molecule, e.g. refraction of light, electric properties and solubility (also are additive properties)
3. COLLIGATIVE PROPERTIES: depend mainly on the number of particles in a solution, e.g. osmotic pressure, vapor pressure lowering, freezing point depression and boiling point elevation.

8.15 CONCENTRATION EXPRESSION

MOLES: Moles is the gram molecular weight of a substance.

GRAM EQUIVALENT WEIGHT: It is the mass of a given substance which will:

- Supply or react with one mole of hydrogen cations H^+ in an acid–base reaction; or
- Supply or react with one mole of electrons− in a redox reaction.

The Concentration of solution can be expressed in following terms:

- MOLARITY (M): Moles of solute in 1 liter of solvent.
- NORMALITY (N): Gram equivalent weight of solute in 1 liter solvent.
- MOLALITY (M): moles of solutes in 1000g of solvent.
- MOLE FRACTION (X): ratio of moles of one constituent of a solution to the total moles of all constituent.

$$X_1 = \frac{n_1}{n_1 + n_2} \qquad X_2 = \frac{n_2}{n_1 + n_2}$$

Where X_1 is the mole fraction of constituent 1 while the X_2 is the mole fraction of constituent 2 and n_1 and n_2 are the numbers of moles of respective constituent in the solution.

- MOLE PERCENT: moles of constituent of 100 moles of the solution.
- PERCENT BY WEIGHT (%W/W): Gram of solute in 100g of solution.
- PERCENT BY VOLUME (%V/V): milliliters of solute in 100mL of solution.
- PERCENT WEIGHT-IN-VOLUME (% W/V): grams of solute in 100mL of solution.
- MILLIGRAM PERCENT: milligram of solute in 100mL of solution.

Molarity is the general unit that used in the most of chemistry calculation; we usually use this unit to define the concentration of the solution in stoichiometry calculation. Molality usually uses to define the physical properties of the solution like vapor pressure, boiling point elevation, and freezing point depression of solution. We use normality in the volumetric calculation especially in the titration calculation.

IDEAL SOLUTION: A solution in which there is no change in the properties of the components, other than dilution, when they are mixed to form a solution; no heat is evolved or absorbed during the process, and the final volume represent the additive properties of the individual constituent. It means complete uniformity of attractive forces.

ESCAPING TENDENCY: The tendency to escape or expand is called escaping tendency. The escaping tendency of hotter body is greater than the escaping tendency of colder one.

8.16 RAOULT'S LAW

Raoult's law states that, any particular temperature, the partial pressure of one component of a binary mixture is equal to the mole fraction of that component multiplied by its vapor pressure in the pure state at this temperature.

According to Raoult's law, in an ideal solution the partial pressure (P) of each volatile constituent is equal to the vapour pressure of the pure constituent (P^o) multiplied by its mole fraction (X).

$$P = P^o \times X$$

REAL SOLUTION: Solution which does not follow the Raoult's Law is called non-ideal solution or real solution.

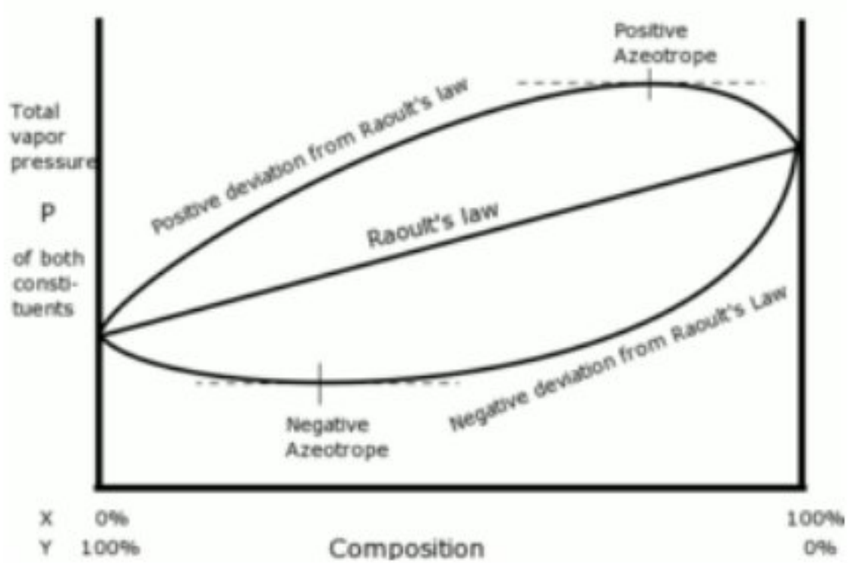
The real solution show deviation from Raoult's Law, which are

8.17 NEGATIVE DEVIATION

When the adhesive attraction between molecules of different species exceed the cohesive attraction between like molecules, the vapour pressure of the solution is less than expected from Raoult's Law and d negative deviation occur.

8.18 Positive Deviation

When the adhesive attraction between molecules of different species is less than the cohesive attraction between like molecules, the vapour pressure of the solution is greater than expected from Raoult's Law and d positive deviation occur.



8.19 Colligative Properties

8.20 Lowering of Vapour Pressure

When a non-volatile solute is combined with a volatile solvent, the solute decreases the escaping tendency of solvent, which on the basis of Raoult's Law lower the vapour pressure of the solution. **Manometric method is used to determine vapour pressure.**

If the vapour pressure of solvent with dilute solute is P_1, and pure solvent is P_1°. X_1 and X_2 are the mole fraction of solvent and solute then according to Raoult's law,

$$P_1 = P_1^o \times X_1$$

We know that,

$$X_1 + X_2 = 1$$
$$X_1 = 1 - X_2$$

Putting the value of X_1 in first equation we get,

$$P = P_1^o(1 - X_2)$$
$$P = P_1^o - P_1^o X_2$$
$$P_1^o - P = P_1^o X_2$$
$$\frac{P_1^o - P}{P_1^o} = X_2$$
$$\frac{\Delta P}{P_1^o} = X_2$$

The relative lowering of vapour pressure depend only on the mole fraction of solute.

As,

$$X_2 = \frac{n_2}{n_1 + n_2}$$

So,

$$\frac{\Delta P}{P_1^o} = \frac{n_2}{n_1 + n_2}$$

As n_2 is negligible in a very dilute solution so $n_1 + n_2 \approx n_1$

$$\frac{\Delta P}{P_1^o} = \frac{n_2}{n_1}$$

Where $n_2 = \frac{w_2}{M_2}$ and $n_1 = \frac{w_1}{M_1}$

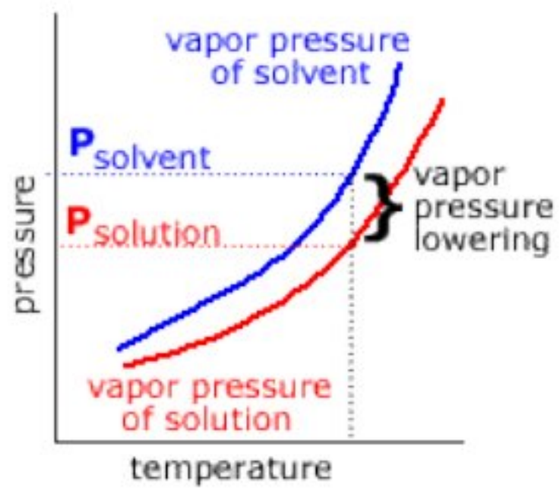
If the weight of the solvent (w_1) is 1000g then

$$\frac{\Delta P}{P_1^o} = \frac{\frac{w_2}{M_2}}{\frac{1000}{M_1}}$$

We know that W_2/M_2= m

So

$$\frac{\Delta P}{P_1^o} = \frac{m}{\frac{1000}{M_1}}$$
$$\frac{\Delta P}{P_1^o} = \frac{M_1 m}{1000}$$



8.21 Elevation of Boiling Point

A solution will boil at higher temperature than a pure solvent boil because of the lowering of vapour pressure; this colligative property is called boiling point elevation. **Cottrell apparatus is used for finding elevation of boiling point.**

Elevation of boiling point

$$T - T_o = \Delta T_b$$

Lowering of vapour pressure

$$\Delta P = P^o - P$$

The ratio of elevation of boiling point is proportional to the lowering of vapour pressure

$$\Delta T_b \propto \Delta P$$
$$\Delta T_b = K\Delta P$$

As P^0 is boiling point constant it can be considered proportional to $\Delta P/P^{\circ}$

$$\Delta T_b = \frac{K\Delta P}{P_o}$$

According to Raoult's Law

$$\frac{\Delta P}{P_1^o} = X_2$$

So

$$\Delta T_b = KX_2$$
$$\Delta T_b = K\frac{n_2}{n_1 + n_2}$$

As

n
$_1 + n_2 \approx n_1$

So

$$\Delta T_b = K\frac{n_2}{n_1}$$

Where $n_2 = \frac{w_2}{M_2}$ and $n_1 = \frac{w_1}{M_1}$

If the weight of the solvent (w_1) is 1000g then

$$\Delta T_b = K\frac{\frac{w_2}{M_2}}{\frac{1000}{M_1}}$$

We know that W_2/M_2= m

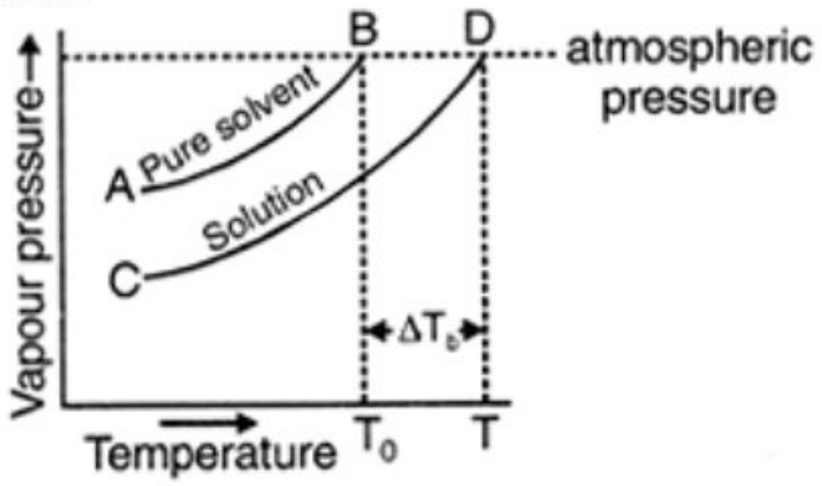
$$\Delta T_b = K\frac{m}{\frac{1000}{M_1}}$$

$$\Delta T_b = K\frac{M_1 m}{1000}$$

OR

$$\Delta T_b = K_b m$$

Where K_b is the ebullioscopic constant, which can be defined boiling point elevation for an ideal 1m solution.



8.22 Depression of Freezing Point

A solution will freeze at low temperature than a pure solvent freeze because of the lowering of vapour pressure; this colligative property is called depression of freezing point. **Beckmann's Apparatus or Equilibrium Apparatus is used to determine depression of freezing point.**

Depression of freezing point

$$T - T_o = \Delta T_f$$

Lowering of vapour pressure

$$\Delta P = P^O - P$$

The ratio of depression of freezing point is proportional to the lowering of vapour pressure

$$\Delta T_f \propto \Delta P$$

$$\Delta T_f = K\Delta P$$

As P^0 is freezing point constant it can be considered proportional to $\Delta P/P^\circ$

$$\Delta T_f = \frac{K\Delta P}{P_O}$$

According to Raoult's Law

$$\frac{\Delta P}{P_1^O} = X_2$$

So

$$\Delta T_f = KX_2$$

$$\Delta T_f = K\frac{n_2}{n_1 + n_2}$$

n
$_1 + n_2 \approx n_1$

So

$$\Delta T_f = K\frac{n_2}{n_1}$$

Where $n_2 = \frac{w_2}{M_2}$ and $n_1 = \frac{w_1}{M_1}$

If the weight of the solvent (w_1) is 1000g then

$$\Delta T_f = K\frac{\frac{w_2}{M_2}}{\frac{1000}{M_1}}$$

We know that W_2/M_2= m

$$\Delta T_f = K\frac{m}{\frac{1000}{M_1}}$$

$$\Delta T_f = K\frac{M_1 m}{1000}$$

OR

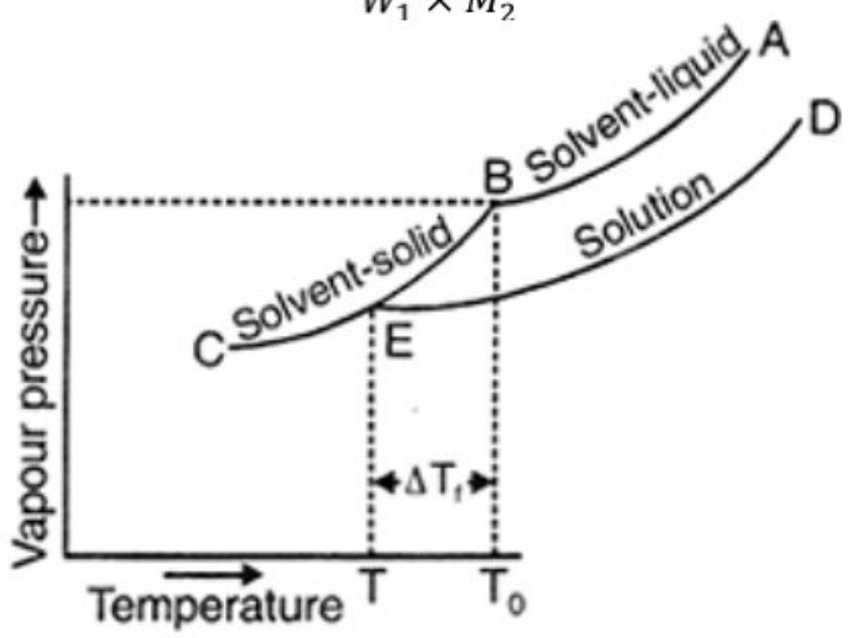
$$\Delta T_f = K_f m$$

Where K_f is the cryoscopic constant, which can be defined freezing point depression for an ideal 1m solution.

As we know $m = \frac{W_2}{W_1 \times M_2} \times \frac{1000}{}$

So the above equation can be written as

$$\Delta T_f = K_f \frac{W_2}{W_1 \times M_2} \times 1000$$



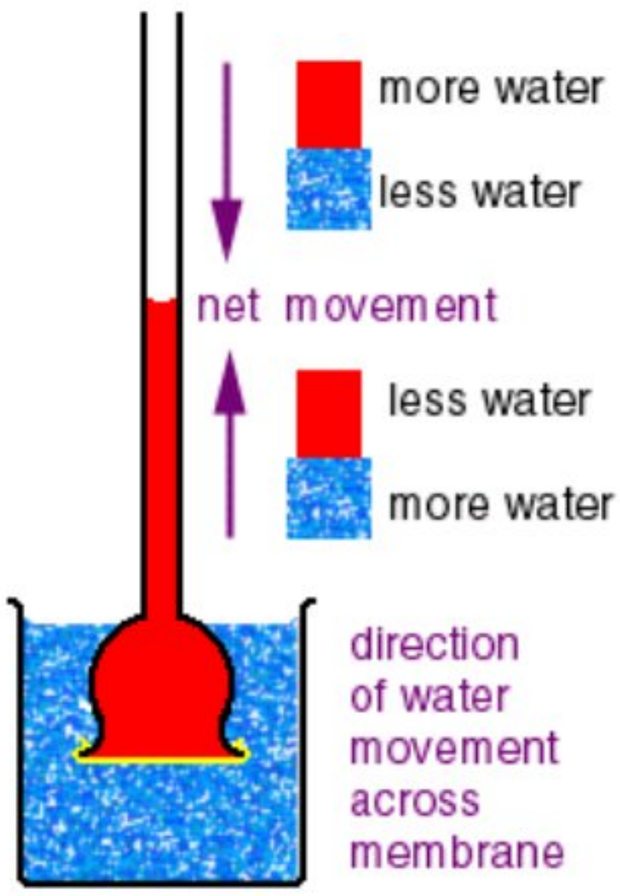
8.23 Osmotic Pressure

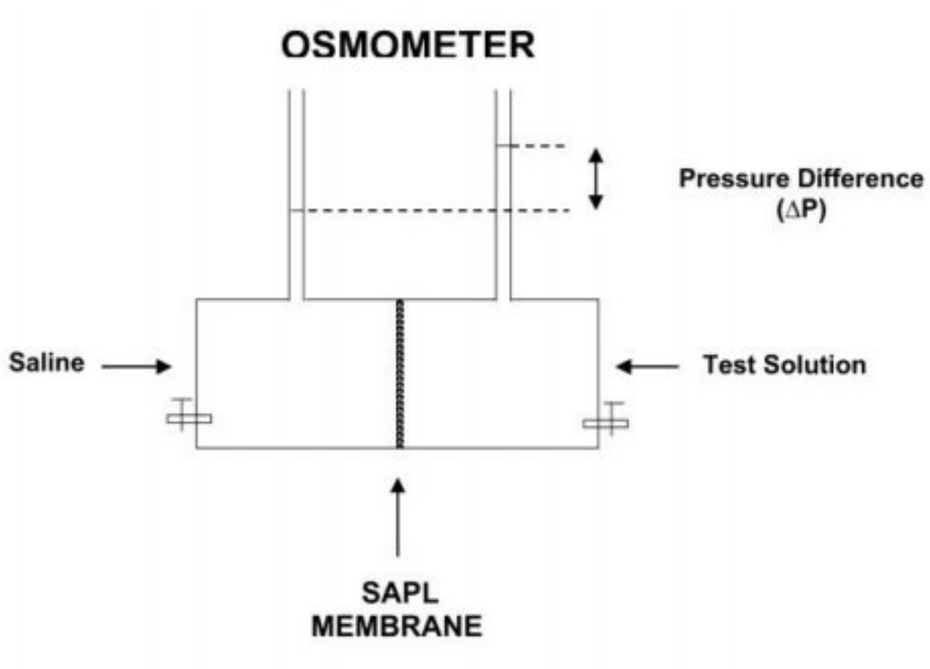
Osmosis is defined as the passage of solvent into a solution through semi-permeable membrane (is barrier which allow only the molecules of one component to pass through). This process tends to equalize the escaping tendency of solvent on both sides of semi-permeable membrane. The escaping tendency can be measured in term of vapour

pressure or the closely related colligative property osmotic pressure.

Osmotic pressure is defined as the pressure greater than that above the pure solvent, that must be applied to the solution to prevent the passage of the solvent through a perfect semipermeable membrane.

The phenomena of osmosis depends upon the fact that the chemical potential of a solvent molecule is less than that exsist in the pure solution.Solvent therefore passes spontaneously into the solution until the chemical potentials of solvent and solution are equal.





Osmotic pressure osmometers are shown in the figure above. It works on the same phenomena. Once equilibrium has been attained, the height of the solution in the capillary tube on the solution side of the membrane is greater by the amount *h* than the height in the capillary tube on the solvent side, the osmotic pressure can be measured by following formula

$$osmotic\ pressure\ \pi\ (atm) = height\ h\ \times solution\ density \rho \times gravity\ acceleration$$

8.24 Molecular Weight Determination

The four colligative properties discuss above can be used to determine the molecular weight of solvent in the following way:

$$\frac{\Delta P}{P_1^O} = \frac{n_2}{n_1 + n_2}$$

As n_2 is negligible in a very dilute solution so $n_1 + n_2 \approx n_1$

$$\frac{\Delta P}{P_1^O} = \frac{n_2}{n_1}$$

Where $n_2 = \frac{w_2}{M_2}$ and $n_1 = \frac{w_1}{M_1}$

$$\frac{\Delta P}{P_1^O} = \frac{\frac{W_2}{M_2}}{\frac{W_2}{M_1}}$$

By rearranging we get,

$$M_2 = \frac{W_2 M_1 P_1^O}{W_1 \Delta P}$$

The molecular weight of a non-volatile solute can similarly determine from depression of freezing point as shown:

$$\Delta T_f = K_f m$$

As we know $1000W_2/W_1$ is the weight of solute per kilogram of solvent , molality can be expressed as,

$$m = \frac{W_2}{W_1 \times M_2} \times 1000$$

So the above equation can be written as

$$\Delta T_f = K_f \frac{W_2}{W_1 \times M_2} \times 1000$$

By rearranging we get,

$$M_2 = K_f \frac{1000 W_2}{\Delta T_f W_1}$$

Similarly by boiling point elevation the equation will become,

$$M_2 = K_b \frac{1000 W_2}{\Delta T_b W_1}$$

8.25 Application:

Disadvantages of determination of molecular weight by boiling point method are that the solute must be nonvolatile and the substance is not decomposed at boiling temperatures.

Advantage of determination of molecular weight by freezing point method is that the solute can be volatile as the freezing point only depends on the vapour pressure of solvent. Freezing point method can be easily carried out and yields high accuracy of result.

Disadvantage of using freezing point or boiling point method is that they must be carried out at definite temperature.

Advantage of using Osmotic Pressure is that there is no need of definite temperature in osmotic pressure, so for high polymers osmotic pressure is use, such as for proteins molecular weight.

Chapter 9 SOLUBILITY

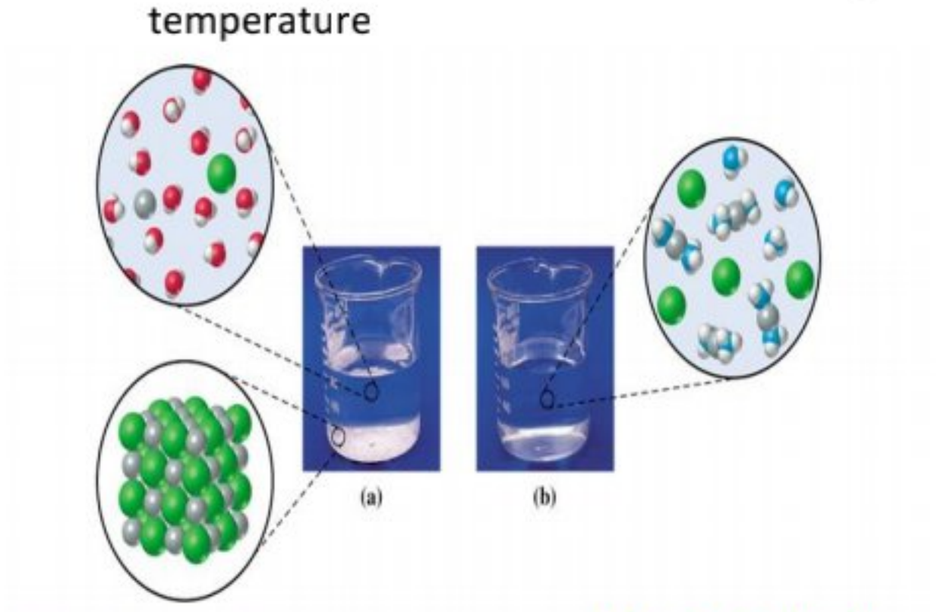
9.1 SOLUBILITY

Solubility in quantitative terms is defined as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.

Solubility is rate and extent of solute to go into solvent to get homogenize until equilibria.

9.2 SATURATED, UNSATURATED, OR SUPERSATURATED

- Saturated solutions are holding as much solute as possible at a given temperature
- Unsaturated solutions will be able to dissolve more
- Supersaturated solutions are holding more than they should be able to at a given temperature

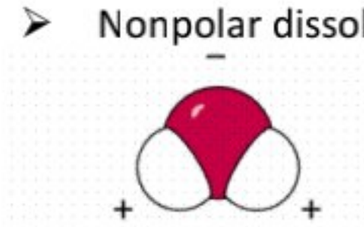


Saturated has some Solid on the bottom

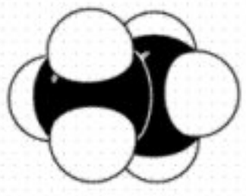
Unsaturated and supersaturated are completely dissolved

9.3 CONCEPTS OF SOLUBILITY

- Like dissolves like.
- Polar dissolves polar.
- Nonpolar dissolves Nonpolar.



Water, a polar molecule



Ethane, a nonpolar molecule

9.4 EXPRESSION FOR APPROXIMATE SOLUBILITY

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely Soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Practically insoluble	More than 10,000

9.5 THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

9.6 PROCESS OF SOLUBILIZATION

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

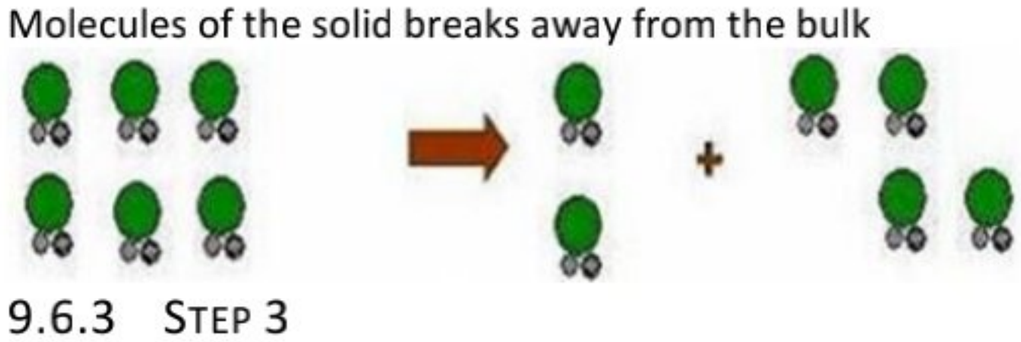
Process is explained in three steps as follow:

9.6.1 STEP 1

Holes Open in the Solvent

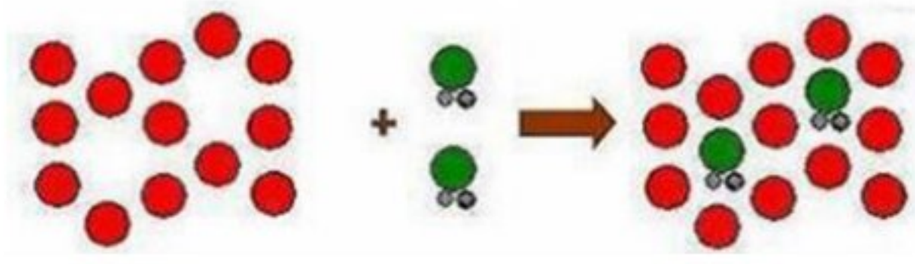
9.6.2 STEP 2

Molecules of the solid breaks away from the bulk



9.6.3 STEP 3

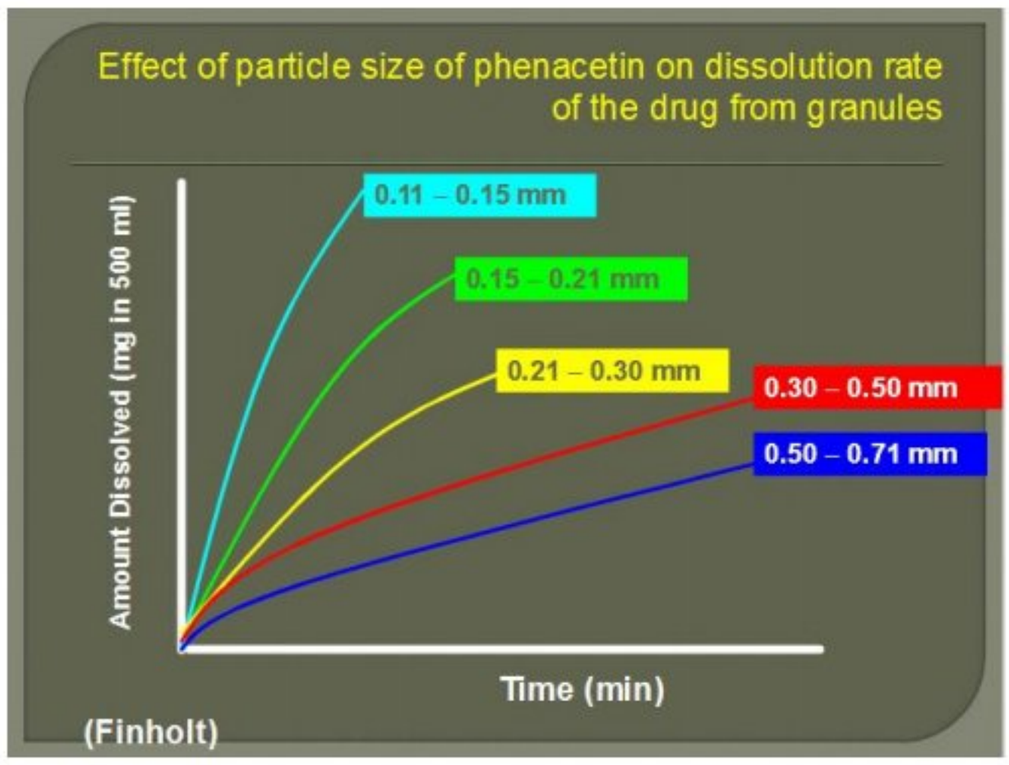
The freed sold molecule is integrated into the hole in the solvent.



9.7 PROCESS OF SOLUBILZATION

A mechanistic perspective of solubilization process for organic solute in water involves the following steps:

1. break up of solute-solute intermolecular bonds
2. break up of solvent-solvent intermolecular bonds
3. formation of cavity in solvent phase large enough to accommodate solute molecule
4. vaporization of solute into cavity of solvent phase
5. formation of solute-solvent intermolecular bonds
6. reformation of solvent-solvent bonds with solvent restructuring



9.8 Factor Influencing Solubility

1. Temperature
2. Surface area of solute
3. Hydrophobicity of solute
4. Pressure
5. Nature of solute and solvent

9.8.1 Effect of Temperature

- Generally in many cases solubility increases with the rise in temperatue and decreases with the fall of temperature but it is not necessary in all cases. However, we must follow tow behaviors:
- In endothermic process solubility increases with the increase in temperature and vice versa.
- For example: solubility of potassium nitrate increases with the increase in temperature.
- In exothermic process solubility decreases with the increase in temperature.
- For example: solubility of calcium oxide decreases with the increase in temperature.
- Gases are more soluble in cold solvent than in hot solvent.

9.8.2 Surface Area of Solute

- The size and shape of small particles (those in the micrometer range) also affect solubility. Solubility increases with the decreasing particle size and hence increasing the surface area of solute.

9.8.3 Effect of Particle Size

9.8.4 Hydrophobicity of Solute

- Hydrophobicity (from the Greek hydro, meaning *water*, and phobos, meaning *fear*) is the physical property of a molecules (known as a hydrophobe) that is repelled from a mass of water.
- Hydrophobic molecules tend to be nonpolar and, thus, prefer other neutral molecules and non-polar solvents. Hydrophobic molecules in water often cluster together, forming micelles.

9.8.5 Effect of Pressure

- The effect of pressure is observed only in the case of gases.
- An increase in pressure increases solubility of gas in liquid.
- For example carbon di oxide is filled in cold drink bottles under pressure.

9.8.6 Nature of Solute and Solvent

- Solubility of a solute in a solvent purely depends on the nature of both solute and solvent.
- A polar solute dissolved in polar solvent.
- And a non-polar solute is freely soluble in a non-polar solvent.
- A polar solute has low solubility or insoluble in a non-polar solvent.

Techniques of Solubility Enhancement

I .Physical Modifications

A. Particle size reduction
   a. Micronization
   b. Nanosuspension

B. Modification of the crystal habit
   a. Polymorphs
   b. Pseudopolymorphs

C. Drug dispersion in carriers
   a. Eutectic mixtures
   b. Solid dispersions
   c. Solid solutions

2.CHEMICAL MODIFICATION
A. Change of the pH
B. Use of buffer

PHYSICAL METHOD:

9.8.7 A) PARTICLE SIZE REDUCTION

9.8.8 A) MICRONIZATION

MICRONISATION INCREASES THE DISSOLUTION RATE OF DRUGS THROUGH INCREASED SURFACE AREA.

CONVENTIONAL METHODS OF PARTICLE SIZE REDUCTION COMMINATION AND SPRAY DRYING, MILLING TECHNIQUES USING JET MILL, COLLOID MILLS ETC.

b)Nanosuspensions

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants.

- increase in dissolution rate due to larger surface area.
- absence of ostwald ripening due to narrow size range of particle.

9.8.8.1 TECHNIQUES FOR PRODUCTION OF NANOSUSPENSION

A) HOMOGENIZATION:

9.8.8.2 CONVENTIONAL HOMOGENIZERS

9.8.8.3 SONICATORS

9.8.8.4 HIGH SHEAR FLUID PROCESSORS

9.8.8.4.1 **B) WET MILLING:**

9.8.8.5 ACTIVE DRUG IN THE PRESENCE OF SURFACTANT IS DEFRAGMENTED BY MILLING.

9.8.9 *O*THER TECHNIQUES FOR REDUCTION OF THE PARTICLE SIZE

- Recrystallization
- Supercritical fluid process
- Spray drying

9.8.10 B. MODIFICATION OF THE CRYSTAL HABIT

POLYMORPHISM

Amorphous >Metastable polymorph >Stable polymorph

9.8.11 C: SOLUBILIZATION BY SURFACTANTS:

MICROEMULSION

- A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant.
- Surfactant having HLB value greater than 18 acts as solubilising agent.

II. CHEMICAL MODIFICATIONS

1) BY CHANGE OF PH

- For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility.
- Change of pH by 1 fold increase solubility by 10 fold

9.8.12 2) USE OF BUFFER

- Buffer maintains the pH of the solution overtime and it reduces or eliminate the potential for precipitation upon dilution. On dilution pH alteration occurs that decrease solubility .
- If it changes by one pH unit ,that decrease ionization of the drug and solubility decreases by 10 fold.

MARKET PRODUCT	BUFFER
Mithohexital sodium	pH 9-11
Phenytoin sodium	pH 10-12.3

9.8.13 OTHER TECHNIQUES

9.8.14 COSOLVENCY:

- Cosolvents are prepared by mixing miscible or partially miscible solvents.
- Cosolvents have some degree of hydrogen bond donating and hydrogen bond accepting ability as well as small hydrocarbon regions.
- The resulting solution has intermediate to that of organic solvent and water that reduce water interaction.

Aqueous solvent - Etahnol,sorbitol, glycerin, propylyne glycol,polyethylene glycol

Non aqueous solvent - glycerol dimethyl ketal,glycerol formal, glycofurol, dimethyl acetamide , ethyl carbonate

COMPLEXATION

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one

molecule (known as guest) into the cavity of another molecule or group of molecules.

Chapter 10 SOLUBILIZATION

Micellar core is Praffin like and so capable of dissolving oil soluble molecules.

10.1 DEFINITION

The process whereby water insoluble substances are brought into solution by incorporation into micelles is termed as solubilization.

10.2 FACTOR AFFECTING SOLUBILIZATION

10.3 NATURE OF SURFACTANT

- In homologous series of Ionic surfactant solubilizing power increases with increase of hydrocarbon chain length
- In non-ionic surfactants an increase in oxyethylene chain length decreases the solubilizing power.

10.4 NATURE OF THE SOLUBILIZATE

- No relation between the amount of solubilized and the physical properties of solubilized molecule exists.
- An increase in alkylation Length of homologous series of solubilizate results into decrease in solubility
- Unsaturated compounds are relatively more soluble than their saturated counter parts
- Branching of solubilizate has no effect but cyclization generally increase the solubilization

10.5 EFFECT OF TEMPERATURE

In most system the amount of solubilized increases with increase in temperature this is particularly true in non-ionic surfactant as an increase in temperature gives/ causes an increase in micellar size.

10.6 PHARMACEUTICAL APPLICATION OF SOLUBILIZATION

A wide range of insoluble drugs have been formulated using the principle of solubilization

- **Phenobic Compounds** (Cersol, Chlorocersol, Chlorokylenol, Thymol etc.) are solubilizing in water exploiting the principle of solubilization. e.g. Dettol
- **Solubilization of Iodine in Non-Ionic Surfactant**
  Such preparation is known as iodophores
  Iodophores are less corrosive when used for surgical sterilization than Iodide-Iodine System.
- **Steroids for ophthalmic Preparation**
  Optical Clarity Requirement limits the use of oily solution so non-ionic surfactants (polysorbate or polyethylene sorbitian, esters of fatty acids are used to prepare solution of steroids in water.
- **Essential/Volatile Oils are solubilized using the principle of solubilization**
- **Water insoluble vitamins (A, D, E and K)**
  Fat soluble vitamins are made water soluble e.g. multivitamin syrups/ drops

❖ Problem of 'Cloud Point' is always there because it is decrease with added substances. Sucrose esters are used though increase hemolytic properties.

- **Many other drugs like**
  - Analgesics
  - Sedatives
  - Sulfonamide
  - Antibiotics etc.

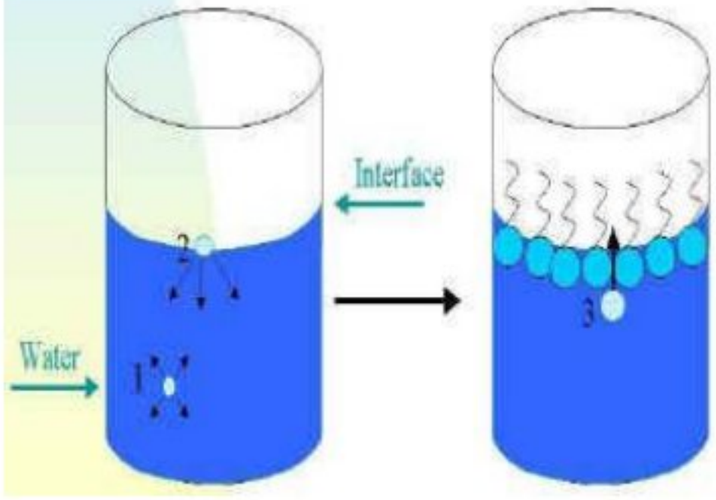
  These drugs are also solubilized using the solubilizing technique.

Chapter 11 SURFACTANTS

11.1 SURFACTANTS

- Surfactants are wetting agents that lower the surface tension of a liquid, allowing easier spreading, and lower the interfacial tension between two liquids.
- A surfactant or surface active agent is a substance that, when dissolved in water, gives a product, the ability to remove dirt from surfaces such as the human skin, textiles, and other solids.
- Each surfactant molecule has a hydrophilic (water-loving) head that is attracted to water molecules and a hydrophobic (water-hating) tail that repels water and simultaneously attaches itself to oil and grease in dirt

  - Surfactants are also referred to as wetting agents and foamers. Surfactants lower the surface tension of the medium in which it is dissolved. By lowering this interfacial tension between two media or interfaces (e.g. air/water, water/stain, stain/fabric)



11.2 NATURAL AND SYNTHETIC ORIGIN SURFACTANTS

They can be either. Surfactants from natural origin (vegetable or animal) are known as oleo-chemicals and are derived from sources such as palm oil or tallow. Surfactants from synthetic origin are known as petro-chemicals and are derived from petroleum.

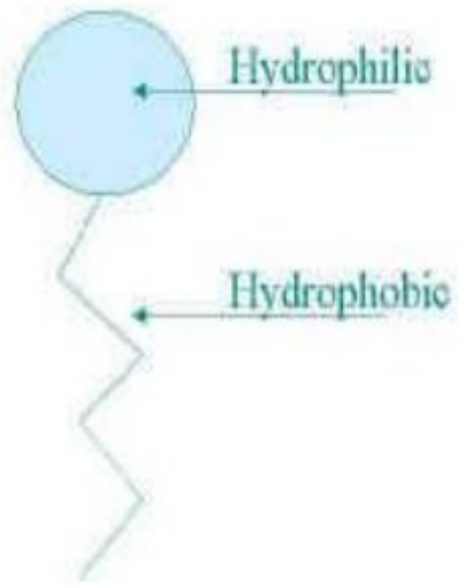
11.3

11.4 CLASSIFICATION OF SURFACTANTS

1) Ionic surfactant
   a) Anionic
   b) Cationic
   c) Zwitterionic (amphoteric)
2) Non-ionic surfactants

11.5 IONIC SURFACTANT

11.6 ANIONIC



In aqueous solution these ionizes into a large anion, responsible for emulsifying ability, and a small cation.
In solution, the head is negatively charged. This is the most widely used type of surfactant for laundering, dishwashing liquids and shampoos because of its excellent cleaning properties and high (based on sulfate, sulfonate or carboxylate anions)
An example : Sodium dodecyl sulfate (SDS)

*The most commonly used anionic surfactants are alkyl sulphates, alkyl ethoxylate sulphates and soaps.

11.7 ANIONIC SURFACTANTS HAVE 5 SUBGROUPS

11.7.1.1 ALKALI METALS AND AMMONIUM SOAPS

These are Na, K or NH4 slats of long chain fatty acids, such as olive, stearic and recinoleic. They usually produce O/W which are stable at pH above 10. They are sensitive to even weak acids. These are incompatible with polyvalent such as Al^{+3}, Ca^{+2}, Mg^{+2}, Zn^{+2} which causes phase inversion. They are not suitable for internal consumption or for broken skin due to high pH.

11.7.1.2 SOAPS OF DIVALENT AND TRIVALENT METALS

Ca^{+2}, Mg^{+2}, Zn^{+2} salts of fatty acids of these elements produce W/O emulsions. They are also not used internally but are less sensitive to acids.

11.7.1.3 AMINE SOAPS

A number of amines form salts with fatty acids. Most important is triethanolamine ($N(CH^2.CH^2OH)_3$).

11.7.1.4 ALKYL SULPHATES

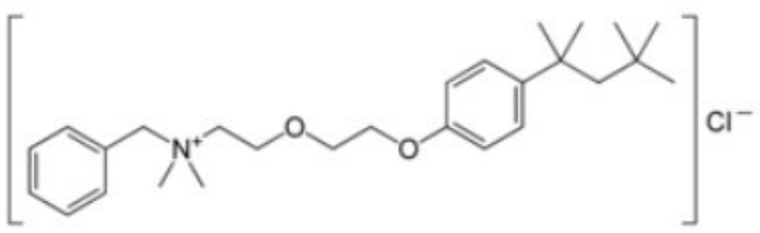
These are esters of fatty alcohols and H2SO4. The most important are Na-Lauryl sulphate and Na-cetostearyl sulphate. They alone produce O/W emulsions of low stability. But produce stable emulsion in conjunction with fatty alcohols.

11.7.1.5 Alkyl Phosphates

These are similar to alkyl sulphates but the alcohols are phosphated instead of sulphated. They are also used in combination with fatty alcohols.

11.8 Cationic

The quaternary ammonium compounds comprises the most important group of cationic surfactants. They have disinfectant and preservative qualities as well as emulsifying properties.
In solution, the head is positively charged. (based on quaternary ammonium cations)
An example : Benzethonium chloride (BZT)

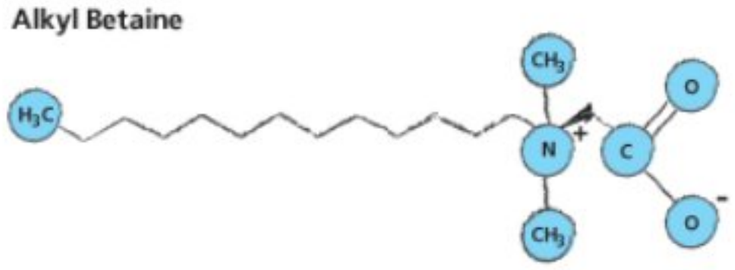


11.9 Zwitterionic (amphoteric)

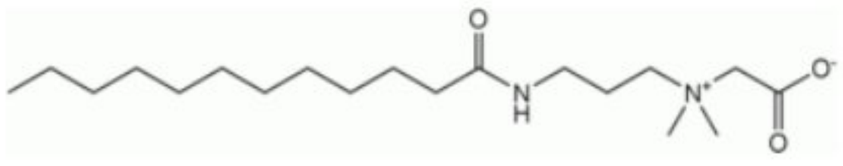
These surfactants are very mild, making them particularly suited for use in personal care and household cleaning products.
They can be:

1) anionic (negatively charged),
2) cationic (positively charged) or
3) non-ionic (no charge) in solution,
   - ❖ depending on the acidity or pH of the water.

An example of an amphoteric/zwitterionic surfactant is alkyl betaine



e.g. :Cocamidopropyl betaine



11.10 Non-ionic surfactants

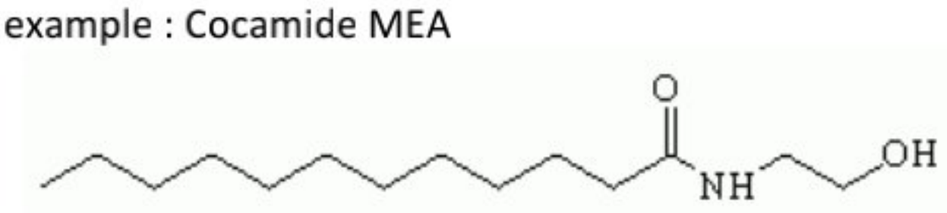
These surfactants do not have an electrical charge, which makes them resistant to water hardness deactivation.
They are excellent grease removers that are used in laundry products, household cleaners and hand dishwashing liquids.
All soluble surface active agents have;

- ❖ A hydrophobic group i.e. a long chain of hydrocarbon
- ❖ A hydorphilic group i.e. carboxy, hydroxy, amino group.

11.11 Types of Non-ionic Surfactants

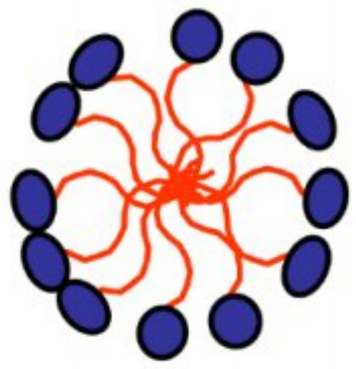
1) Glyco and Glycerol Esters
2) Sorbitan Esters
3) Macrogol Esters (Polyethylene or Polyoxyethylene glycol esters)
4) Macrogol Ethers
5) Poly-sorbates
6) Poloxalkols
7) Polyvinyl alcohols
8) Higher fatty alcohols
   - ❖ The most commonly used non-ionic surfactants are ethers of fatty alcohols

An example : Cocamide MEA



11.12 Micelle

A micelle (rarely micella, plural micellae) is an aggregate of surfactant molecules dispersed in a liquid colloid.



A typical micelle in aqueous solution forms a roughly spherical or globular aggregate with the hydrophilic "head" regions in contact with surrounding solvent, sequestering the hydrophobic tail regions in the micelle center.

11.13 Mechanism of Surfactant

Surfactants can work in three different ways:

1) Roll-up,
2) Emulsification, and
3) Solubilization

11.14 Roll-up mechanism

The surfactant lowers the oil/solution and fabric/solution interfacial tensions and in this way lifts the stain of the fabric.

11.15 Emulsification

The surfactant lowers the oil-solution interfacial tension and makes easy emulsification of the oily soils possible.

11.16 Solubilization

Through interaction with the micelles of a surfactant in a solvent (water), a substance spontaneously dissolves to form a stable and clear solution.

11.17 Applications of Surfactant

Surfactants play an important role in many practical applications and products, including:

11.18 Detergent

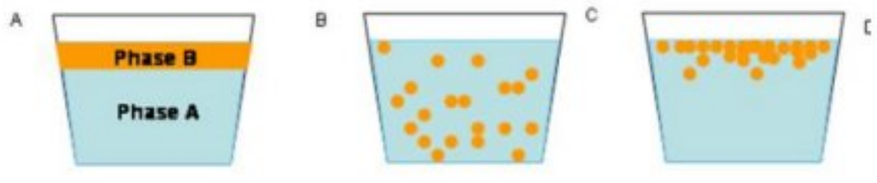
Detergent is a compound, or a mixture of compounds, intended to assist cleaning. The term is often used to differentiate between soap and other chemical surfactants used for cleaning purposes.

11.19 Fabric Softener

Fabric softenr (also called Fabric Conditioner) is used to prevent static cling and makes the fabric softer.

11.20 Emulsifier

Emulsifier (also known as an emulgent or surfactant) is a substance which stabilizes an emulsion.



11.21 Adhesive

Adhesive is a compound that adheres or bonds two items together.

11.22 Ink

Ink is a liquid containing various pigments and/or dyes used for colouring a surface to render an image or text. Ink is used for drawing or writing with a pen or brush.

11.23 Laxative

Laxative is a preparation used for encouraging defecation, or the expulsion of feces. Laxatives are most often taken to treat constipation.

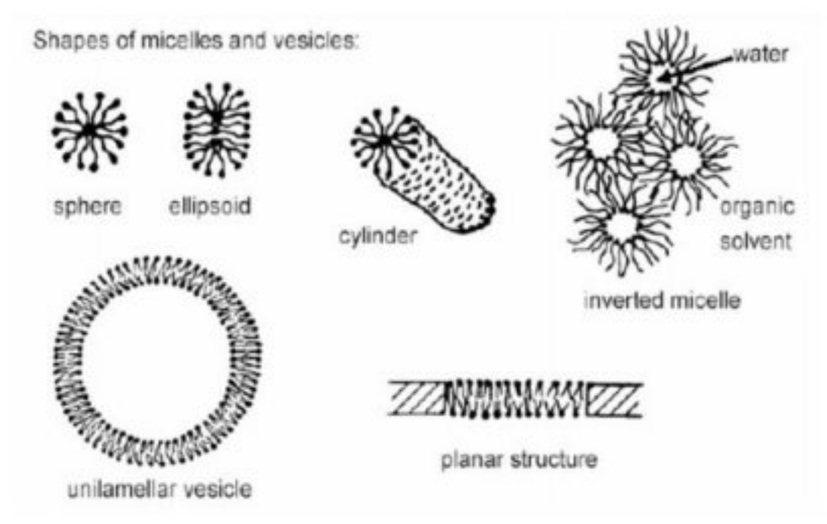
11.24 Other Application of Surfactants

- Wetting
- Ski Wax
- Snowboard Wax
- Foaming
- Defoaming
- Quantum dot coating
- Biocides (Sanitizers)
- Hair Conditioners (after shampoo)
- Spermicide (Nonoxynol 9)

Chapter 12 MICELLIZATION

- With the increasing concentration of amphiphiles i.e. after CMC certain physical properties show profound deviation from their general trends
- Some of these properties show increasing trend while other show decreasing trend
- This is due to the self-association of monomers to form micelles
- The process of forming micelles is known as micellization.
- Micelles are always of dynamic equilibrium that means, number of monomers associate to form micelle remain same however some monomers leave micelle while other monomers from the bulk join micelles to keep the number constant.
- MICELLES: As the concentration of monomer is increased, aggregation occurs over a narrow concentration range. These aggregates which may contain 50 or more monomers are called micelles. A micelles lie within the size range of colloidal system.
- CMC: the concentration of monomer at which micelles form is termed as the critical micelle concentration.
- MICELLIZATION: the process of micelle formation is known as micellization
- Compounds forming micelles are called: Surfactant, surface active agent or amphiphiles
- There are drugs which also from micelles and are known as micellar drugs e.g. cholorquine, diphenhydramine, orphenadrine, chlorphenoramine etc.

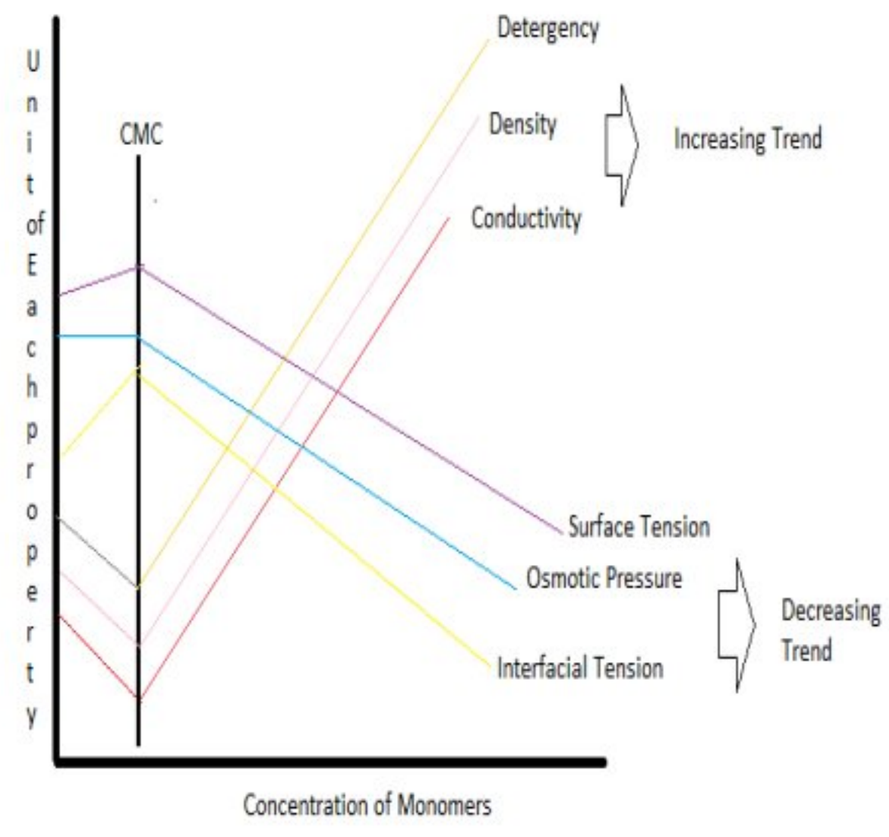
12.1 TYPES OF MICELLES



12.2 MICELLE SHAPE AS PER TYPE OF SURFACTANT

General Surfactant Type	Expected Aggregate Structure
Simple surfactants with single chains and relatively large head groups	Spherical or ellipsoidal micelles
Simple surfactants with relatively small head groups, or ionic surfactants in the presence of large amounts of electrolyte	Relatively large cylindrical or rod-shaped micelles
Double-chain surfactants with large head groups and flexible chains	Vesicles and flexible bilayer structures
Double-chain surfactants with small head groups or rigid, immobile chains	Planar extended bilayer structures
Double-chain surfactants with small head groups, very large, bulky hydrophobic groups	Reversed or inverted micelles

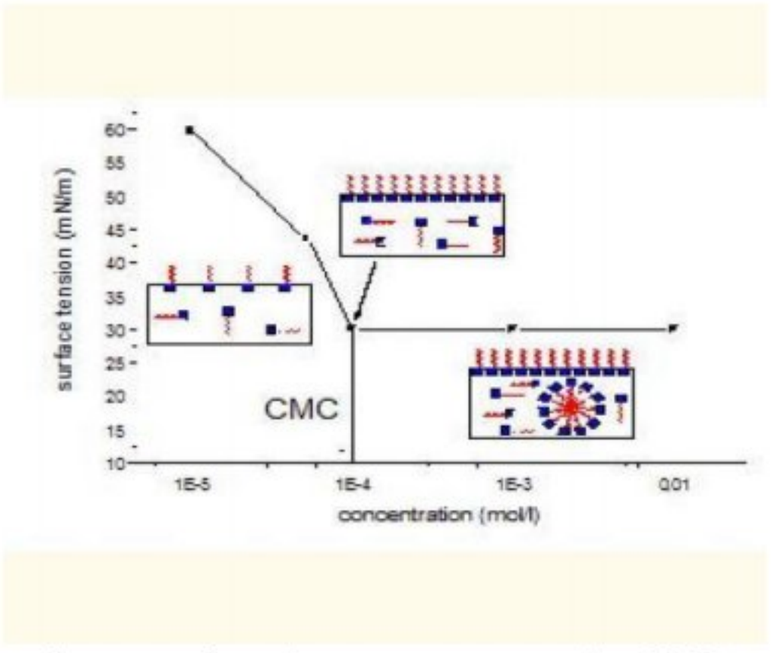
12.3 INCREASING AND DECREASING TREND OF MICELLES



These properties can be used to determine the CMC.

12.4 Determination of CMC

Below the CMC the concentration of amphiphiles undergoing adsorption at the air-water interface increases as the total concentration of amphiphiles is raised. Eventually a point is reached at which both the interface and the bulk phase become saturate with monomers. This is called CMC. Any further amphiphiles added in excess of this concentration aggregates to form micelles in the bulk phase and in this manner the free energy of the system is reduced. It affects some physical properties of the system. Some properties shows increasing trend while some other shows decreasing trend.



E.g. the surface tension decreases up to the CMC and above the CMC, the surface tension remains constant, this shows that the interface is saturated and micelle formation has taken place in the bulk phase.

12.5 Factors affecting the CMC and Micelle Size

12.6 Nature of the Hydrophobic Group

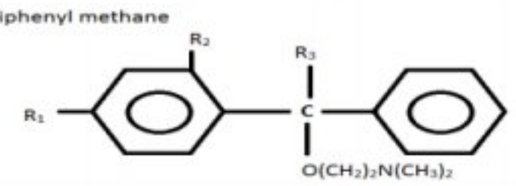
Hydrophobic group plays important role in determining type of association of group. Micellar amphiphiles have hydrocarbon groups' constracted from hydrocarbon chains. Increase in length of this chain will decrease CMC and increase aggregation number.

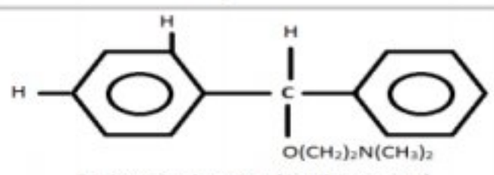
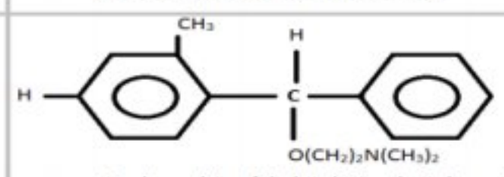
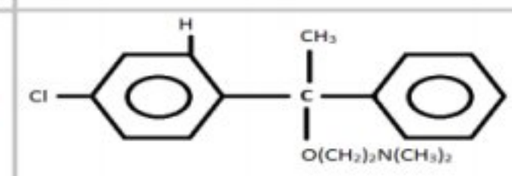
Many drugs are surface active agents and form micelles. For example, diphenyl methane drugs. (diphenhydramine, orpheradrine, chlorphennoxamine etc.)

Hydrophilicity/ Hydrophobicity and substitute on such drugs play very important role in the determination of CMC and Aggregation number

Some representative examples:

Diphenyl methane



	Drug	CMC (mol/kg)	Micellar Aggregation Number
	 Diphenyhydramine (Antihistamine)	0.132	03
	 Orphenadrine (Skeletal Muscle Relexant)	0.096	07
	 Chlorphenoxamine (Antiparkinonism)	0.045	13

- Antiparkinoism Drugs are used to reduce muscular rigidity neurological disorder marked by hypokinesia (abnormally diminished motor activity tremor and muscular rigidity).

12.6.1.1 Other Examples

12.6.1.1.1 Phenothiazine Tranqulizer

- Priomazine
- Chlorpromazine
- Promethazine

12.6.1.1.2 Antidepressants

- Imipramine
- Amitriptyline
- Nor-triptyline

They have tricyclic hydrophilic moieties

- Many aromatic and hetero aromatic ring structure (dyes, purines, pyrimidine) associate in non-micellar process.

12.7 Nature of Hydrophilic Group

- Ionic hydrophilic groups of amphiphiles show different properties then Non- ionic hydrophilic groups may be due to difference in charge.
- In general non-ionic surfactants have "low CMC" and high

aggregation numbers although they have same length of hydrocarbon chain. This is because in non-ionic surfactant no electrical work during the process of micellization.

12.8 Effect of the Counter-ion

- In case of cationic surfactant as the counter ion is charged in series, Cl^-, Br^-, I^- , micelle size is an increase in order for $Cl^- < Br^- < I^-$.
- In case of anionic surfactant as the counter ion is charged in series ,Na^+, K^+, Cs^+, micelle size is an increase in order for $Na^+ < K^+ < Cs^+$.
- More weakly hydrated a counter ion larger the micelle formed.

12.9 Effect of hydrophobic group

- If hydrophobic group is aromatic, micelle does not form.
- Length of hydrocarbon chain is directly proportional to micelle size & inversely proportional to CMC. We express this in mathematical term,

$$\text{Log [CMC]} = A - Bm$$

Where,

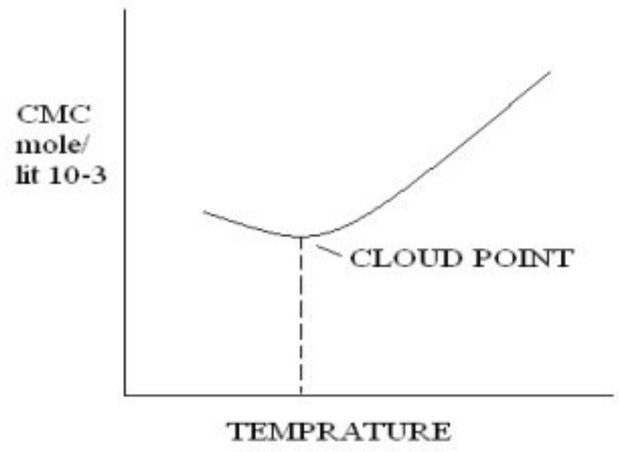
- A & B are homologous series constant.
- m is the no. of carbon atom in chain.

12.10 Addition of Electrolytes

Electrolytes reduce the charges (force) on ionic surfactants so there is reduction in the magnitude of the force of repulsion between the charges had groups on the micelles. Hence, there is reduction in CMC and increase in aggregation number.

12.11 Effect of Temperature

- This effect in particularly seen in non-ionic surfactants.
- Solution of non-ionic surfactants when heated they turn turbid at a characteristic temperature known as “cloud temperature”
- Turbidity at “cloud point” is due to separation of the solution into “two” phases. i.e. dispersed phase of dispersion medium.
- At temperature up to cloud point there is increase in Aggregation No. and decrease in CMC.
- Temperature has no profound effect on CMC and aggregation No. of Ionic Surfactant.



12.12 Application

- Micelle increases bioavailability of poorly soluble drugs.
- Polymeric micelle is used to target the tumor site by passive as well as active mechanism.
- Micelle is used in ophthalmic drug delivery system that effectively delivers the drug to posterior tissue of eyeball.
- Micelle is used to encapsulate the antibiotic & anticancer drugs.

Chapter 13 IONIZATION

13.1 THEORY OF IONIZATION

Ionization theory was presented by Arrhenius in 1887 which consist of following postulates:

- The substances called electrolytes are believed to contain electrically charged particles called ions. These charges are positive for H+ ion or ions derived from metals and negative for the ions derived from non-metals. Number of electrical charges carried by an ion is equal to the valency of corresponding atom.
- Molecules of electrolytes (acids, bases and salts) dissociate into oppositely charged ions on dissolution in water, e.g.

$$NaCl \rightleftharpoons Na^+ + Cl^-$$

$$HCl \rightleftharpoons H^+ + Cl^-$$

$$NaOH \rightleftharpoons Na^+ + OH^-$$

- The number of positive and negative charges on the ions must be equal so that the solution as a whole remains neutral.
- In solution, the ions are in a state of disorderly or random motion. Upon colliding they may combine to give unionized molecules. Thus ionization is a reversible process in which the solution contains ions of electrolyte together with unionized molecules.

$$H_2SO_4(aq) \rightleftharpoons 2H^+(aq) + SO_4^{-2}(aq)$$

- The extent of ionization or the degree of ionization depends upon the nature of electrolyte.strong electrolytes such as HCl etc. ionize completely in water. Weak electrolytes such as acetic acid (CH_3COOH) ionize only slightly
- Ionization is not affected by electric current.
- When electric current is passed through an electrolytic solution, charges move towards their respective electrodes, i.e. cations towards anode and anions towards cathode. When these ions reached their respective electrodes, they change into neutral species by the gain or loss of electron.

- The dissociation of electrolyte depend upon:
  - Nature of electrolyte
  - Degree of dilution
  - Temperature
- The electrical conductivity depends upon :
  - The number of ions present in the solution
  - Speed of ions

13.2 LAW OF MASS ACTION

- Law of mass action is stated by Guldberg and Waage. It states about the influence of the concentration of the reactants on the rate of reaction.
- Law of mass action states that the rate at which substance reacts is proportional to its active mass and the rate of chemical reaction is proportional to the product of the active masses of the reactants.
- Active mass is the number of moles per liter. It is represented by placing the chemical formula of the substance in square brackets. For example HCl is represented as [HCl].

13.3 EXPLANATION OF LAW OF MASS ACTION

Consider a sample reaction of

$$A + B \leftrightarrow X + Y$$

As per the law of mass action the rate of forward reaction = α [A] [B]

= Kf [A] [B]

Where Kf is proportionality constant and is termed as rate constant for forward reaction.

Similarly, rate of backward reaction= α [X] [Y]

=Kb [X] [Y]

Were Kb is the proportionality constant and is termed as rate constant for backward reaction.

13.4 LAW OF CHEMICAL EQUILIBRIUM

When the above stated law of mass action is applied to a reaction in equilibrium, the result is termed as the law of chemical equilibrium.

For example the reaction,

$$aA + bB \leftrightarrow xX + yY$$

According to law of mass action:

The rate of forward reaction= α [A]a [B]b

= Kf [A]a [B]b

Similarly, the rate of backward reaction= α [X]x [Y]y

=Kb [X]x [Y]y

Similarly, the rates of both the reactions are same at the state of equilibrium.

$$K_f [A]^a [B]^b = K_b [X]^x [Y]^y$$

$$\frac{k_f}{K_b} = \frac{[X]^x [Y]^y}{[A]^a [B]^b}$$

Kf and Kb are constant at constant temperature and the ratio of Kf / Kb is also constant at constant temperature. It is represented by K and is termed as equilibrium constant. The above reaction is given as

$$K = \frac{[X]^x [Y]^y}{[A]^a [B]^b}$$

and the expression is termed as law of chemical equilibrium.

The law of chemical equilibrium states the product of molar concentration of the products raised to the power equal to its co-efficient, divided by the product of the molar concentration of the reactants raised to its co-efficient, is constant at constant temperature and is termed as equilibrium constant.

13.5 Characteristics of Equilibrium Constant

- Its value remains constant at a given temperature irrespective of the direction of approach.
- The value of the equilibrium constant remains constant at given temperature and pressure irrespective of the concentration of the reactants and products.
- The value of equilibrium constant depends on the nature and temperature of the reaction but it remains unaffected in the presence or absence of catalyst.
- It gives information about the reaction proceeding in a particular direction at a given temperature.

13.6 Degree of Ionization

The degree of ionization refers to the proportion of neutral particles, such as those in a gas or aqueous solution that are ionized into charged particles. A low degree of ionization is sometimes called partially ionized, and a very high degree of ionization as fully ionized.

13.7 Measurement of Degree of Ionization

$$\%\text{age degree of ionization} = \frac{\text{Molecular conductivity of given dilution}}{\text{Molecular conductivity of infinite solution}} \times 100$$

13.8 Ionization of Water

The ions are produced by the self-ionization reaction

$$H_2O \rightleftharpoons H_3O^+ + OH^-$$

This equilibrium applies to pure water and any aqueous solution.

Approximating activities by concentrations, the chemical equilibrium constant, Keq, for this reaction is given by:

$$K_{eq} = \frac{[H_3O^+][OH^-]}{[H_2O]^2}$$

If the concentration of dissolved solutes is low, the concentration [H2O] can be taken as being constant at c.

Expressed with activities a, instead of concentrations, the thermodynamic equilibrium constant for the water ionization reaction is:

$$K_w = \frac{a_{H_3O^+} a_{OH^-}}{a_{H_2O}^2}$$

Which is numerically equal to the more traditional thermodynamic equilibrium constant written as:

$$K_w = \frac{a_{H^+} a_{OH^-}}{a_{H_2O}}$$

under the assumption that the sum of the chemical potentials of H+ and H3O+ is formally equal to twice the chemical potential of H2O at the same temperature and pressure.

In infinitely dilute aqueous solution, the activity of water solvent is unity.

The ionization constant, dissociation constant, self-ionization constant, or ionic product of water, symbolized by Kw may be given by:

$$K_w = [H_3O^+][OH^-] = K_{eq} \times [H_2O]^2$$

where $[H_3O^+]$ is the concentration of hydrogen or hydronium ion, and [OH−] is the concentration of hydroxide ion.

The ionic product of water can be also expressed on activity basis as:

$$K_w = a_{H_3O^+} a_{OH^-}$$

At 25 °C Kw is equal to 1.0×10−14.

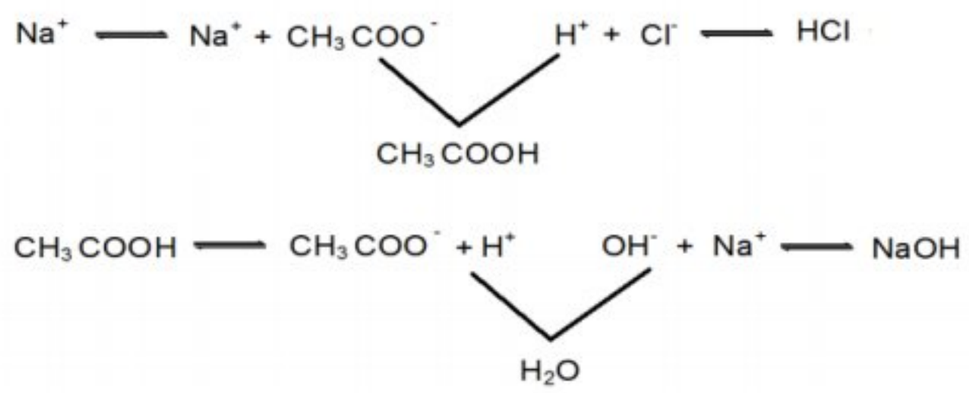
13.9 pH

pH is a measure of the acidity or basicity of an aqueous solution. Solutions with a pH less than 7 are said to be acidic and solutions with a pH greater than 7 are basic or alkaline. Pure water has a pH very close to 7.

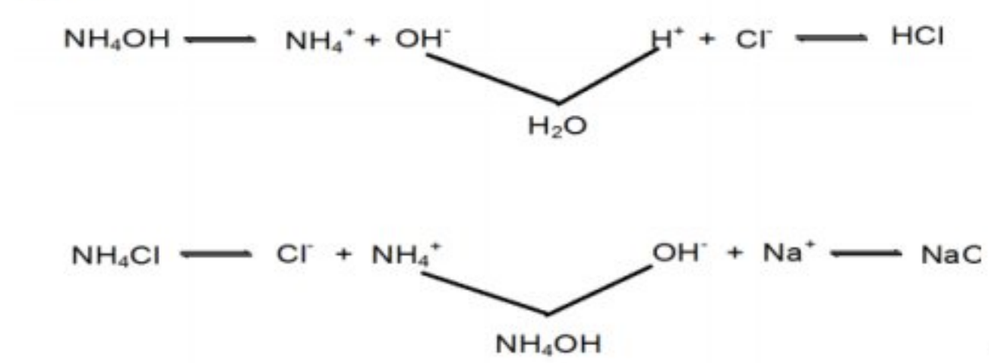
13.10 Buffer

- Buffers are compounds or mixture of compounds that by their presence in their solution resists change in pH upon the addition of small quantities of acid or alkali. The resistance to a change in pH is known as buffer action.
- The substances used to produce buffer action are called buffers and usually consists of mixture of:
  Type "A": A weak acid and its conjugate base that is a salt
  Type "B": A weak base and a conjugate acid

Type A



Type B



Thus pH does not change and solution remain in acidic nature.

13.11 Common Ion Effect and Buffer Equation for a Weak Acid and Its Salt

13.12 Type A

This expression is developed by considering the effect of a salt on the ionization of a weak acid when the salt and acid has a common ion

e.g. when sodium acetate is added to acetic acid, the dissociation constant for a weak acid is

$$Ka = \frac{[Ac^-][H_3O^+]}{[HAc]} = 1.75 \times 10^{-5}$$

distributed due to the acetate ion supplied by the salt. Hence in order to maintain the constant 1.75×10^{-5}, the hydrogen ion in nominator will decrease and the HAc in demoniatior increases. So that the constant Ka remains unaltered and the equilibrium is subjected towards the reactants. The ionization of acetic acid is represented

$$HAc + H_2O \rightleftharpoons Ac^- + H_3O^+$$

by the addition of common ion Ac-. This is an example of common ion effect.

The pH of the final solution is obtained by arranging the equilibrium equation of dissociation constant.

$$[H_3O^+] = \frac{Ka[HAc]}{[Ac^-]}$$

If the acid is weak and ionized only slightly then the expression HAc may be considered to represent the total concentration and it may be simply written as acid in a slightly ionize acetic solution. The Ac^- ion only comes from the salt that is sodium acetate since one mole of sodium acetate yields one mole of acetate ion. The total concentration of Ac^- ion may be replaced by the term salt.

$$[H_3O^+] = \frac{Ka[Acid]}{[Salt]}$$

Equation may be expressed in term of log

$$-\log [H_3O] = -\log Ka - \log [Acid] + \log [Salt]$$

From this buffer equation is obtained for weak acid and its salt

$$pH = pKa + \log \frac{[Salt]}{[Acid]}$$

This equation can give you calculation in range of 4 – 10 pH.

13.13 Type B

Buffer solution of weak bases and their salts are ordinarily not prepared because of volatility and instability of the base and secondly because of the dependence of pH on pKw which is often affected by temperature change e.g. ephedrine and ephedrine HCl is often used in pharmaceutical solution as buffer. Their buffer equation can also derive analogous to deserve weak acid buffer.

$$[OH^-] = \frac{Kb[Base]}{[Salt]}$$

$$[OH^-] = \frac{Kw}{[H_3O^+]}$$

Comparing both equations we get,

$$\frac{Kw}{[H_3O^+]} = \frac{Kb[Base]}{[Salt]}$$

$$pH = pKw - pKb + \log \frac{[Base]}{[Salt]}$$

13.14 Factors Effecting pH of a Buffer Solution

- Addition of neutral salts to buffers, change the pH of the solution by altering the ionic strength.
- Dilution of buffer solution i.e. the addition of H_2O in moderate quantities may not change pH but can cause small positive or negative deviation because it can act as weak acid or base.
- Temperature

  The pH of acetate buffers increases with temperature whereas pH of boric acid and sodium borate buffer decreases with increase in temperature and basic buffers are more effected by change in temperature.

13.15 pH Indicators

- Indicators may be considered as weak acid or weak basis that act like buffers and also exhibit color changes as heir degree of dissociation varies with pH. E.g. methyl red shows its fuel alkaline color yellow at pH about 6 and full acid color red at pH 4.
- So indicator offers a convenient way of calorimetric method of determining the pH of solution.
- The dissociation of an acid indicator can be expressed as

$$Kin = \frac{[H_3O^+][In^-]}{[HIn]}$$

- HIn is unionized form and In- is the ionize form, unionize form gives acid color and ionize form gives basic colour. When an acid is added to the solution of indicator, the H^+ ion concentration increases and HIn predomination and give acid colour. When a base is added $[H_3O^+]$ is reduced and more ionized form is produce so the color changes.

$$pH = pKin + \frac{[Base]}{[Acid]}$$

13.16 Buffer Capacity

The magnitude of a resistance of a buffer to pH change is reffered as buffer capacity β.

It is also called buffer efficiency, buffer index and buffer value.

It is the ratio of the increment of strong base (or acid) to the small change in pH brought by this addition.

$$\beta = \frac{\Delta B}{\Delta pH}$$

Δ β is the small increment in gram equivalent per liter of strong base added to a buffer solution to produce a pH change of ΔpH.

According to equation, the buffer capacity has a value of one when one gram equivalent of base produce a pH change of 1 in one liter buffer solution.

13.17 Buffers in Pharmaceutical and in Biological System

Blood is maintained at a pH of about 7.4 by 8.0 called primary buffers in erythrocytes. The plasma contains carbonic acid/ bicarbonates and acid/alkali Na salts of H_3PO_4 as buffers. Plasma proteins which behave as acid in blood can combine with bases and so act as buffers. In erythrocytes two buffer systems consist of hemoglobin / oxhemoglobin and acid/alkali K salts of H_3PO_4. When the pH of blood goes 7 or above 7.8 Life is in serious danger. The pH of blood in diabetic coma is alleged to drop as low as 6.8. Lacrimal fluids or tears have pH of 7.4. They have a high dilution value of 1:15 with neutral distilled water before an alternation in pH is noticed.

13.18 Preparation of Pharmaceutical Buffers

Following steps should be followed:

- Select a weak acid having pKa value approximately equal to the pH at which the buffer is to use.
- By the help of the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired (pH).
- Consider the original concentration of buffer salt and acid needed to obtain a suitable

buffer capacity. Concentration of 0.05 – 0.5 M is sufficient and a buffer capacity of 0.01 – 0.1 is sufficient.

- Other factors like availability, stability, toxicity, sterility etc. are also considered.
- Finally determine the actual pH and buffer capacity with the help of the pH paper of pH meter.

13.19 Buffered Isotonic Solution

- In addition to pH adjustment pharmaceutical solution should also have same osmotic pressure so that of the body fluids. Isotonic solutions cause no swelling or contraction of tissue with which they come in contact. It can be demonstrated by mixing as small quantity of blood with aqueous sodium chloride solution with different toxicity (NaCl➔ 0.9g/100 ml) is considered to be isotonic and other solution containing higher is considered hypertonic and less than 0.9g is considered hypertonic 2.0% boric acid solution is iso-osmotic with blood but can also pass through cell membrane easily. Therefore a solution containing a drug calculated to be isosmotic with blood is isotonic only when the blood is isotonic only when the blood cells are impermeable to solvent only.
- Mucous lining of eye act as true semi-permeable membrane which does not allow toxic acid to cross.

13.20 Measurement of Toxicity

- The toxicity of solutions may be determined by one of two methods.
- First is the hemolytic method in which the effect of various solution of drug is observed on the appearance of red blood cells suspended in the solution.
- Second approach used to measure toxicity is based on any of the methods that determine colligative properties. The most important are:
  - White Vincent Method
  - The Sprowls Method

Chapter 14 HYDROLYSIS

The reaction of water with esters and salts of weak acids or weak bases is called hydrolysis. It is a chemical process in which a molecule is cleaved into two parts by the addition of a water molecule. One fragment of the molecule gains a H^+ ion from water and other group gains –OH negative ion.

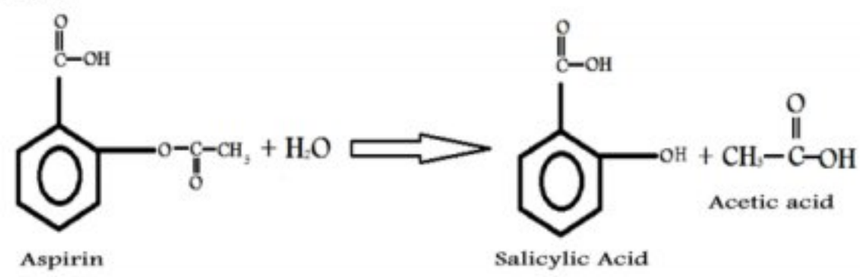
There are two types of hydrolysis:

- Molecular hydrolysis
- Ionic hydrolysis.

14.1 IONIC HYDROLYSIS

It occurs when salts of weak acids or bases interacts with water to give an alkaline of basic solution e.g. Sodium Acetate hydrolyzes in water into acetic acid and NaOH. The solution is alkaline (because of NaOH). We are more concerned with molecular hydrolysis of aspirin, procaine, and atropine. In daily life hydrolysis process is involved in different reactions e.g. in saponification, triglyceride (fats) are hydrolyzed with an aqueous base like NaOH. Fatty acids react with base to form soaps. Hydrolysis is also used in liberation of energy from ATP, phosphate linkage is broken down by hydrolysis to release energy which is used in the biosynthesis of molecules and active transport of ions or molecules through cell membrane.

Aspirin is particularly susceptible to hydrolysis above pH 10.



According to Higuchi et al, procaine decomposes mainly by hydrolysis, the degradation being due, primarily to the breakdown of the uncharged and singly charged forms. The reaction is catalyzed by hydroxyl ions.

It was found that atropine undergoes alkaline and acidic hydrolyses at different pH levels. Above pH 4.5, the catalytic reaction involves hydroxyl ions and below pH 3, hydrogen ions are involved. pH for maximum stability is between 4.1-3.2 at 100°C.

14.2 FACTORS AFFECTING HYDROLYSIS:

- Moisture
- pH
- Temperature
- Solvent

14.3 PROTECTION AGAINST HYDROLYSIS:

14.4 ADJUSTING PH

Drugs may be stabilized by adjusting the pH of the solution to a value at which the compound is found to exhibit lowest rate constant. If the reaction is subject to general acid- base catalysis, the buffer used for pH adjustment must be chosen carefully. The buffer should provide an optimum pH for both maximum stability and greatest therapeutic activity of the drug. In most cases the therapeutic activity depends upon the presence of free base rather than ionized salt in solution. e.g. pylocarpine exist as 99% base a pH 9 and only 0.1% at pH 4.

14.5 COMPLEXATION

Some dugs form complexes with others which exhibit their hydrolysis e.g. benzocaine in aqueous solution forms a complex with caffeine to form benzo-caffeine complexes. Only the benzocaine which is free in the solution will be hydrolyzed.

14.6 SUPPRESSING THE SOLUBILITY OF DRUG

By suppressing the solubility, decreases the concentration of drug in solution e.g. the rate of degradation of penicillin in procaine penicillin solution was shown to be due to that portion which is in solution form. It is found that solubility may be reduces by the use of various additives such as gluconate, sorbitol, dextrose and citrates.

14.7 REMOVAL OF H_2O

Hydrolytic decomposition may further be prevented by the removal of water. The drug may be stored in dry form and used as such or suspended as an insoluble powder in a suitable vehicle. Even in the solid state, drug may decompose e.g. decomposition of solid aspirin due to temperature and humidity.

Chapter 15 MICROMETRICS

15.1 MICROMETRICS

The Science and Technology of small particles is known as Micrometrics.

15.2 MICROMETRICS DEALS WITH

- Particle size and Size Distribution
- Methods of Determining particles size
- Particle shape and surface area
- Pore size
- Angle of repose

15.3 IMPORTANCE OF STUDY OF MICROMETRIC

1. Knowledge and control of the size and the size range of particle is of profound importance in pharmacy.
2. Size and surface area can be related to the physical, chemical and pharmacological properties of a drug.
3. Particle size affect its release from dosage forms that are administered orally, parenterally, rectally and topically
4. Physical stability and pharmacologic response of suspensions, emulsion and tablets depends on particle size.
5. It is also important in flow properties and proper mixing of granules and powders in tableting.
6. Both Tablets and capsules are produced using equipments which controls the mass of drug and other particles by volumetric filling. Therefore any interference with the uniformity of fill, volumes may alter the mass of drug incorporated into the tablet or capsules. Thus reduce the uniformity of the medicine.
7. Powders with different particle sizes have different flow and packing properties which alter the volumes of powder during each encapsulation or tablet compression.
8. The rate of solution depends on the several factors. One factor is the particle size. Thus particles having small dimensions will tend to increase the rate of solution.

   For example:
   - Griseofulvin has a low solubility after oral administration but is rapidly distributed following absorption. The solubility of Griseofulvin can be greatly increased by particle size reduction.
   - Reduction of particles size also increase the rate of absorption of tetracycline, Aspirin and Sulphonamides.
9. Reduction of particle size of nitrofurantoin increased the rate of absorption. Therefore the toxic effect due to rapid absorption.
10. Before being used in the preparation of pharmaceuticals, solid materials are first characterized to determine their chemical and physical features, including;
    - Morphology
    - Purity
    - Solubility
    - Flow ability
    - Stability
    - Particle size/ Size distribution
    - Compatibility with any other formulation components

15.4 DIFFERENT MEANS OF EXPRESSING PARTICLE SIZE

Different means of expressing particle size.:

There are different means of expressing particle size: Millimeter (mm)..... 10^{-3} meter
Micro meter (µ m) ..... 10^{-6} meter
nano meter (nm)..... 10^{-9} meter
pico meter ..... 10^{-12} meter
fanto meter..... 10^{-15} meter

Particle Dimension in Pharmaceutical Disperse system

Particle size		
Micrometer (µm)	**Millimeter (mm)**	**Disperse systems**
0.5- 10	0.0005 - 0.01	Suspension, fine emulsion
10 - 50	0.01- 0.050	Coarse emulsion, flocculated suspension
50 - 100	0.50- 0.100	Lower range of sieve range, fine powder range
150-1000	0.150-1.000	Coarse powder range
1000- 3360	1.000- 3.360	Average granule size

15.5 METHODS OF DETERMINING PARTICLE SIZE

- Optical Microscopy
- Sieving Methods
- Sedimentation Methods

15.6 PARTICLE VOLUME MEASUREMENT

- Coulter Counter Method (Electrical stream sensing method)
- Laser light scattering methods

15.7 Methods of Determining Surface Area

- Adsorption method
- Air permeability method

15.8 Sieving Method

Sieving method is an ordinary and simple method. It is widely used as a method for the particle size analysis.

15.9 Range of analysis

The International Standards organization (ISO) sets a lowest sieve diameter of 45 µm and since powders are usually defined as having a maximum diameter of 1000 µm, this could be considered to be the upper limit.

In practice sieves can be obtained for size analysis over a range from 5 to 125,000 µm.

Sieve analysis is usually carried out using dry powders Although, for powders in liquid suspension or which agglomerate during dry sieving, a process of wet sieving can be used.

15.10 Principle of Measurement

- Sieve analysis utilizes a woven, punched or electroformed mesh often in brass, bronze or stainless steel with known aperture (hole) diameters which form a physical barrier to particles.
- Most sieve analysis utilize a series, stack (Load /Mountain or nest (layer) of sieves which have the smallest mesh above a collector tray followed by meshes which get progressively coarser towards the top of the series.
- A sieve stack usually comprises 6-8 sieves with a progression based on a √2 or 2√2 change in diameter between adjacent aperture.
- Powder is loaded on to the coarsest sieve of the assembled stack and the nest is subjected to mechanical vibration for, say 20 minutes.
- After this time, the particles are considered to be retained on the sieve mesh with an aperture corresponding to the minimum or sieve diameter.
- A sieving time of 20 minutes is arbitrary and BS 1796 recommends sieving to be continued until less than 0.2% material passes a given sieve aperture in any 5 minutes interval

15.11 Advantages

1. This method is very simple.
2. Not expensive
3. Easy to operate

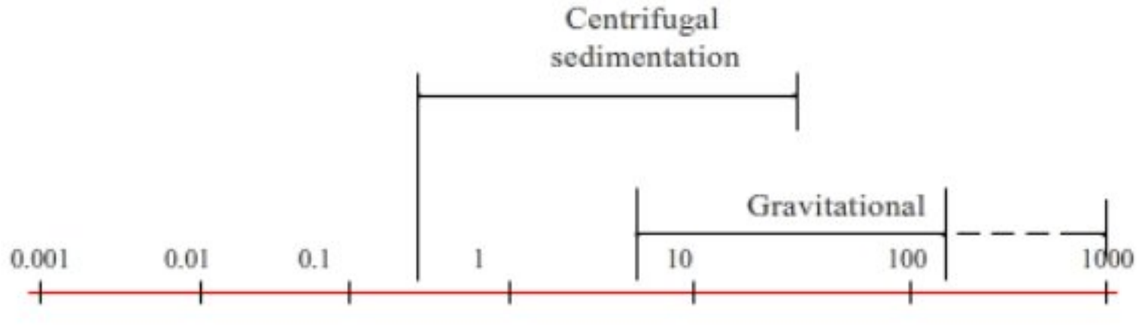
15.12 Disadvantages

1. Not too much precise method.
2. Not applicable for all disperse systems.

15.13 Sedimentation Methods

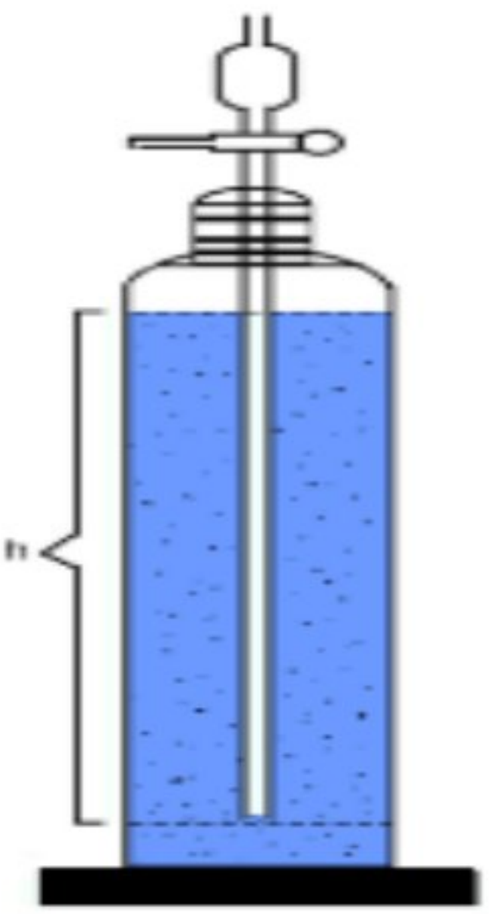
Sedimentation Method is also an ordinary and simple method. It is widely used as a method for the particle size analysis.

15.14 Range of analysis



15.15 Sample Preparation and Analysis Conditions

- In this method particle size can be determined by examining the powder as it sediments out.
- In cases where the powder is not uniformly dispersed in a fluid it can be introduced as a thin layer on the surface of the liquid.
- If the powder is lyophobic, e.g. hydrophobic in water, it may be necessary to add dispersing agent to aid wetting of the powder.



- In case where the powder is soluble in water it will be necessary to use non- aqueous liquids or carry out the analysis in a gas.

15.16 Principle of Measurement

- Particle size analysis by sedimentation method can be divided into two main categories according to the method of measurement used.
- One of the type is based on measurement of particle in a retention zone.
- Another type uses a non-retention measurement zone.
- An example of a non-retention zone measurement is known as the pipette method.
- In this method , known volumes of suspension are drawn off and the concentration differences are measured with respect to time.
- One of the most popular of the pipette methods was that developed by Andreasen and Lundberg and commonly called the Andreasen pipette.
- The Andreasen fixed-position pipette consists of a 200 mm graduate cylinder which can hold about 500 ml of suspension fluid.
- A pipette is located centrally in the cylinder and is held in position by a ground glass stopper so that its tip coincides with the zero level.
- A three way tap allows fluid to be drawn into a 10 ml reservoir which can then be emptied into a beaker or centrifuge tube.
- The amount of powder can be determined by weight following drying or centrifuging.
- The weight of each sample residue is therefore called the weight of undersize and the sum of the successive weight is known as the cumulative weight of undersize. It can be expressed directly in weight units or percent of the total weight of the final sediment.
- The data of cumulative weight of undersize is used for the determination of particle weight distribution, number distribution.
- The largest particle diameter in each sample is then calculated from Strokes' Law.
- The particle size may be obtained by gravity sedimentation as expressed in Strokes' law.

$$v = \frac{h}{t} = \frac{d_{st}^2 (\rho_s - \rho_o)\, g}{18\eta_o}$$

$$\text{or} \qquad d_{st} = \frac{\sqrt{18\eta_o\, h}}{(\rho_s - \rho_o)\, gt}$$

ANDREASEN PIPETTE

Where,

v = rate of settling

h = Distance of the fall in time, t

d_{st} = the mean diameter of the particles based on the velocity of sedimentation

ρ_s = density of the particles

ρ_o = density of the dispersion medium

g = Acceleration due to gravity

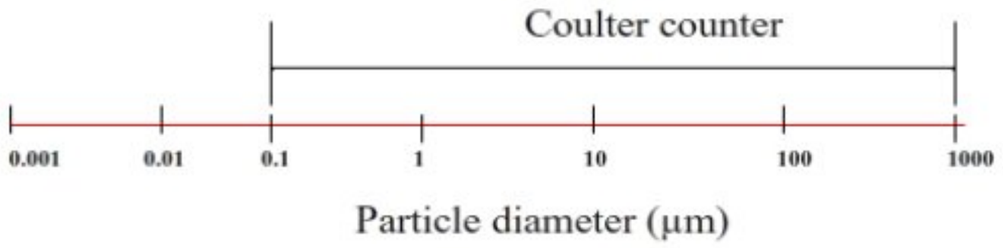
η_o = Viscosity of the medium

❖ Note: The question holds spheres falling freely without hindrance and at a constant rate.

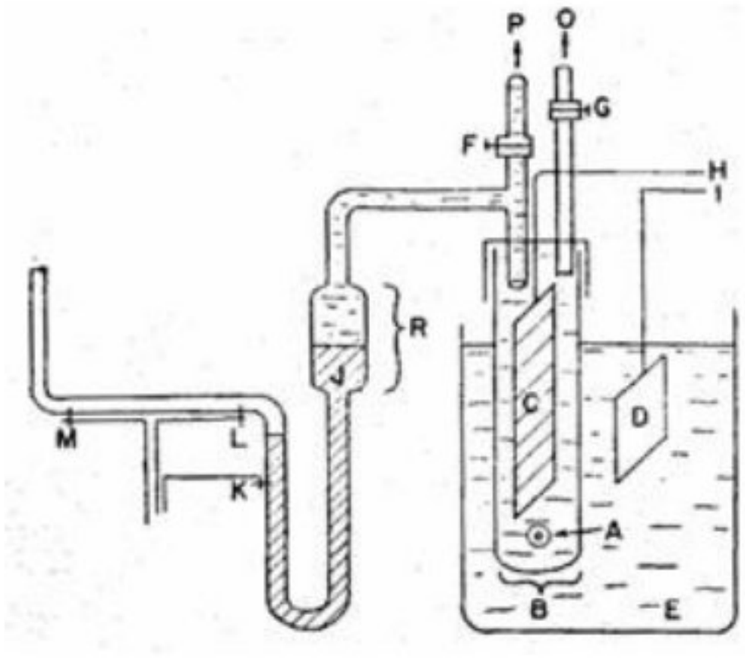
15.17 Coulter Counter Method (Electrical Stream Sensing Zone Method)

Coulter Counter Method (Electrical stream sensing zone method) is a sophisticated method. It is a precise and accurate method.

15.18 Range of analysis



15.19 Sample Preparation and Analysis Conditions



- Powder samples are dispersed in an electrolyte to form a very dilute suspension.
- The suspension is usually subjected to ultrasonic agitation for a period to break up any particle agglomerates.
- A dispersant may also be added to aid particle deagglomeration.
- A typical Coulter counter has one or more micro channels that separate two chambers containing electrolyte solutions. As fluid containing particles or cells is drawn through each micro channel, each particle causes a brief change to the electrical resistance of the liquid. The counter detects these changes in electrical resistance that is proportional to the volume of the particle passing the orifice.

15.20 Advantages

1. It is one of the precise and accurate methods.
2. Analysis range is wide.

15.21 Disadvantages

1. It is a sophisticated method
2. It is an expensive method

15.22 Laser Light Scattering Methods

Light scattering is measured by two different instruments

15.23 Classical Light Scattering / Static Light Scattering

Here, the intensity of the scattered light is measured as a function of angle

15.24 Dynamic Light Scattering (DLS)

Dynamic light scattering (DLS), sometimes referred to as Quasi-Elastic Light Scattering (QELS), is a non-invasive, well-established technique for measuring the size and size distribution of molecules and particles typically in the submicron region, and with the latest technology lower than 1nm.

Typical applications of dynamic light scattering are the characterization of particles, emulsions or molecules, which have been dispersed or dissolved in a liquid. The Brownian motion of particles or molecules in suspension causes laser light to be scattered at different intensities. Analysis of these intensity fluctuations yields the velocity of the Brownian motion and hence the particle size using the Stokes-Einstein relationship.

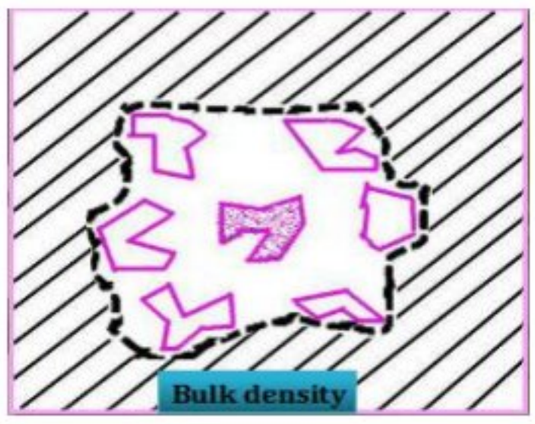
15.25 Bulk Density

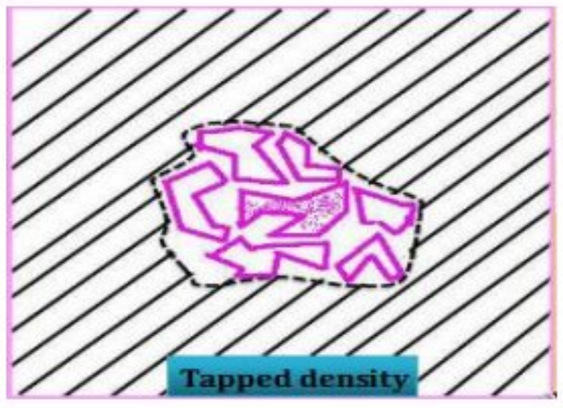
Bulk density = Mass of Powder/Bulk volume

Bulk density depends primarily on particle size distribution, particle shape and tendency of particles to adhere together.

Based on bulk density powders are classified as:

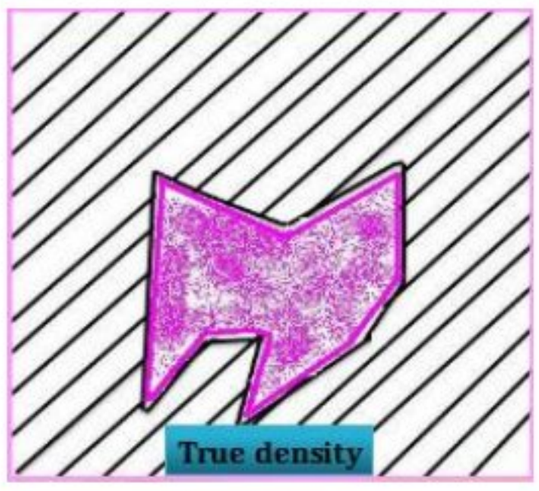
- Heavy – high bulk density (low bulk volume)
- Light - Low bulk density (high bulk volume)





15.26 Applications

- To check the uniformity of bulk chemicals (Quality control measures)
- Determination of size of capsule for a given dose of material.(higher the bulk volume, lower will be bulk density and bigger the size of capsule)



- It helps in selecting the proper size of a container, packing material, mixing apparatus in the production of tablets and capsules.

15.27 True Density

It is the density of the material itself.

True density= Weight of Powder/True Volume of Powder

True volume is the volume obtained excluding the void volume and intra particle pores

15.28 Method to Determine True Density

15.28.1 Gas Displacement Method (Porous):

In this method helium pycnometer is used to determine the true volume from the equation:

COULTER COUNTER

$$Vt = V_c + \frac{V_r}{1 - \frac{P_1}{P_2}}$$

- V_c is the volume of the empty sample chamber (known from a prior calibration step)
- V_r is the volume of the reference volume (again known from a prior calibration step)
- P_1 is the first pressure (i.e. in the sample chamber only)
- P_2 is the second (lower) pressure after expansion of the gas into the combined volumes of sample chamber and reference chamber.

By substituting this Vt and true weight of the sample in the equation we can determine the true density.

15.28.1.1 Liquid Displacement Method (Non-Porous):

Pycnometer or specific gravity bottle may be used.

True density = W 2 -W 1 /W 4 – W 2

Where,

W1 = weight of pycnometer
W2 = weight of pycnometer + sample
W3 = weight of sample(W 2 –W 1)
W4 = weight of pycnometer with powder and filled with the solvent

15.29 Granule Density

Granule density is determined for the granules that are employed in the manufacture of tablets.

Granule density = Granule wt / Granule volume

15.30 Method

Mercury displacement method: Granule volume is related to the weight of mercury that is displaced by the granules in the pycnometer.

15.31 Porosity

Porosity is defined as the ratio of void volume to the bulk volume.

Porosity(€) = void volume/bulk volume

€ = (V b – V p)/ V b

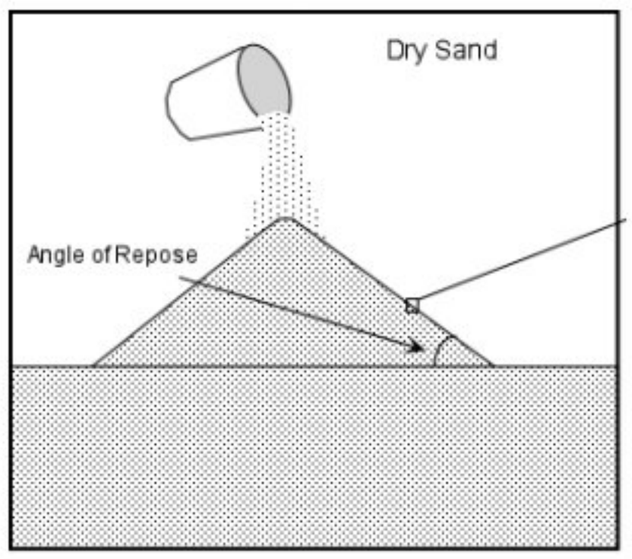
%€ = (1- V p /V b)100

In general the porosities will be between 30 to 50%.However they vary based on packing arrangement.

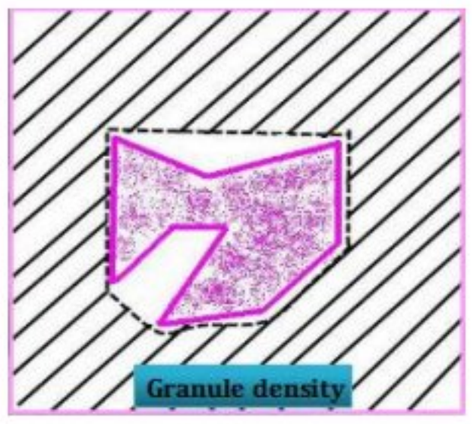
Porosities	Type of packing
26%	closed packing
48%	loose packing
30%	if particles differ greatly in size distribution
50%	aggregates or flocculates
<1%	crystalline materials compressed under a force of 1,00,000 lb./ sq. inch

15.32 Applications of Porosity:

- Porosity influences the rate of disintegration and dissolution. Higher the porosity faster the rate of dissolution.



- Based on porosity solids can be classified as porous and non-porous.
- Porosity is applied in the studies of adsorption and diffusion of drug materials.



15.33 Angle of Repose:

It is the maximum angle possible between the surface of pile of powder and horizontal plane.

Angle of repose helps in quantifying the frictional forces.

The frictional forces mainly contribute to improper flow of powder.

Tan ∂ = h/r

Where,
h = height of pile
r = radius of the base of pile

Angle of repose	Powder flow :
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

15.34 Carr's Consolidation Index

It is also known as compressibility.
It is indirectly related to flow rate, cohesiveness and particle size.

Carr's index= Tapped density-Fluff density/ Tapped density

15.35 Method

Fluff density = w/v_o g/cc
Tapped density = w/v_{50} g/cc

Carr's index (%)	Flow
5-15%	Excellent
12-16%	Good
18-21%	Fair-passable
23-25%	Poor
33-38%	Very poor
>40	Very very poor

15.36 Hauser's Ratio

Hauser's ratio = Tapped dens

Hauser's Ratio

1.25

>1.25

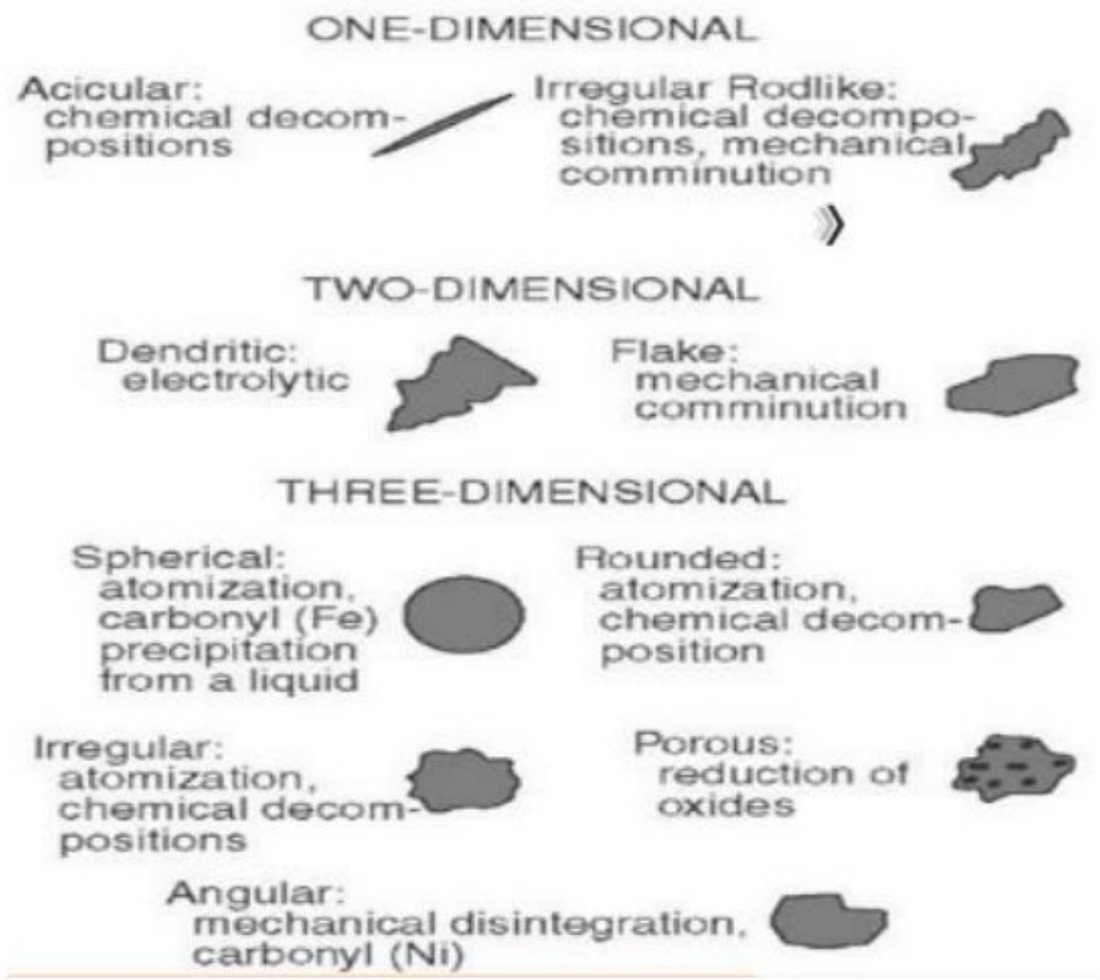
15.37 Applications of Micrometrics

- Release and dissolution
- Absorption and drug action
- Physical stability
- Dose uniformity

15.38 Particle shape

Particle shape Powder particles are very complicated objects with no definite form. It is generally very difficult to describe their shapes.
They have therefore been conventionally described and classified by the use of various terms:

qualitative description



15.39 Importance of Particle Shape

Particle shape is important because it can influence many critical powder properties such as:

- The powder flow ability
- Compatibility
- Content uniformity
- Dissolution
- Drug release
- Bioavailability
- Stability

❖ These factors ultimately affect the safety and efficacy of a dosage form,.

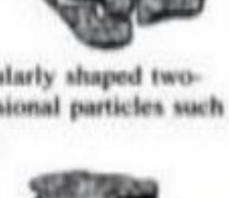
➢ Spherical particles tend to have greater flow ability than irregularly shaped particles as the irregularly shaped particles can interlock with each other resulting in poor flow and bridging in hoppers, etc.

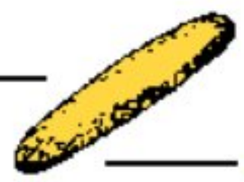
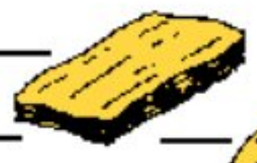
➢ On the other hand, materials with larger irregularly shaped particles which fragment to a limited degree during compression have higher compatibility. This is due to a higher number of interparticulate contact points that allow more interparticulate bonding.

➢ Also the edges and corners of the irregularly shaped particles can undergo higher degree

of deformation due to the existence of lattice defects thus allowing higher bonding strength between compact particles.

- As the surface roughness of the particle increases, the possibility for a particle to find a position at an adjacent surface which promotes bond formation will increase thus more force is needed to break these bondings which yield a higher crushing strength.
- Particle shape can also influence particle size analysis. The particle size distribution measured by sieve analysis can be influenced by particle shape, because irregularly shaped particles take longer to reach their final sieve.

General shapes	Effects on powder flow
(a) Spherical shape 	Often produces good flowability
(b) Oblong shape with smooth edges 	Often produces good flowability
(c) Equidimensional shape with sharp edges 	Less flowable than (a) or (b)
(d) Irregularly shaped interlocking particles	Often shows poor flowability and causes bridging
(e) Irregularly shaped two-dimensional particles such as flakes	Often produces greater flowability than (d) but less flowability than (a), (b), and (c) and may cause bridging
(f) Fibrous particles	Shows very poor flowability and bridges easily

Term	Shape
Cylindrical	
Discoidal	
Spherical	
Tabular	
Ellipsoidal	
Equant	
Irregular	

Chapter 16 DISPERSED SYSTEM

Dispersed systems consist of one phase, known as the dispersed phase, distributed throughout a continuous phase or dispersion medium.
There are two types of dispersed system

16.1.1.1 HOMOGENEOUS DISPERSE SYSTEM

A homogeneous mixture is a mixture where the components that make up the mixture are uniformly distributed throughout the mixture.
E.g. Air, saturated sugar water
Homogeneous Disperse System is further divided into:

16.1.1.2 IONIC DISPERSION

Dispersion which consists of ions as a dispersed phase is known as Ionic Dispersion.
E.g. NaCl + H2O → Na+ + Cl- (ions)

16.1.1.3 MOLECULAR DISPERSION

Dispersion which consists of molecules as a dispersed phase is known as Molecular Dispersion
SIZE OF DISPERSED PHASE: 0.1 nm to 1.0nm

16.1.1.4 HETEROGENEOUS DISPERSE SYSTEM

A heterogeneous mixture is one which has a non-uniform composition.
E.g. Colloidal Kaolin Solution
Heterogeneous Dispersed System is further divided into:

16.1.1.5 COLLOIDAL SOLUTION

A heterogenous system in which the size of the dispersed phase is from 1.0 nm to 500 nm. (500nm = 0.5 um)
Disperse phase may be:

- Single large molecule (proteins)
- Group of small molecule (Colloidal solution of Gold)
- Group of Ions (Aqueous soap solution)

16.1.1.6 2. COARSE DISPERSION

A heterogeneous system in which the size of the dispersed phase is above 500nm (or 200nm)

Disperse phase may be group of large molecules e.g.Bismuth Carbonate in H_2O.

There are two major dosage forms in coarse dispersion which includes Emulsion and Suspension

16.2 TYPES OF DISPERSE SYSTEM ON THE BASIS OF SIZE

On the basis of particle size of dispersed phase in dispersed system, dispersed system is divided into three types:

	Molecular Dispersion	Colloidal Dispersion	Coarse Dispersion
Size	0.1 to 1.0 nm	1.0 to 500 nm	Greater than 500 nm
Seen under electron microscope	No	Yes	Yes (Seen through ordinary microscope as well)
Pass through ordinary filter paper	Yes	Yes	No
Pass through semi-permiable membrane	Yes	No	No
Diffusion Rate	Rapidly	Very Slowly	No Diffusion
Example	Ions, Glucose, O2 molecules	Colloidal Silver Solution, Natural and Synthetic Polymers	Pharmaceutical Emulsion, Suspension, RBC

16.3 DISPERSED SYSTEM EXAMPLES FROM DAILY LIFE

Dispersed Phase	Dispersed Medium	Colloidal dispersion Example	Coarse Dispersion Example
Liquid	Gas	Fog	Spray
Solid	Gas	Smoke	Dust
Liquid	Liquid	Oil Granules	Emulsion
Solid	Liquid	Colloidal Gold Solution in Water	Kaolin in Water

16.4 COLLOIDAL DISPERSED SYSTEM

16.4.1.1 CLASSIFICATION OF COLLOIDAL SYSTEM

On the basis of the interaction between dispersed phase and dispersion medium, colloidal solution may be classified into three types:-

1. Lyophilic Colloids
2. Lyophobic Colloids
3. Association/Amphiphilic Colloids

16.5 Lyophilic Colloids

Systems containing colloidal particles that interact to an appreciable extent with the dispersion medium are referred as lyophilic (solvent-loving) colloids.
Lyophilic Colloids are furthersub-classed into two groups:

16.5.1.1 Hydrophilic

In which the dispersion medium is water (aqueous).
E.g. Colloidal solution of gelatin, acacia, insulin or albumin in H2O.

16.5.1.2 2. Lipophilic

In which the dispersion medium is organic solvent (non-aqueous) or we may say lipid loving.
E.g. Colloidal solution of rubber or polystyrene in benzene.

16.5.1.2.1 Solvation

Solvation, also sometimes called dissolution, is the process of attraction and association of molecules of a solvent with molecules or ions of a solute.

16.5.1.2.2 Hydration

Hydration is the process of attraction and association of molecules of water with molecules or ions of a solute. It is similar to solvation but is specific to water only.

16.6 Lyophobic Colloids

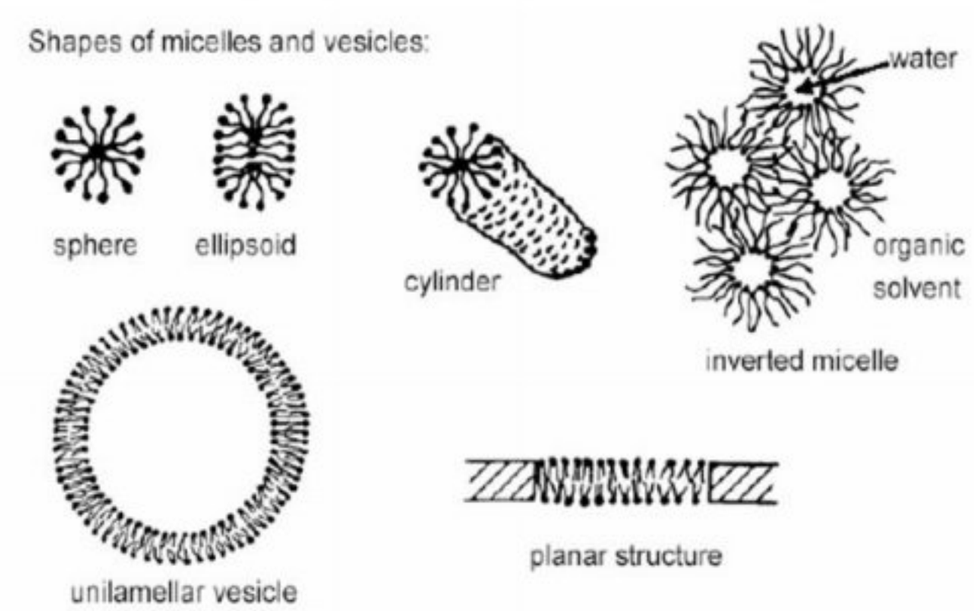
Systems containing colloidal particles that have little or no interaction with the dispersion medium are referred as lyophilic (solvent-hating) colloids.
E.g. colloidal solution of inorganic particles (silver, sulfuretc.) in H_2O.
Special treatment is needed for the preparation of lyophobic colloids which include high degree of super-saturation followed by formation and growth of nuclei.

16.7 Association Colloids

Association or Amphiphilic colloids consists of amphiphiles (surface-active agents, or monomers) are characterized by having two distinct regions of opposing solution affinities within the same molecule or ions.
Monomers: It consists of polar (hydrophilic) and non-polar (hydrophobic) part within same molecule.

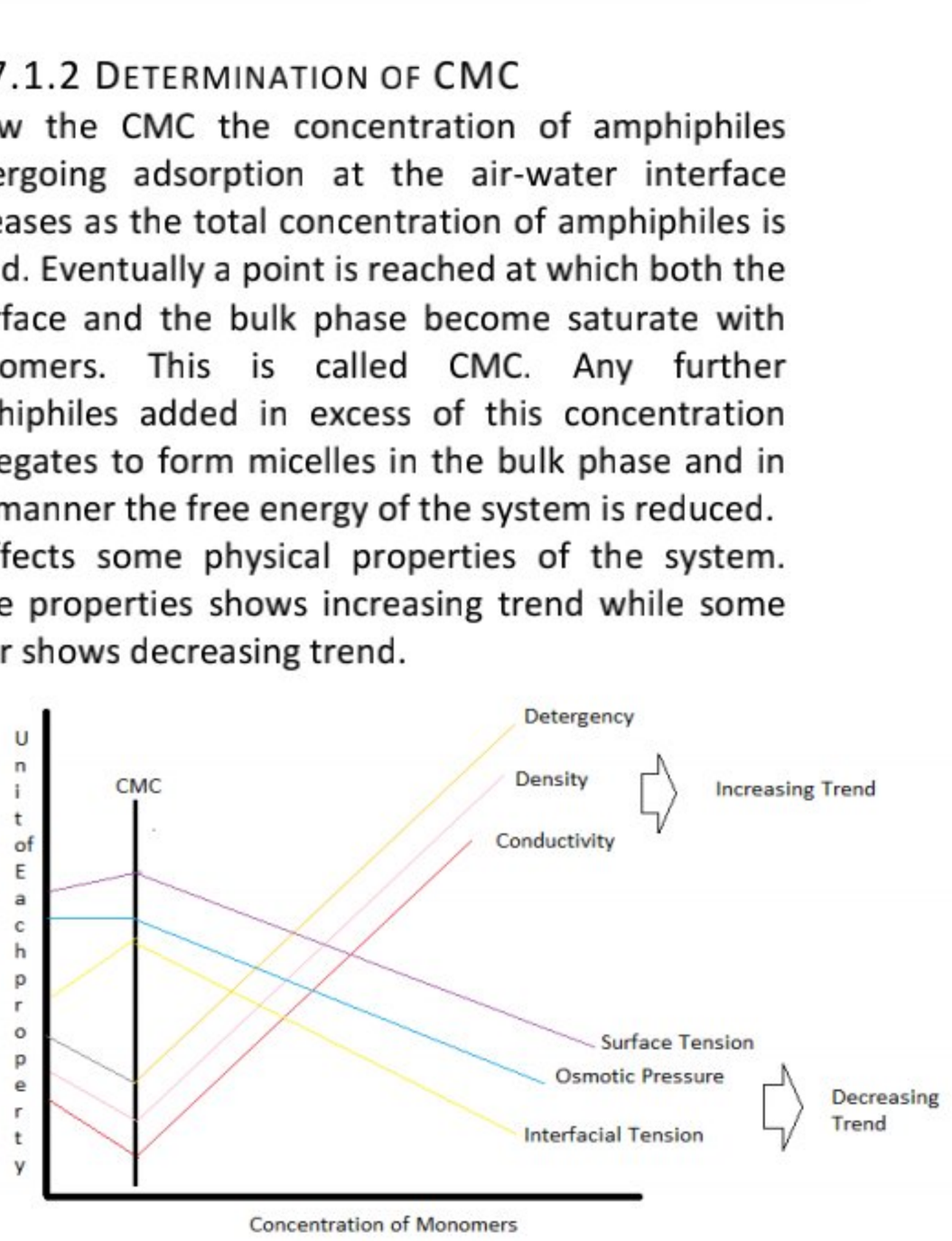
Sub-colloidal: When present in liquid medium at low concentration, the amphiphiles exist separately are of such a size as to be sub colloidal.
Micelles: As the concentration of monomer is increased, aggregation occurs over a narrow concentration range. These aggregates which may contain 50 or more monomers are called micelles. A micelles lie within the size range of colloidal system.
CMC: the concentration of monomer at which micelles form is termed as the critical micelle concentration.
Micellization: the process of micelle formation is known as micellization

16.7.1.1 Types of Micelles on the Bases of Their Shape

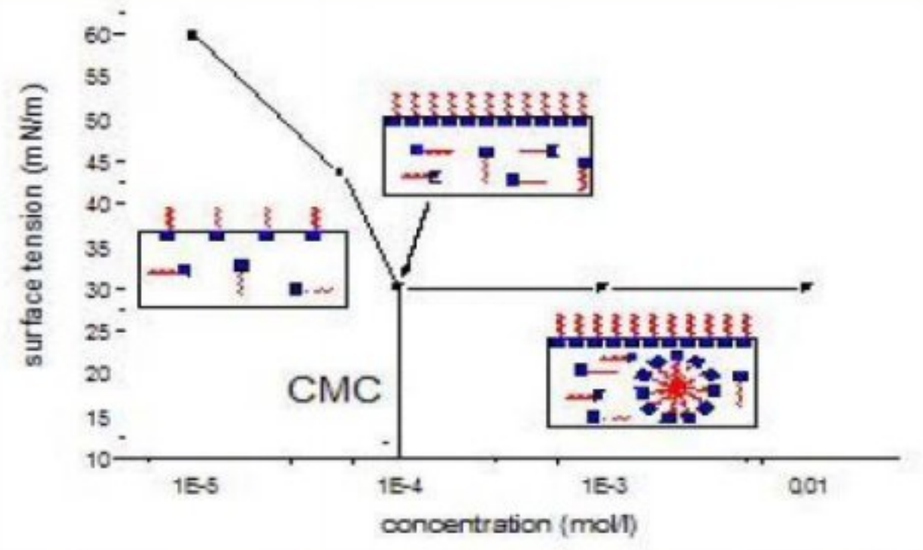


16.7.1.2 Determination of CMC

Below the CMC the concentration of amphiphiles undergoing adsorption at the air-water interface increases as the total concentration of amphiphiles is raised. Eventually a point is reached at which both the interface and the bulk phase become saturate with monomers. This is called CMC. Any further amphiphiles added in excess of this concentration aggregates to form micelles in the bulk phase and in this manner the free energy of the system is reduced.
It affects some physical properties of the system. Some properties shows increasing trend while some other shows decreasing trend.



These properties can be used to determine the CMC.



E.g. the surface tension decreases up to the CMC and above the CMC, the surface tension remains constant, this shows that the interface is saturated and micelle formation has taken place in the bulk phase.

16.7.1.3

16.7.1.4 Classification of Association Colloids

Type	Compound	Amphiphile	Gegenion (ion of opposite charge)
Ionic	Sodium Lauryl SO4	$CH_3(CH_2)_{11}OSO_3^-$	Na^+
Cationic	Cetyltrimethyl-ammonium bromide	$CH_3(CH_2)_{15}N^+(CH_3)_3$	Br^-
Ampholytic (Zwitterionic)	Dimethyl dodecylammonio-popanesulfonate	$CH_3(CH_2)_{11}N^+(CH_3)_2(CH_3)_3OSO_2^-$	-

16.8 Properties of Colloids

1. Optical Properties
2. Kinetic Properties
3. Electro-Kinetic Properties

16.9 Optical Properties

16.9.1.1 The Faraday-Tyndall Effect

When strong beam of light is passed through a colloidal solution, a visible cone, resulting from the scattering of light by the colloidal particles is formed. This is Faraday-Tyndall Effect.

An intense light beam is passed through the solution against a dark background at right angles to the plane of observation, and, although the particles cannot be seen directly the bright spots corresponding to particles can be observed and counted.

16.9.1.2 Electron Microscope

The electron microscope is capable of yielding pictures of the actual particle even those approaching the molecular dimension is now widely used to observe the size, shape and structure of colloidal particles.

16.9.1.3 Light Scattering

This property depends on the Faraday-Tyndall effect and is widely used for the determination of molecular weight of colloids. It can also be used to obtain information on the shape and size of particle.

16.9.1.4 Particle Size

Above describe properties can be used to determine the particle size of the colloidal system.

16.10 Kinetic Properties of Colloids

Grouped under this heading are several properties of colloidal systems that relate to motion of particles with respect to the dispersion medium the motion may be thermally (Brownian movement, diffusion osmosis) gravitationally induced (sedimentation) or applied externally (viscosity)

16.10.1.1 Brownian Motion

The particles are observed to be in continual and erratic motion due to the bombardment of the particle by molecules of the suspension medium. The amount of the displacement is inversely proportional to the mass of the particle and the viscosity of the suspension medium. Brownian movement is seen in microscopic particles. It was studied by Zsigmondy then Robert Brown in 1827 first recorded the Brownian movement with pollen grains.

16.10.1.2 Diffusion

Particles diffuse spontaneously from a region of higher concentration to one of lower concentration until the concentration of the system is uniform throughout. Diffusion is a direct result of Brownian movement.

16.10.1.3 Osmotic Pressure

The osmotic pressure π of a dilute colloidal solution is described by Van't Hoff equation

$$\pi = cRT$$

Where c is the concentration of solute. This equation can be used to calculate the molecular weight of colloid in dilute solution.

Sedimentation

The velocity, v, of sedimentation of spherical particles having density ρ in a medium of density ρ_0 and viscosity h_0 is given by Stoke's law:

$$v = \frac{2r^2(\rho - \rho_0)g}{9\eta_0}$$

Where g is the acceleration due to gravity. If the particles are subjected only to force of gravity then the lower size limit of particles obeying Stoke's equation is about 0.5 µm. This because Brownian movement becomes significant and tends to offset sedimentation due to gravity and promotes mixing instead.

16.10.1.4 Viscosity

Viscosity is an expression of the resistance to flow of a system under an applied stress. The more viscous a liquid is the greater is the applied force required to make it flow at a particular rate.

The shape of particles of the disperse phase effect the viscosity of colloidal dispersion. Sphero-colloids form dispersion of relatively low viscosity whereas linear particles system is more viscous.

The relationship of shape and viscosity reflect the degree of solvation of particles.

In lyophilic colloids viscosity increases while lyophobic colloids do not have much effect on viscosity.

16.11 Electrical Properties of Colloids

The properties of colloid that depends on or are affected by the presence of ca charge on the surface of particle are discussed under this heading.

16.11.1.1 Electro-Kinetic Phenomena

The movement of a charged surface with respect to an adjacent liquid phase is the basic principle underlying four electro-kinetic phenomenal:

1. Electrophoresis
2. Electroosmosis
3. Sedimentation Potential
4. Streaming potential

16.11.1.2 Electrophoresis

Electrophoresis involves the movement of charged particle through a liquid under the influence of applied potential difference (electric field).

An electrophoresis cell is fitted with two electrodes:

Anode → Anion (negativelycharged) and,

Cathode→ Cation (positively charged) contains the dispersion

When a potential is applied across the electrodes the particles migrate to oppositely charged electrode. The rate of particle migration is observed by means of ultra-microscopeand is a function of the charge on the particle. Because the shear plane of the particle is located at the periphery of the tightly bound layer the rate determining potential is the zeta potential.

16.11.1.2.1 Influence of pH

pH plays very important role in electrophoresis for example, "protein". The carboxylic acid and amino groups of protein behave differently in different pH.

- **In Alkaline pH (OH^-)**
  Protein behaves as anion (negatively charged) because of carboxylic acid portion.
- **In Acid solution**
  Protein behaves as cation (positively charged) due to protonation of amino group.
- **At intermediate pH or balance pH**
  Protein appears as neutral i.e. no charge on protein
  - ➢ Such ions are known as Zwitter ions leading to participation of protein.
  - ➢ This point at which precipitation occurs is called **isoelectric point.**
  - ➢ Each protein has its specific isoelectric point
  - ➢ Only a particular protein precipitates a particular isoelectric point so this property is utilized to purify proteins/ protein like compounds.

16.11.1.3 Electroosmosis

Electroosmosis is essentially opposite in principle to electrophoresis. In it the application of potential causes a charged particle to move relative to the liquid which is stationary. If the solid is rendered immobile the liquid now moves relative to the charged surface. This is electroosmosis, so called because liquid moves through a plug or membrane across which a potential is applied. It also provide another method for obtain the zeta potential by determining the rate of flow of liquid through the plug under the standard conditions

16.11.1.4 Sedimentation Potential

The potential difference between top and bottom due to sedimentation under the influence of gravity.E.g. In suspension.

Sedimentation Potential occurs when dispersed particles move under the influence of either gravity or centrifugation in a medium. This motion disrupts the equilibrium symmetry of the particle's double layer. Within the double layer, the viscous flow around the layer because the particle drags ions away from the particles, which causes a slight displacement between the surface charge and

the electric charge of the diffuse layer. As a result, the moving particle gains dipole moment. These dipole moments generate an electric field which is called sedimentation potential.

16.11.1.5 STREAMING POTENTIAL

It is the potential difference set up when a liquid is forced through a fixed plug of porous nature.

16.12 ELECTRICAL DOUBLE LAYER

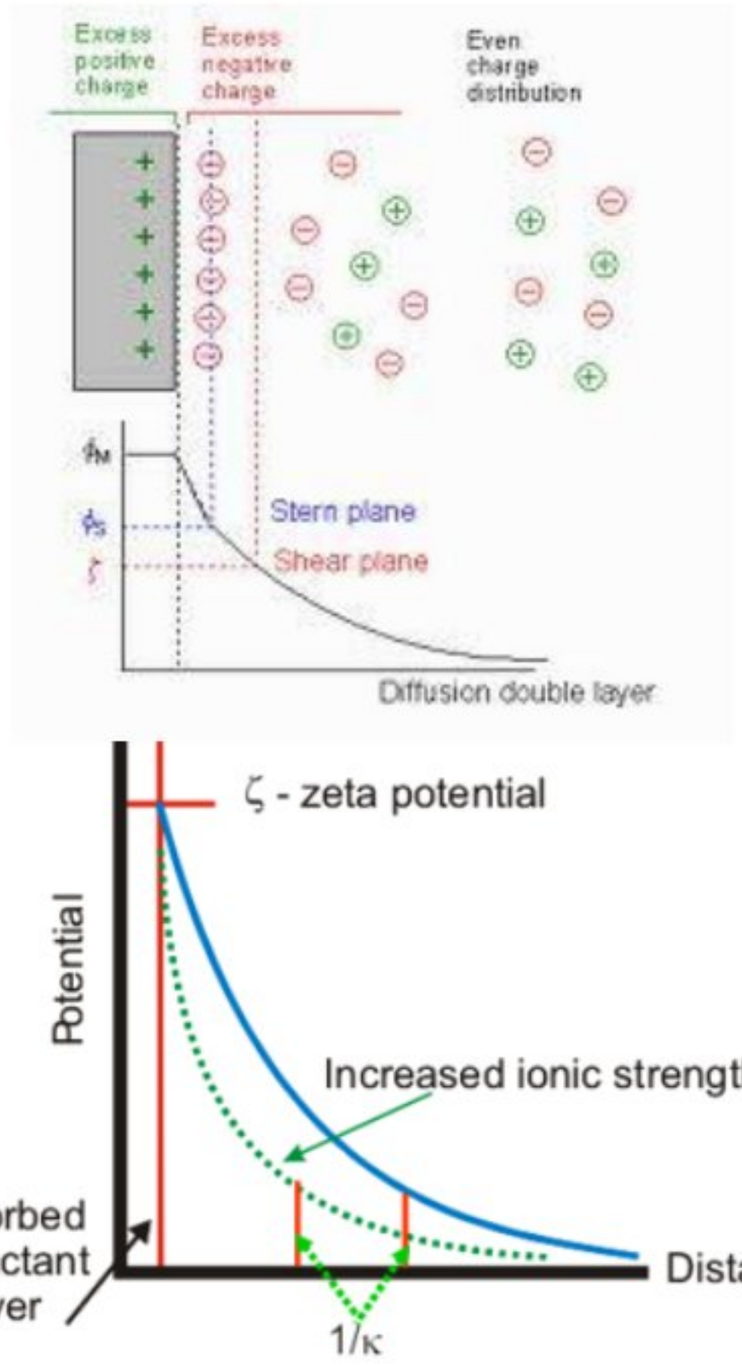
When a solid is immersed in a liquid it acquires an electric charge on its surface and there is a non-uniform distribution of ions of opposite charge in the liquid adjacent to the sold. The liquid in the region of the solid surface is considered to be in two parts, the diffuse double layer. One part consists of a layer of ions fixed in relation to the surface; the second part extends some way into the liquid until there is a uniform distribution of positive and negative ions in the bulk of the liquid (diffuse layer).

There is rapid fall in potential between the solid surface through the fixed layer and then a gradual fall in potential through the diffuse layer to the bulk of the liquid.

The difference in potential between the outer surface of the fixed layer and the bulk of the liquid phase is termed as the zeta potential (ζ), or electro-kinetic potential.

Since the fixed layer remains attached to the solid it is the zeta potential that is responsible for electrophoresis and for the streaming potential since the diffuse layer is in the movable liquid.

The addition of the electrolytes to a solid-liquid system reduces the zeta potential or even reverses the sign. Thee electrolyte supplies addition anions and cations so that the density of ions of opposite charge to the charge on the wall is increases. Thus the ionic atmosphere is compressed near the surface and the potential gradient in the fixed layer is greatly increased so that the potential in the diffuse mobile layer is decreased.



16.13 EFFECT OF MIXING DIFFERENT COLLOIDS

16.13.1.1 MUTUAL PRECIPITATION

When twosolutions of oppositely charged colloids are mixed, the particles of opposite sign are attracted to each other and the charges neutralized. Coagulation can then take place and precipitation occurs. However, if a large excess of one of the solution is used the neutralized particles adsorb the excess charged particle and the system remain stable.

16.13.1.2 COACERVATE FORMATION

The addition of an electrolyte to a hydrophilic colloid brings about precipitation by neutralizing the charge and by removing the water layers enveloping the colloid. If this is carried out gradually an intermediate stage is reached where liquid droplets separate which coalesce to form a separate phase; this is coacervation.

A layer of hydrophilic colloid formed around the dispersed phase, and the process is known as coacervation.

It may also be referred as hydration when water is the continuous medium.

16.13.1.3 SENSITIZATION

At low concentration of hydrophilic colloids various hydrophobic particles come together due to

adsorption of hydrophilic colloids on different particle at the same time.

16.13.1.4 PROTECTION

A high concentration of hydrophilic colloids each of hydrophobic colloidal particle will have separate layer of hydrophilic colloid leading to the protective effect. Hence increasing the stability of phobic particles or phobic colloids.

16.13.1.4.1 PROTECTION EFFECT

Quantity of hydrophilic colloids required to stabilize/ protect phobic particle is based on the following

Gold Number

It is the number of mg of protective colloids that must be added to 10 cm3 of standard colloidal suspension of gold to prevent flocculation on the addition of 1cm3 of 10% NaCl solution.

Congo red Number

Depends on the flocculatin of a standard dispersion of congro red by a given amount of KCl.

16.13.1.5 PRECIPITATION OF HYDROPHILIC COLLOIDS

High concentration of salts (NaCl, KCl etc.) results into neutralization of charge and dehydration leading to precipitation of hydrophilic colloids.

16.13.1.6 GEL AND JELLIES (SOLID COLLOIDS)

Gel and jellies are colloids with a liquid as dispersion medium and solid as dispersed phase.

According to x-ray examination gel is crystalline structure while jellies are not crystalline in structure.

Low concentration is required to form jellies.in it Individual particles forming a frame work of ramifying aggregates in which the liquid dispersion medium is enmeshed.

16.13.1.7 HEAT REVERSIBLE JELLIES

Jelly is only a dissolved into the water. It will change state to a solid when cooled, but, when heated, it will melt. If heated (slowly) the water will evaporate and leave the jelly crystals behind. Sort of like salty water. They might not look the same, but the water will return to its original state. Thus, jelly is a reversible change.

E.g. gelatin, pectin, agar etc.

16.13.1.7.1 HYSTERESIS

- Time interval between cooling and settling i.e. melting of jellies, called hysteresis.
- Settling of jellies promoted by heating, by addition of hydroxyl compound (like glycerin).
- Setting is delayed by NO and Cl.
- It is totally prevented by KI.

16.13.1.7.2 SYNERESIS

Syneresis is the extraction or expulsion of a liquid from a gel or jelly.

16.14 COMPARISON OF PROPERTIES OF DIFFERENT COLLOIDS

Properties/Characteristics	Lyophilic Colloids	Lyophobic Colloids	Association Colloids
Dispersibility and Disperse Phase	Protein(single molecule) Group of smaller molecules (colloidal gold solution) Group of ions (aq. Soap solution) Easily Dispersed	Inorganic Particles (silver, $Fe(OH)_3$, Sulphur etc.) Not easily dispersed	Aggregate of monomers Micelles of Organic Compound Colloidal Range Easily Dispersed
Interaction and dispersion medium	Interact → Solvation/ hydration and so stable	Very little interaction unstable	Hydrophilic, lipophilic part interaction Stable
Viscosity	High (acacia in H_2O; rubber in benzene)	No such effect	High with high conc. Micelles because e asymmetrical
Stability towards electrolytes	Stable with high conc. Of salts, salting out effect due to neutralizat	Unstable at very low concentration of salt is	In aqueous solution CMC is reduce

	ion and dehydration	required (neutralization and dehydration)	d by the addition of electrolyte
Reversibility of precipitation	Reversible	Not reversible	Not Seen
Stability after prolong dialysis	Stable	Unstable	Not Seen
Protective Effect	Has at high concentration	Has not	Not seen
Tyndall Cone Effect	Weak	Strong	Scatter light but not formation of cone

16.15 Nature of the Dispersed Particles

AGGREGATE: primary particles are joined together at crystal faces like clusters

AGGLOMERATE: Particles are joined only at edges or corners forming loose or more open structure then aggregate.

COALESCENCE OR FUSION: Particles fuse with concomitant loss in surface area

FLOCCULATION (F): Surface sites of particles may be blocked which mean no fusion to a new particle. Flocculation can be Reversible flocculation or irreversible flocculation

16.16 Stability of Colloids/ Disperse System

A stable dispersion is the one that resists any change in the state of the system which consists of free particles undergoing Brownian motion.

Two stand point regarding stability are

- Kinetic
- Energy

Kinetic

It is determined by the stability ration "W" as a degree of stability i.e. $W = \frac{K_r}{K_s}$

K_r is the rapid flocculation while K_s stand for slow flocculation in the presence and absence of energy barrier.

16.16.1.1 Energy

Particles are under constant Brownian motion, so stability is determined by the interaction between the particles.

Two types of the forces are involved

- Repulsive forces
- Attractive forces

Theoretically→ if repulsive forces are dominating, the system will be stable and if attractive forces are increasing the dispersion will coalesce/fuse.

Practically→ repulsive forces are necessary to counteract the attractive forces (mainly Van der Waal attractive forces) and are generated by two ways as under

- By electrical Double Layer or surface charge of particles and is called electrical stabilization or electrostatic stabilization.
- By the repulsion due to interaction between the adsorbed polymer layers, including the adsorbed molecules of dispersion medium and is called steric stabilization or polymeric stabilization or steric hindrance.

16.16.1.2 Electrical or Electrostatic Stabilization

DLVO Theory by Derjaguin and Landan (from Soviet Union) and Verwey and Overbeek (from Netherland) is related to surface charge to stability. It also known as classical theory for colloidal stabilization.

- It works through balance between attractive and repulsive forces. Total potential i.e. $V_T = V_A + V_R$
- Where V_A = Van der Waal attractive forces and V_R = electrical repulsive forces.
- V_A increases rapidly as particle approach each other and this effect is less in V_R
- The sharp increase in V_R at very close approach of particles is due to repulsion between the electron clouds of atoms of the particles and is known as V_R^{Born} (i.e. Born Repulsive Energy)

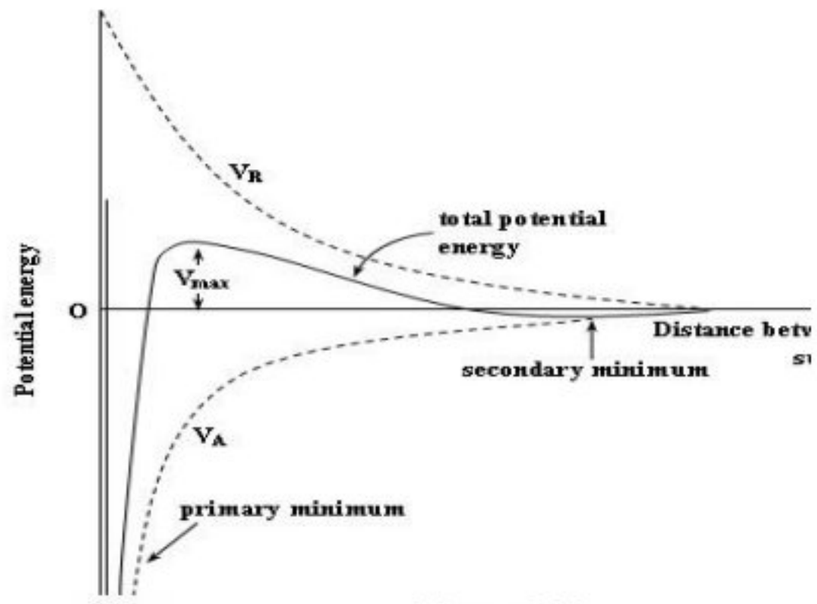
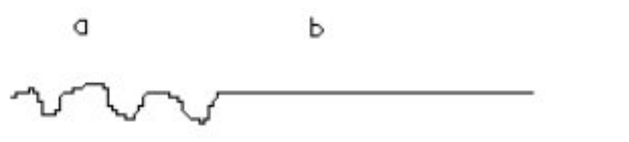


Figure 2.16

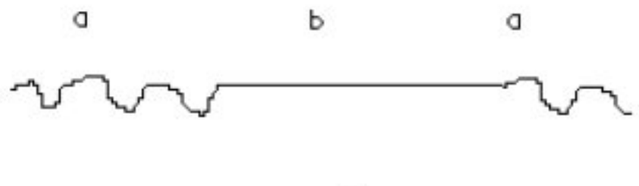
- Potential Energy curve passes through maximum called Vmax which constitute an energy barrier against the adherence of the particles.
- Primary minimum is formed due to very close approach of particles.
- V_R^{Born} is also due to close approach of particles
- Lower the value of Vmax greater the chance of particles to adhere and vice versa.
- Height of Electric barrier/ activation energy prevents particles to adhere. To overcome this Vmax , some energy is required. Thermal energy (KT) is present in the system, if Vmax is >> KT dispersion will be stable and if KT >>Vmax then instability will result.
- According to DLVO theory the magnitude of Vmax depends on dimension of particles and their surface charge or surface potential
- If particles are sufficiently large then VT may develop secondary minimum at a quite distance from primary minimum.
- If secondary minimum is greater than KT then flocculation of the system will result but will be reversible
- Flocculation at primary minimum is irreversible
- Stability of the system can be increased by preventing the particles form approaching each other i.e. by a balance between repulsive and attractive forces.

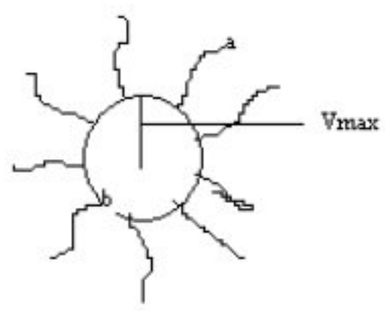
16.16.1.3 Steric or Polymeric Stabilization

From the shape of total Potential (VT) curve the height of Vmax can be increased by constructing a physical barrier around the particle by non-ionic surfactants. It will increase the distance of particles from their centers.



a= polar portion of surfactant
b= non-polar portion of surfactant



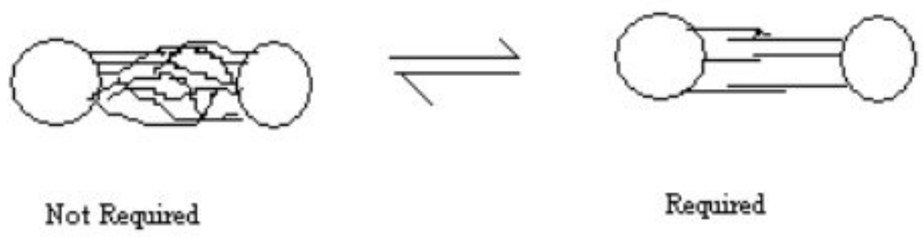


- By the adsorption of polymer a layer will be formed in whichPhobic portion of polymer adsorbs onto phobic surface and philic will dangle around and will develop interaction with the dispersion medium due to philicity. (I.e. phobic surface is covered by a layer with its outer philic portion).

The stabilization of dispersion due to adsorbed layers of polymer is generally known as steric stabilization and is considered of two types:

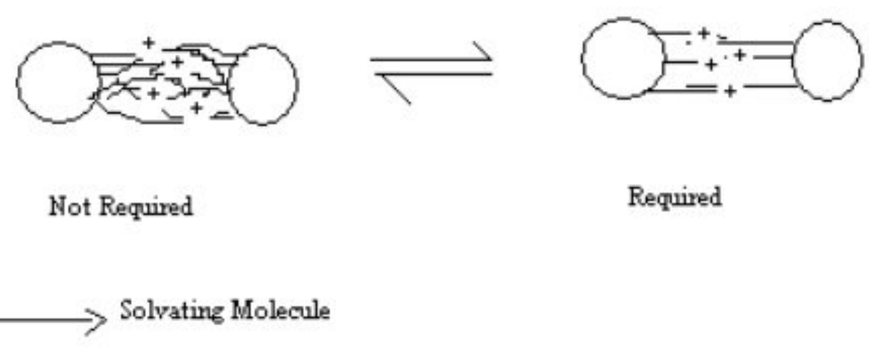
16.16.1.3.1 Entropic Stabilization

Interpenetration of adsorbed layers leads to concentration of polymer chains and loss of configuration entropy
Energetically Unfavorable



16.16.1.3.2 Enthalpic Stabilization

Adsorbed polymer chains solvated and interpenetration would require some desolvation
Unfavorable enthalpic change



16.16.1.4 Conclusion

- Five possible forces can be identified

- Electrostatic force of repulsion including ψ_s, ψ_σ,ζ (zeta potential) and d.
- Van der Waal attractive forces or electromagnetic forces of attraction
- Born repulsive forces
- Steric stabilization as steric forces depends upon the geometry and conformation of molecules at the interface.
- Solvation forces

16.17

16.18 Forces between Molecules Ions and Atoms

Two Types:

- Repulsive forces
- Attractive forces

16.18.1.1 Repulsive Forces

Repulsive forces are of two types:

16.18.1.2 General Repulsion

General reluctance of electron clouds when atoms are too close. Reluctancy is proportion to the distance of atoms.

$$\text{Repulsions} \propto 1/r^{12}$$

16.18.1.3 Columbic Repulsion

Columbic repulsion between two similarly charged ions

$$F = \frac{Q_1 Q_2}{4\pi E_0 r^2}$$

$$Q_1 \& Q_2 \; similarly \; charge \; ions$$
$$E_0 = pemittivily \; of \; vacuum$$
r = *distance*

If other than E_0 *then* $E_0 = E_r$ *so*

$$F = \frac{Q_1 Q_2}{4\pi E_r r^2}$$

$E_0 = E_r$ *which is relative*

16.18.1.4 Attractive forces

Attraction is based on nature of components.

16.18.1.4.1 Components

Components are of three types

1. Ions
2. Permanent dipole
3. Induced dipole

16.18.1.5 Formation of Ions

Formation of ions takes place by transferring of electrons from one atom to other.

16.18.1.6 Permanent Dipole Moment

- In covalent bond when their complete sharing of electron does not occur
- Sharedelectrons are closer to electronegative atom
- Positive and negative centers do not coincide
- This separation of charge gives rise to permanent dipole movement.
- In a compound various bond giver overall permanent dipole movement
- If it is finite i.e.>0 then molecules is P.D.M. if its value is zero then molecule is non-polar.
- Non polar molecule may still contain polar bonds since zero value for dipole moment may be due to opposing bond moment i.e. bond moment with equal value but in opposite direction.

16.18.1.7 Induced Dipole moment

- Completely Covalent bonds are formed by complete equal sharing of electron of two atoms so no dipole moment.
- If ions or molecule with permanent dipole moment is brought near on end of this bond the shared electron may be displaced towards one or other involved atoms.
- This will give induced dipole movement (I.D.M).

Three components i.e. Ions, P.D.M and I.D.M are present so six types of attraction can be formed i.e.

1. Ion-ion
2. Ion – PDM
3. Ion- IDM
4. PDM- PDM
5. PDM- IDM
6. IDM – IDM

Ion involvement leads to electrostatic charges other than ions i.e.

- PDM –PDM
- PDM – IDM
- IDM- IDM

Those are the Van der Waal's attractive forces.

16.18.1.8 London or Dispersion Attractive Forces

Force between non-polar molecules due to vibration of electrons or mutual induction of dipole s within the molecule.

16.18.1.9 Hydrogen Bonding (Solvation)

Attraction between hydrogen atom and electronegative atoms e.g. O_2, N_2, F_2 etc.

16.19 Preparation of Colloids

16.19.1.1.1 LYOPHILIC COLLOIDS

Because of the affinity of the lyophilic colloids for the dispersion medium these colloids are relatively easy to form. As there is a considerable interaction between the disperse phase and the dispersion medium, they form spontaneously by placing the colloidal material in contact with proper solvent. For example acacia and gelatin disperse easily to form colloidal dispersion when kept in contact with water.

16.19.1.1.2 HYDROPHOBIC COLLOIDS

Since there is a lack of affinity between the molecules of disperse phase and dispersion medium, lyophobic colloids are more difficult to prepare.

There are three methods to prepare colloids

1. Dispersion
2. Condensation
3. Peptization

16.19.1.2 DISPERSION

Dispersion can be done in three ways:

1. Physical
2. Electrical
3. Mechanical

16.19.1.3 PHYSICAL DISPERSION

Lyophilic colloids showing affinity for dispersion medium.

Hydrophilic → e.g. gum acacia and gelatin in hot water

Lipophilic →e.g. polysterene in benzene and pyroxylin in alcohol.

16.19.1.4 ELECTRICAL DISPERSION

Electrical current passes through/ between poles of metal submerged in water or other dispersion medium which make the particles disrupted and form colloids.e.g. colloids of Au Ag etc.

16.19.1.5 MECHANICAL DISPERSION

Colloids are prepared by reducing into smaller particles.

→By Colloidal Mill (which consist of two parts, one is fixed and other is mobile).

E.g. Colloidal Kaolin, Zinc Oxide, Sulfur etc.

→By irradiation cavities are formed which collapse into smaller particles

16.19.1.6 CONDENSATION OR MOLECULAR AGGREGATION

Simple reaction are involved like

- Oxidation
- Reduction
- Hydrolysis
- Precipitation

16.19.1.7 OXIDATION

E.g. Colloidal solution of sulfur

$$2H_2S + SO_2 \rightarrow 3S + 2H_2O$$

16.19.1.8 REDUCTION

Colloidal solution of silver form $AgNO_3$ with the help of various reducing agents like hydrogen tannic acid, formaldehyde etc.

16.19.1.9 HYDROLYSIS

Colloidal solution $Fe(OH)_3$ by adding solution of ferric salts into boiling water

16.19.1.10 PRECIPITATION

Colloidal solution of arsenic sulfide, H2S passes through arsenic trioxide, Resin form Tincture.

16.19.1.11 PEPTIZATION

For neutral particles charge creating agents are used e.g. Glycerin, Sucrose, Lactose, Dextrose etc. Due to charge particles repel each other and so colloids are formed.

16.20 PHARMACEUTICAL APPLICATION OF COLLOIDS

Colloids have found a number of pharmaceutical applications including the following:

- Because of their **large surface area**colloids show greater efficiency for absorption or adsorption. Kaolin because of its small particle size show good adsorption properties for toxins. Similarly Colloidal Aluminum hydroxide shows better rate of neutralization of stomach acid.
- **Particle Size Reduction** also alters some of the therapeutic properties of drugs. For example colloidal iron is less severewhile colloidal iodine is less toxic than their ionic salts. Similarly colloidal silver is more effective germicidal while colloidal mercury is effective for the treatment of syphilis
- Hydrophilic colloids are used as **suspending agents** and as protective for hydrophobic colloids
- **Dextran Injection** is a colloidal dispersion and is used as plasma substitute.
- Colloidal preparations have also been used as **diagnostic agents**. For example, Lange's Gold Solution is used to detect syphilis inpatient. Normal spinal fluid protects the gold solution from the precipitating effect of sodium chloride whereas in syphilitic case, it fails to prevent it.

Chapter 17 EMULSION

17.1 COARSE DISPERSION

Coarse Dispersion consists of dispersed phase of size above 500 nm. Two dosage forms in coarse dispersion are

- Emulsion
- Suspension

17.2 EMULSION

A heterogeneous system in which two immiscible liquids are used one is distributed into the other and the system is stabilized by stabilizing agent (emulsifier).

17.3 TYPES

One liquid phase in emulsion is essentially polar (e.g. Aqueous) and the other is relatively non polar (e.g oil) Followings are the types:

17.3.1.1 OIL IN WATER (O/W)

In this type of emulsion oil globules are dispersed in continuous aqueous medium.

17.3.1.2 WATER IN OIL (W/O)

In this type of emulsion water particles are in dispersed phase while oil is as a continuous medium.

17.3.1.3 MULTIPLE EMULSION (O/W/O, W/O/W)

Multiple emulsions are complex polydispersed systems where both oil in water and water in oil emulsion exists simultaneously which are stabilized by lipophilic and hydrophilic surfactants respectively.

17.3.1.4 MICRO-EMULSION

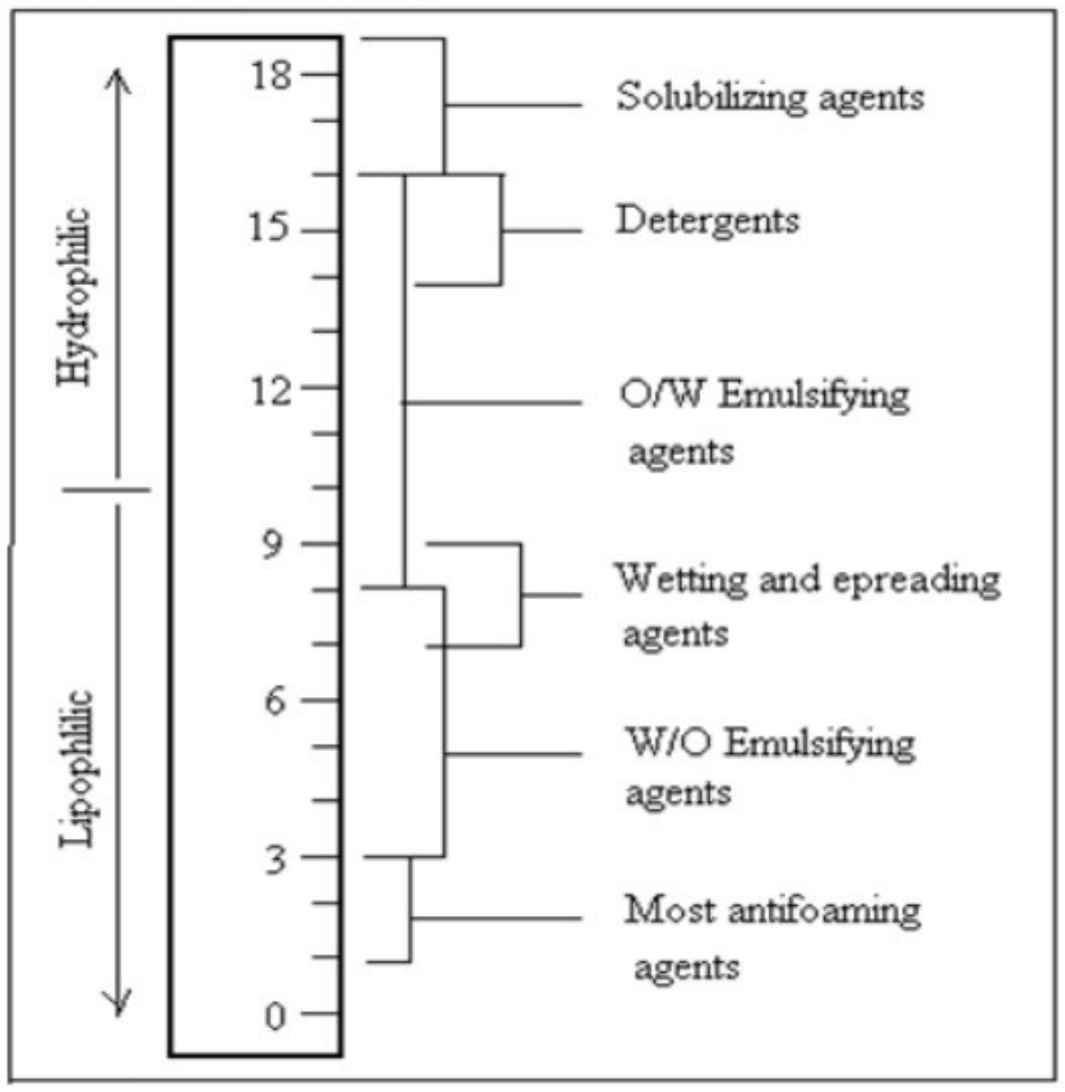
Emulsion in which the dispersed phase is in the form of very small droplets usually produced and maintained with the aid of surfactants and having diameters of from 50 to 500 angstroms for drug delivery.

17.4 EMULSIFYING AGENT

An agent used for stabilizing Emulsion is known as emulsifying agent, stabilizing agent for emulsion, emulsifier, emulgent.

17.5 HYDROPHILIC-LIPOPHILIC BALANCE (HLB)

The Hydrophilic-lipophilic balance of a surfactant is a measure of the degree to which it is hydrophilic or lipophilic, determined by calculating values for the different regions of the molecule.
The HLB value can be used to predict the surfactant properties of a molecule.



17.6 MECHANISM OF EMULSION STABILIZER/ EMULSIFIER FOR EMULSION STABILITY

17.6.1.1 MONOMOLECULAR ADSORPTION

Stability of Emulsion may be due to:

- Reduction in interfacial tension by the formation of monolayer of emulsifiers
- Combination of emulsifier are used rather than single emulsifier

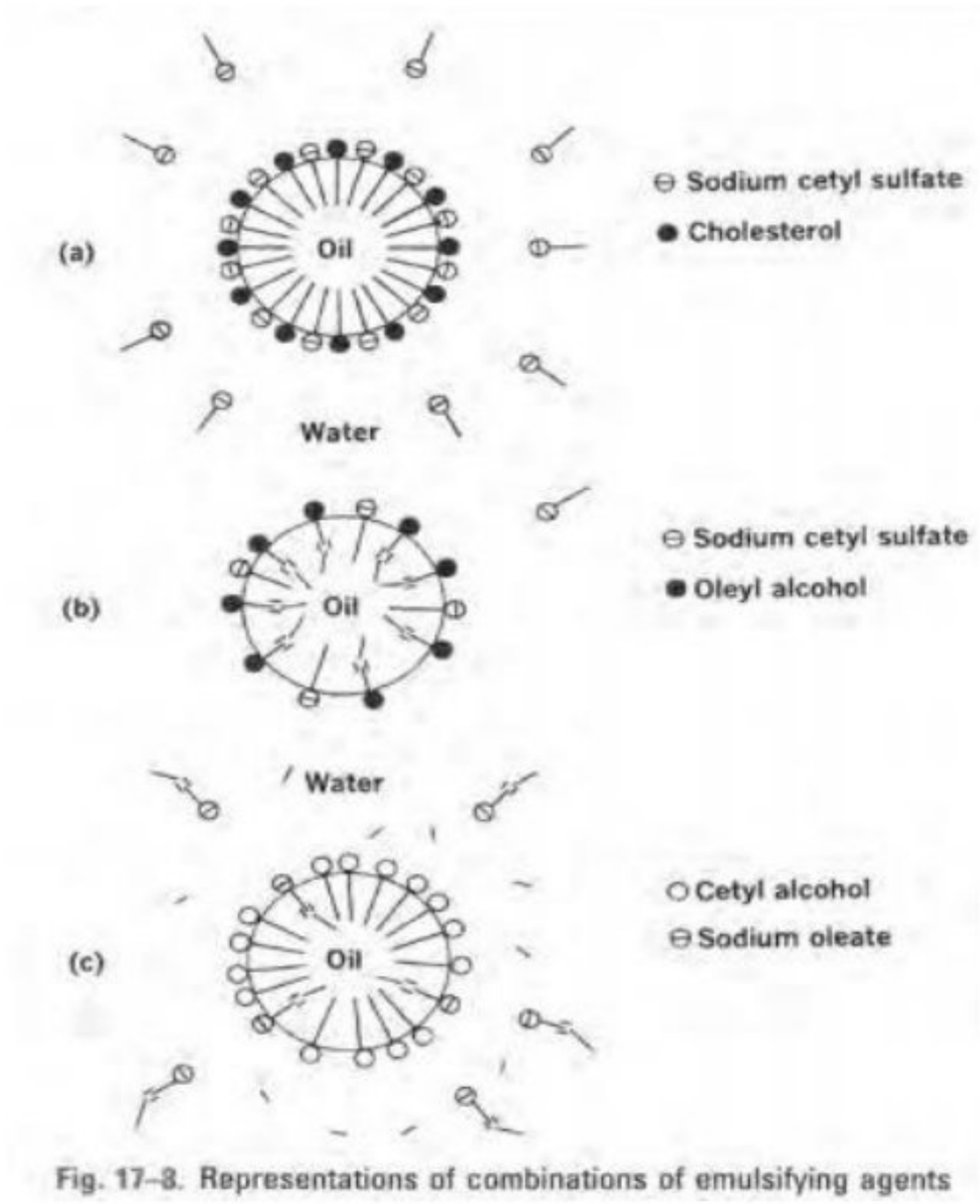


Fig. 17–8. Representations of combinations of emulsifying agents

Some combination gives complex film, closely packed film, so excellent combination of emulsifiers (a) while other don't give closely packed film and not a good complex so it will be poor combination of emulsifiers (b). There are some combinations which give closely packed but poor complexation so are not favorable combination (c).

17.6.1.2 Multi-Molecular Adsorption

Stability of emulsion is due to following two reasons

- Hydrated lyophilic colloids
- Protective effect of colloids

17.6.1.3 Solid Particle Adsorption

Solid particles welted by oil and water and concentrated at the interface. Example

- Bentonite (hydrated Alumunium silicate)
- Veegum (magnesium alumiunum silicate)
- Carbon black etc

17.7 Stability of Emulsion

Stability of pharmaceutical emulsion is characterized by

17.7.1.1 Absence of coalescence of internal phase

Coalescence is the process by which two or more droplets, bubbles or particles merge during contact to form a single daughter droplet, bubble or particle. If there is no coalescence of internal phase emulsion will remain stable.

17.7.1.2 Not being creamed

Creaming, in the laboratory sense, is the migration of the dispersed phase of an emulsion, under the influence of buoyancy. The particles float upwards or sink, depending on how large they are and how much less dense or denser they may be than the continuous phase

17.7.1.3 Maintenance of Elegance

Appearance, color, odor and other physical parameter should remain same in case of stable emulsion.

17.8 Instability of Pharmaceutical Emulsion

Instability is indicated by

- Flocculation and creaming
- Coalescence and breaking
- Other physical and chemical changes
- Phase inversion

17.8.1.1 Creaming

Creaming, in the laboratory sense, is the migration of the dispersed phase of an emulsion, under the influence of buoyancy. The particles float upwards or sink, depending on how large they are and how much less dense or denser they may be than the continuous phase. It may be upward or downward creaming.
Creaming is mostly reversible and shaking of emulsion gives original shape.

17.8.1.2 Flocculation

It is a process in which is a process wherein colloids come out of suspension in the form of floc or flake. It could be reversible or irreversible.

17.8.1.3 Coalescence and Breaking

Coalescence is the process by which two or more droplets, bubbles or particles merge during contact to form a single daughter droplet, bubble or particle. If there is no coalescence of internal phase emulsion will remain stable. Dispersed phase totally serpearted from the dispersion medium

17.8.1.4 Other Physical and Chemical Changes

Following parameter should be kept in optimum:

17.8.1.5 Viscosity

Phase volume ratio (relative volume of water and oil in emulsion).

- Critical Point is the concentration of internal phase which emulsion break down.
- 50/50 ratio is the best ratio between water and oil concentration.

17.9 Phase Inversion

It means internal phase is inverted to external phase i.e O/W emulsion is changed to W/O emulsion or vice versa.

Phase Inversion is usually due to:

- Finer particles
- Addition of some chemicals
  For example O/W emulsion stabilized with sodium seterate and can be inverted to W/O by adding calcium chloride which causes inversion.
- Temperature
- Microbial Growth
- Altering Phase Volume Ratio

17.10 Explanation for Phase Inversion

- ✓ In O/W emulsion, non-ionic surfactants are used. This O/W emulsion contains oil swollen micelles and emulsified oil/globules
- ✓ With increase of temperature
- ✓ Oil swollen micelles start breaking, size of emulsified globules start increasing.
- ✓ With further increase of temperature oil phase, surfactant and water phase completely separate
- ✓ Near this temperature water insoluble surfactant starts forming w/o emulsion contain water swollen micelles and emulsified droplets.

17.11 Continental Method of Emulsion Preparation

In O/W emulsion, emulsifier is mixed with oil, it is shaken well and then gradually water is added to prepare emulsion. This procedure is sometime known as continental method.

17.12 Emulsifying Agents

There are two types of emulsifying agent

17.12.1.1 Natural Emulsifying Agents:

- Gums (Acacia, Tragacanth etc.)
- Mucilages
- Waxes
- Proteins (Gelatin, Casein etc)
- Phospholipids (Eggs phospatidyl choline EPC)
- Carbohydrates (Dextran)
- Cellulose Derivatives (Sodium Alginate)
- Cholesterol

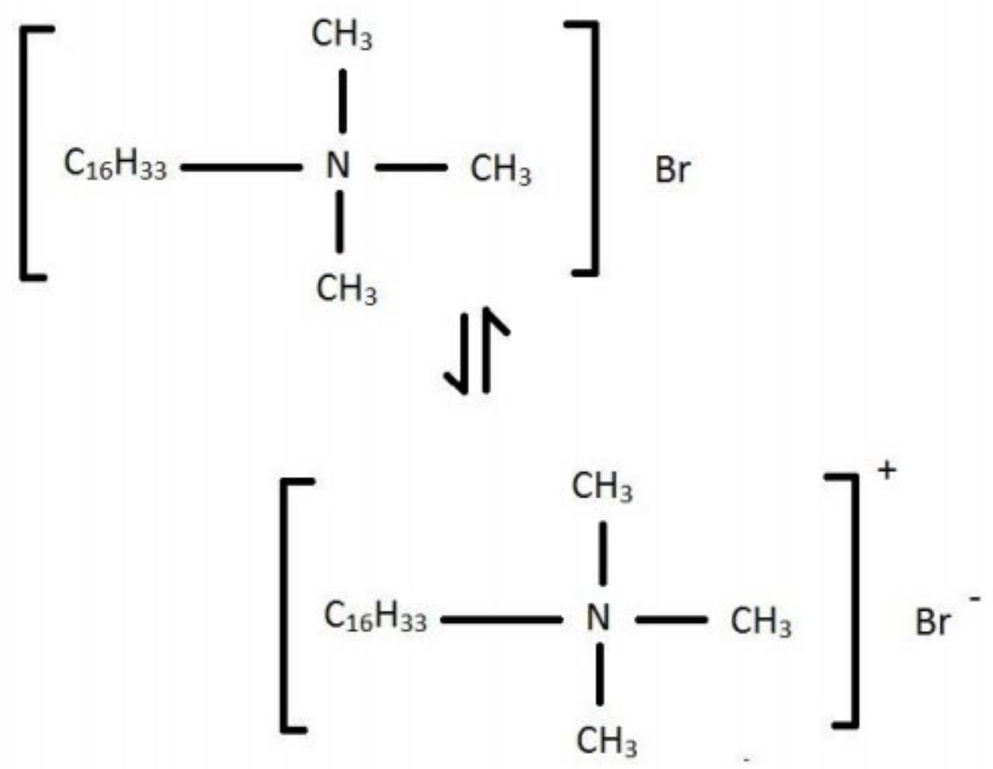
17.12.1.2 Synthesis

17.12.1.3 Non-Ionizing:

- Ester of higher fatty acids and alcohol e.g sorbitan monooleate for W/O emulsion
- Polyoxyethylene sorbitan mono oleate for O/W emulsion.

17.12.1.4 Ionizing

- Cationic (quaternary ammonium Compound)
- e.g. Cetyl trimethyl ammonium bromide, cetyl trimethyl ammonium iodide.



17.12.1.4.1 Anionic (e.g. Alkali soaps or soaps of inorganic elemets)

17.12.1.4.1.1 Monovalent alkali soaps

$RCOO^- + Na^+ \leftarrow RCOONa^+ \rightarrow$ O/W emulsion

Divalent alkali soaps

$(RCOO)_2 Ca \rightarrow (RCOO)_2 + Ca^{2+} \rightarrow$ W/O emulsion

Sodium Oleate

$C_{17}H_{33}COONa \leftrightarrow C_{17}H_{33}COO^+ + Na^-$

17.12.1.4.1.2 Sulphate (Sodium Lauryl SO_4)

Sulphonate (Sodium Cetyl Suphonate)

17.12.1.4.1.3 According to HLB (Hydrophilic-Lipophilic Balance).

17.13 Theories of Emulsification

1. Theory of Viscosity
2. Fischer's Theory of Hydrate
3. The Interfacial Tension Theory
4. The Adsorption Theory (Film Formation)
5. Oriented Adsorption Theory
6. Molecular Complex Formation Theory

17.13.1.1 Theory of Viscosity

It states that more viscous emulsion the greater is the stability. But it is not always true.

E.g. Milk has low viscosity but most stable, O/W emulsion.

Cold Cream is an example of more viscous emulsion, O/W emulsion.

17.13.1.2 Fischer's Theory of Hydrate

It states that disperse phase form colloidal hydrate or colloidal complex. E.g. O/W emulsion, oil form colloidal complex and in W/O emulsion water form colloidal complex and known as solvate.
However, the theory fails to answer and explain the stability of emulsion.

17.13.1.3 Interfacial Tension Theory

Greater is the interfacial tension, less table will be the emulsion as more attraction of the dispersed globules experiences.

17.13.1.4 The Adsorption Theory

Upon the addition of solute, surface tension is reduced due to solute – solvent attraction and due to adsorption of solute molecules at the surface.
Formation of surface film is film of emulsifier at the interface and is hydrated from both the sides of phases. Tension on both sides reduced. Greater tension will pull the film and form concave shape.
The phase on the concave side readily form globules and enveloped by the other phase.

17.13.1.5 Oriented Adsorption Theory

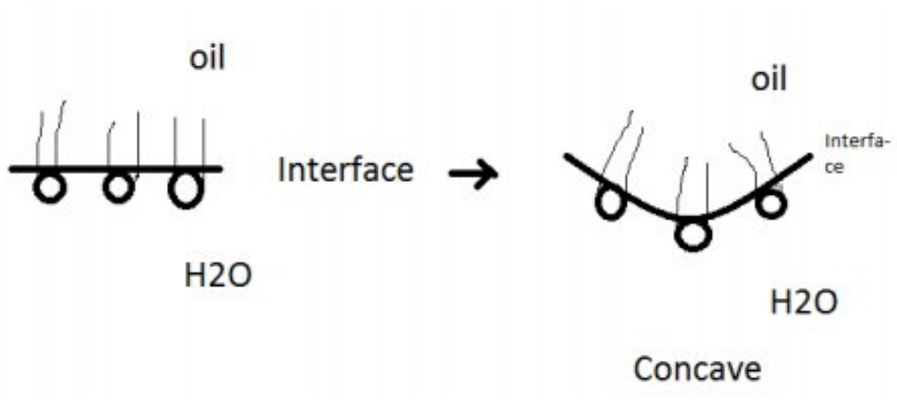
The types of substances are

- Non-Polar like ethane, where electrical charge is balanced.
- Polar like ethyl Alcohol and water where charge is not balance.

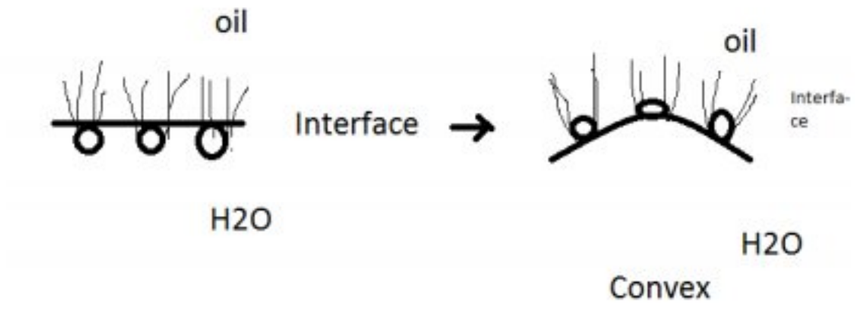
Polar substances are dissolved/arranged in polar solvent and non-polar towards non-polar solvent (e.g. Paraffin).

17.13.1.6 Harkin's Oriented Wedge Theory

Alkali Soap like: Na and K salts (Monovalent) more loving to water



Divalent and Trivalent salts e.g. Ca^{++} and Mg^{+++}



17.13.1.7 Molecular Complex Formation

When two substances form complex at the interface then immediate emulsification will result due to "Complex Formation" for example solution of Sodium Cetyl Sulphate when mixed with Cholesterol.

Applications of Emulsion

Cosmetic and Pharmaceutical Application

- Pharmaceutical applications according to rate of administration like topical, oral and parenteral.
- Cosmetic and tropical applications are the same.

17.13.1.8 Patient compliance/acceptance

Medicinal agents having objectionable taste and texture are best formulated in emulsion. Examples: mineral oil bared laxatives, oil soluble vitamins (A, D, E and K) and high fat nutritive preparation.

17.13.1.9 Bioavailability

- Some therapeutic agents shows high bioavailability in emulsion form. Example Griseofulvin.
- High Nutrition Value with minimum volume of triglyceride fat emulsion.
- Example I/V fat emulsion, Intralipids, lipofundin and lipofundin –S.
- Particle Size of these emulsions is controlled.
- These are isotonic and must not be diluted during administration.

17.13.1.10 Modern Drug Delivery Concept

- Unabsorbable macromolecules are absorbed to some extent when given orally.
- Example: insulin and heparin are absorbed when given orally in emulsion.

17.13.1.11 Tropical and Cosmetics Preparation

Patient acceptance can be improved for example by improving:

- Viscosity
- Appearance
- Degree of greasiness
- O/W emulsion used for washable drug bases and W/O emulsion are useful for dry skin and used as an emollient
    - Emollient is an agent which softens or soothes the skin or soothes irritated internal surface.

17.13.1.12 Radiopaque Emulsion in X-Ray

- Radiopacity is quality or property of obstructing the passage of radiant energy as in X-ray, the represented areas appearing light or white on exposure.

17.13.1.13 PREVENTION OF CRYSTALLIZATION IN INJECTABLE

- Emulsifiers presence in parenteral dosage form reduce tendency of crystallization responsible for thrombophlebitis (inflammation of vein associated with thrombus formation).
    - Thrombus is a solid mass formed in living heart/vein from blood constituents.

17.13.1.14 EMULSION USED AS OXYGEN CARRIERS IN BLOODS REPLACEMENT.

Emulsification of perflourinated hydrocarbons is required for using them as oxygen carriers in blood replacement.

17.14 BIOPHARMACEUTICAL ASPECTS OF EMULSIONS

- Improving drug bioavailability by the use of lipid O/W emulsions as vehicle for lipophilic drugs (Diazepham, Propofol) for IV use.
- It increases of bioavailability of Griseuflavin given an emulsion form: [Fats are emulsified by bile salts and administration of already emulsified form.
- Increase the opportunity for solublilization and hence transport across the microvilli by fat absorption pathways.
- Emulsion of Indoxole has greater bioavailability than other dosage form.
- Medium chain triglycerides and mono and di glycerides promotes the adsorption of cefrioxone and cefoxitin as well as that of cyclosoprin A.
- Emulsifier also enhances he membrane permeability.
- Absorption of particles from the gut by the lymphoid tissue suggests revision regarding absorption of many drugs from GIT.

Chapter 18 SUSPENSIONS

18.1 DEFINITION

- Suspensions may be defined as coarse dispersion containing finely divided drug particles (the suspensoid) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility.
- The diameter of the disperse phase may range from 0.5 to 100 µm.
- A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1 µm in diameter

Class	Particle Size*
Molecular dispersion	Less than 1 nm
Colloidal dispersion	From 1 nm to 0.5 µm
Coarse dispersion	Greater than 0.5 µm

18.2 CHARACTERISTICS

The characteristics of an acceptable pharmaceutical suspension include the following:

- A low rate of sedimentation
- The disperse phase must be easily redispersed with gentle shaking
- The flow properties of the suspension should enable the formulation to be easily removed from the container (e.g. bottle, injection vial)
- Aesthetically pleasing.

18.3 ADVANTAGES

- Pharmaceutical suspensions are a useful drug delivery system for therapeutic agents that have a low solubility.
- Pharmaceutical suspensions may be formulated to mask the taste of therapeutic agents.
- Pharmaceutical suspensions may be employed to administer drugs to patients who have difficulty swallowing solid-dosage forms.
- Pharmaceutical suspensions may be formulated to provide controlled drug delivery, e.g. as intramuscular injections

18.4 DISADVANTAGES

- Pharmaceutical suspensions are fundamentally unstable and therefore require formulation skill to ensure that the physical stability of the formulation is retained over the period of the shelf-life.
- The formulation of aesthetic suspension formulations is difficult.
- Suspension formulations may be bulky and therefore difficult for a patient to carry.

18.5 TYPES OF SUSPENSIONS

- A flocculate or floc is a loose open structure or cluster of particles.
- A suspension consisting of particles in this state is termed flocculated
- And a suspension without floc is termed deflocculated.

Flocculated suspension	Deflocculated suspension
Loose aggregate	No aggregate
High sedimentation rate	Low sedimentation rate
Loose packing of sediments	Compact packing of sediments
Easily redisperse	Difficult to redisperse
No pleasing appearance	Pleasing appearance
Floccules stick to wall of bottle	Don't stick to wall of bottle

18.6 NATURE OF SOLIDS

- Diffusible
- Poorly wettable
- Indiffusible

18.6.1.1 DIFFUSIBLE SOLIDS

- Insoluble but wettable
- Readily mixed
- Remain suspended for long period of time
- e.g. Mg trisilicate, kaolin

18.6.1.2 POORLY WETTABLE SOLIDS

- Insoluble and poor wettable
- Difficult to disperse
- Form clumps
- Wetting agent is required
- E.g. sulphur

18.6.1.3 Indiffusible Solids

- Insoluble
- Not remain dispersed
- Viscosity enhancer is required
- e.g. Zinc oxide, chalk

18.7 Suspending Agents

- Natural (acacia, tragacanth, starch)
- Semisynthetic (MC, HEC, Sod CMC)
- Synthetic (carbomers)
- Inorganic agent (Clay, bentonite)
- Miscellaneous (gelatin)

Or they may be classified as:

- Polysaccharides
- Natural (acacia, tragacanth, starch)
- Semisynthetic (MC, HEC, Sod CMC)
- Synthetic (carbomers)
- Inorganic agent (Clay, bentonite)

18.7.1.1 Acacia

- Acacia senegal
- Gum arabic
- Acacia gum is a brittle, odorless and generally tasteless material that contains a number of neutral sugars, acids, calcium and other electrolytes
- It is very soluble in water, but does not dissolve in alcohol.

18.7.1.2 Methylcellulose

- Methylcellulose is available in several viscosity grades.
- The difference in viscosity is due to difference in methylation and polymer chain length.
- Methylcellulose is more soluble in cold water than hot water.
- Methylcellulose is stable at pH range of 3-11.

18.7.1.3 Hydroxy Ethylcellulose

- Hydroxyethylcellulose (HEC) is another good suspending agent having somewhat similar characteristics to methylcellulose.
- In HEC hydroxyethyl group is attached to cellulose chain.
- Unlike methylcellulose, HEC is soluble in both hot and cold water and do not form gel on heating.

18.7.1.4 Carboxy Methylcellulose (CMC)

- Carboxy methylcellulose is available at different viscosity grades.
- Low, medium and high viscosity grades are commercially available.
- In case of HV-CMC, the viscosity significantly decreases when temperature rises to 40 ºC from 25 ºC.
- Therefore, to improve viscosity and stability of suspension MV-CMC is widely accepted.

18.7.1.5 Carbomers

- Carbomer is any of a series of polymers of acrylic acid
- Used as thickening agents and emulsion stabilizers.
- readily absorb water to form gels or thick solutions that are non-toxic, stable, and resist spoilage
- The various types indicated by a numerical suffix such as Carbomer 940 or Carbomer 973, which indicates the average molecular weight of the polymer chains.

18.8 Preparation of Suspensions

Suspensions for oral administration are usually manufactured in one of two methods:

(1) Dispersion method (direct incorporation)
(2) Condensation method (precipitation method)

18.8.1.1 Dispersion method

- In this method the soluble components are normally dissolved in the appropriate volume of diluent (vehicle).
- The solid therapeutic agent is then dispersed into the vehicle with the aid of mixing, prior to correction for volume.
- The mixing rate employed during the addition is an important determinant in the manufacture of the formulation.
- The particle size of the suspended drug within the formulation may then be reduced using a ball mill. Alternatively, the particle size of the active ingredient may be optimized (by particle size reduction techniques) prior to incorporation into the vehicle.

18.8.1.2 Condensation (Precipitation method)

- In this method the drug is dissolved in the vehicle (or a portion of the available volume), prior to precipitation (the salt formed is insoluble).
- Such systems are frequently deflocculated and are therefore mixed at low shear rates.

- The excipients are then dissolved in the vehicle, or dissolved in a portion of the vehicle, which is then added to the suspension of drug.
- At this stage the formulation may be exposed to high shearing rates to ensure homogeneity.
- The volume of the formulation is then corrected by adding the required mass of diluent.
- One potential problem with this technique is the production of ionic byproducts from the precipitation interaction. If the concentration of these is too high, then the precipitated therapeutic agent requires to be washed with an aqueous solvent.

18.9 Problem in Stability of Suspension

- Caking
- Flocculation
- Particle growth
- Adhesion of particles to container wall
- Sedimentation

18.10 Sedimentation Rate of the Particles of a Suspension

The various factors involved in the rate of settling of the particles of a suspension are embodied in the equation of Stokes law.

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

dx/dt is the rate of settling,
d is the diameter of the particles,
ρ_i is the density of the particle,
ρ_e is the density of the medium,
g is the gravitational constant, and
η is the viscosity of the medium.

CONDITION	RATE OF SETTLING (CM/S)
2.5 µm powder in water	1.02×10^{-4}
0.25 µm powder in water	1.02×10^{-6}
2.5 µm powder in glycerin	4.25×10^{-8}
0.25 µm powder in glycerin	4.25×10^{-10}

18.11 Free Settling & Hindered Settling

- Stokes' equation was derived for an ideal situation in which uniform, perfectly spherical particles in a very dilute suspension settle without producing turbulence, without colliding with other particles of the suspensoid, and without chemical or physical attraction or affinity for the dispersion medium, which is called free settling.
- But suspensions are
  - Concentrated
  - Particles are not spherical

  This is called Hindered Settling.

18.12 Sedimentation Parameters

Two parameters to assessment of the sedimentation of drug:

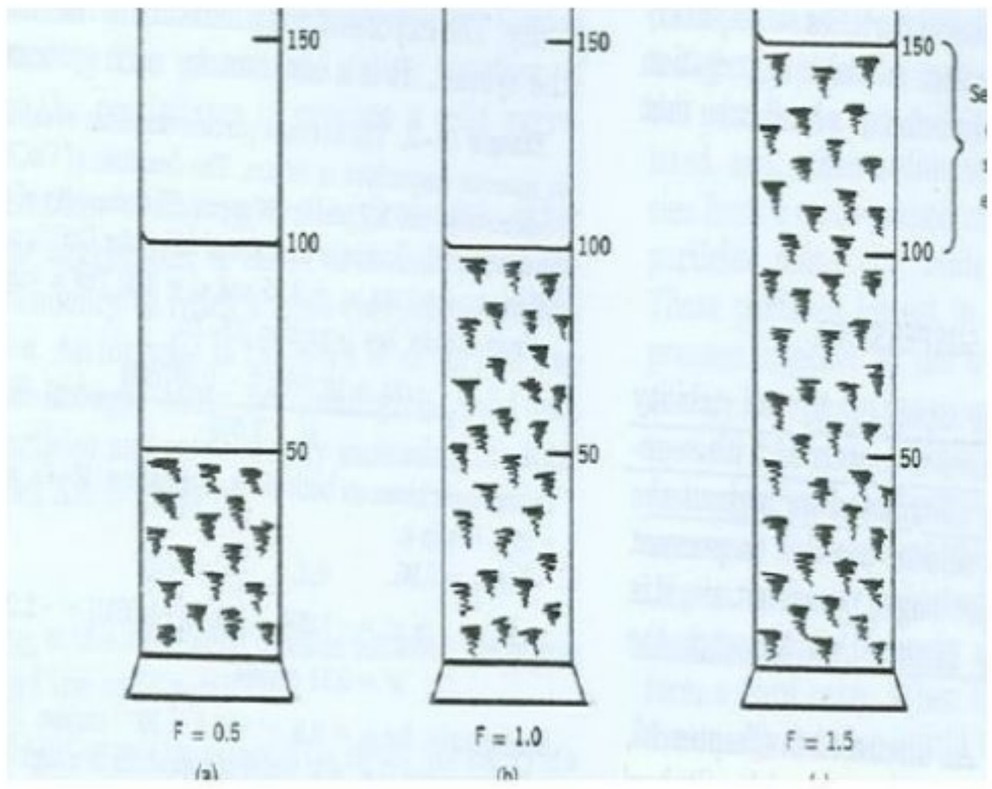
(1) Sedimentation volume
(2) Degree of flocculation

18.12.1.1 Sedimentation volume (F)

- This is the ratio of the volume of the sediment (Vs) to the initial volume of the suspension (Vi):

$$F = \frac{V_s}{V_i}$$

- The sedimentation volume may range from



18.12.1.2 Degree of flocculation (β)

- The degree of flocculation is defined as the ratio of the ultimate sedimentation volume of the flocculated suspension to the ultimate sedimentation volume of the deflocculated suspension.

$$\beta = \frac{(Vs/Vi)\ \text{flocculated}}{(Vs/Vi)\ \text{deflocculated}}$$

$$\beta = \frac{F}{F_{\infty}}$$

- This is usually the preferred measurement as it provides a point of reference, i.e. the suspension before and after flocculation.
- The minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.

18.12.1.3 Example

Suppose:

- Initial volume of the suspension (Vi) = 100 ml
- Volume of the sediment (Vs) = 44 ml
- Sedimentation volume F = ?
- Degree of flocculation (β) = 1.5
- Sedimentation volume of deflocculated suspension= ?

18.12.1.4 Solution

$$F = \frac{V_s}{V_i}$$

$$F = 44 / 100$$

$$F = 0.4$$

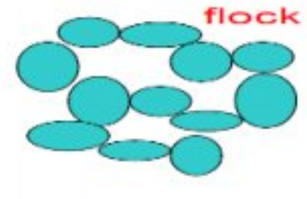
$$\beta = \frac{F}{F_{\infty}}$$

$$F\infty = 0.4 / 1.5$$

$$F\infty = 0.29$$

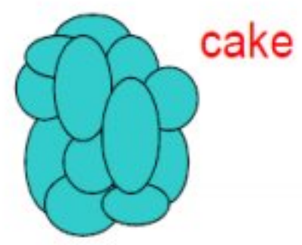
18.13 Flocculation and Deflocculation in Suspensions

18.13.1.1 Flocculated



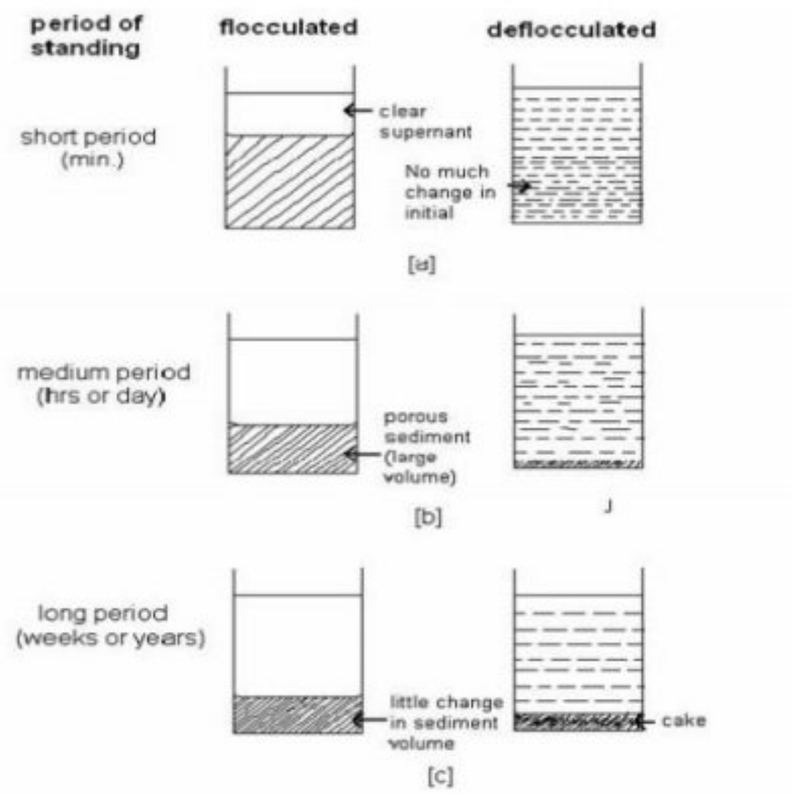
- Rapid settle down
- Not elegant

18.13.1.2 Deflocculated



- Slow settle down
- Cake

Therefore, partially deflocculated suspensions are ideal preparation



18.14 Zeta Potential

- The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and electro-neutral region of the solution

- Since this potential governs the degree of repulsion between the adjacent, similarly charged, dispersed particles.
- Zeta potential has practical application in stability of systems containing dispersed particles.
- If the zeta potential is reduced below a certain value, the attractive forces exceed the repulsive forces, and the particles come together.
- This phenomenon is known as flocculation.

- Thus the phenomenon of flocculation and deflocculation depends on zeta potential carried by particles.
- The flocculated suspension is one in which zeta potential of particle is -20 to +20 mV.
- Deflocculation of particles is obtained when the zeta potential is higher than the critical value and the repulsive forces supersede the attractive forces.
- These deflocculated particles when sediment form a close packed arrangement with the smaller particles filling the voids between the larger ones. -SOLID HARD CAKE
- When this zeta potential goes below the critical value, the attractive forces supersede the repulsive forces and flocculation occurs.
- These loosely packed particles or floccs settle faster than the defflocculated particles because of their larger sizes.
- But unlike deffloculated particles this sediment of floccs does not form solid cake.
- This sediment of floccs is easy to redisperse by minute agitation.

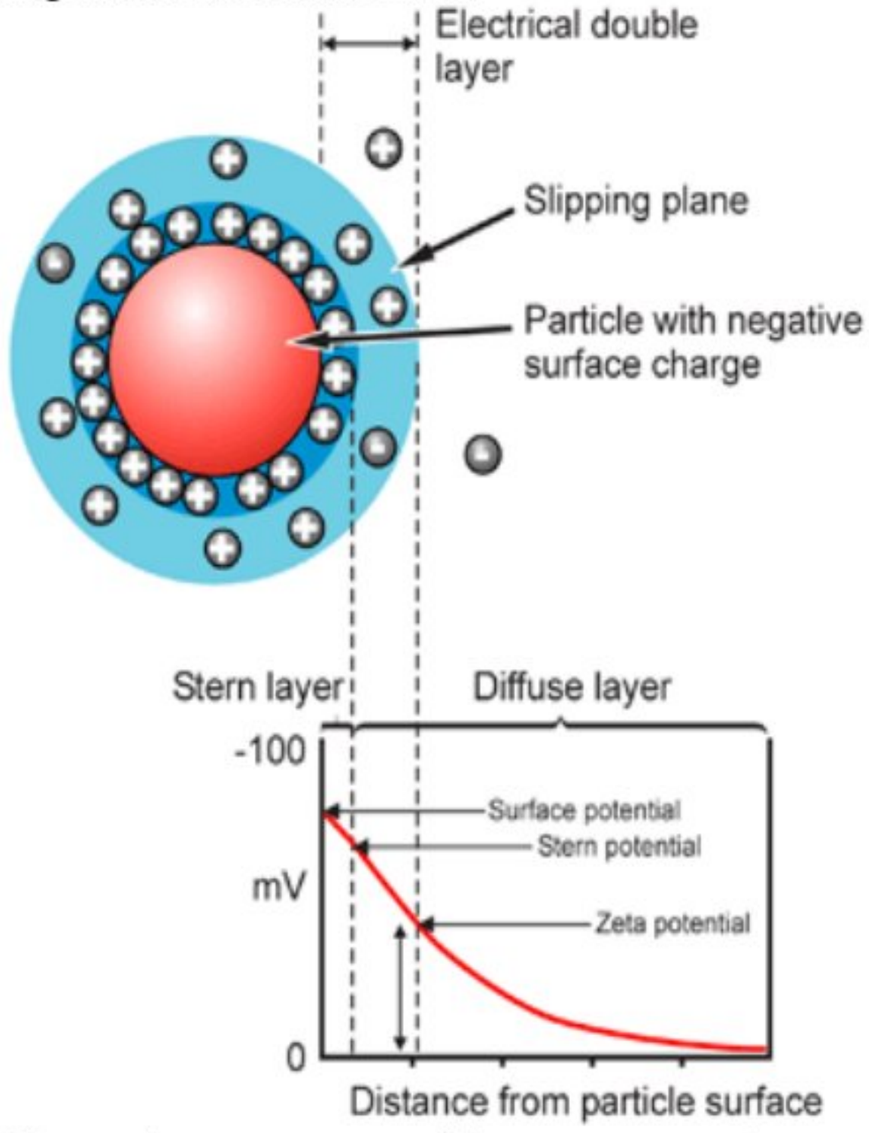
18.15 CONTROLLED FLOCCULATION

Controlled flocculation of particles is obtained by adding flocculating agents, which are:

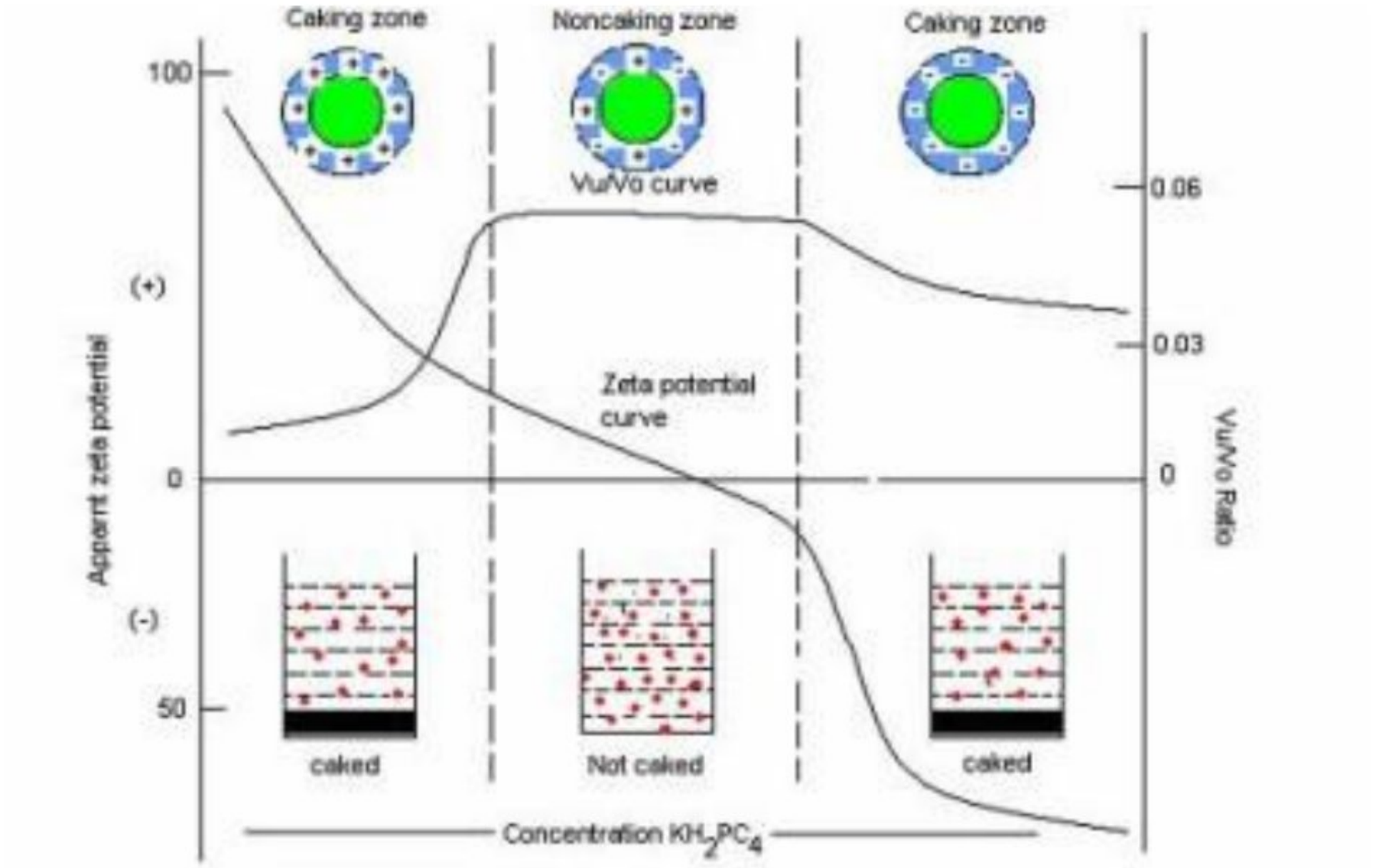
- Electrolytes
- Surfactants
- Polymers

18.15.1.1 ELECTROLYTES

- Electrolytes decrease electrical barrier between the particles and bring them together to form floccules.



- They reduce zeta potential near to zero value that results in formation of bridge between adjacent particles, which lines them together in a loosely arranged structure.
- If we disperse particles of bismuth subnitrate in water
- the system is deflocculated.
- By increasing concentration of monobasic potassium phosphate co-relation between apparent zeta potential and sedimentation volume, caking, and flocculation can be demonstrated.



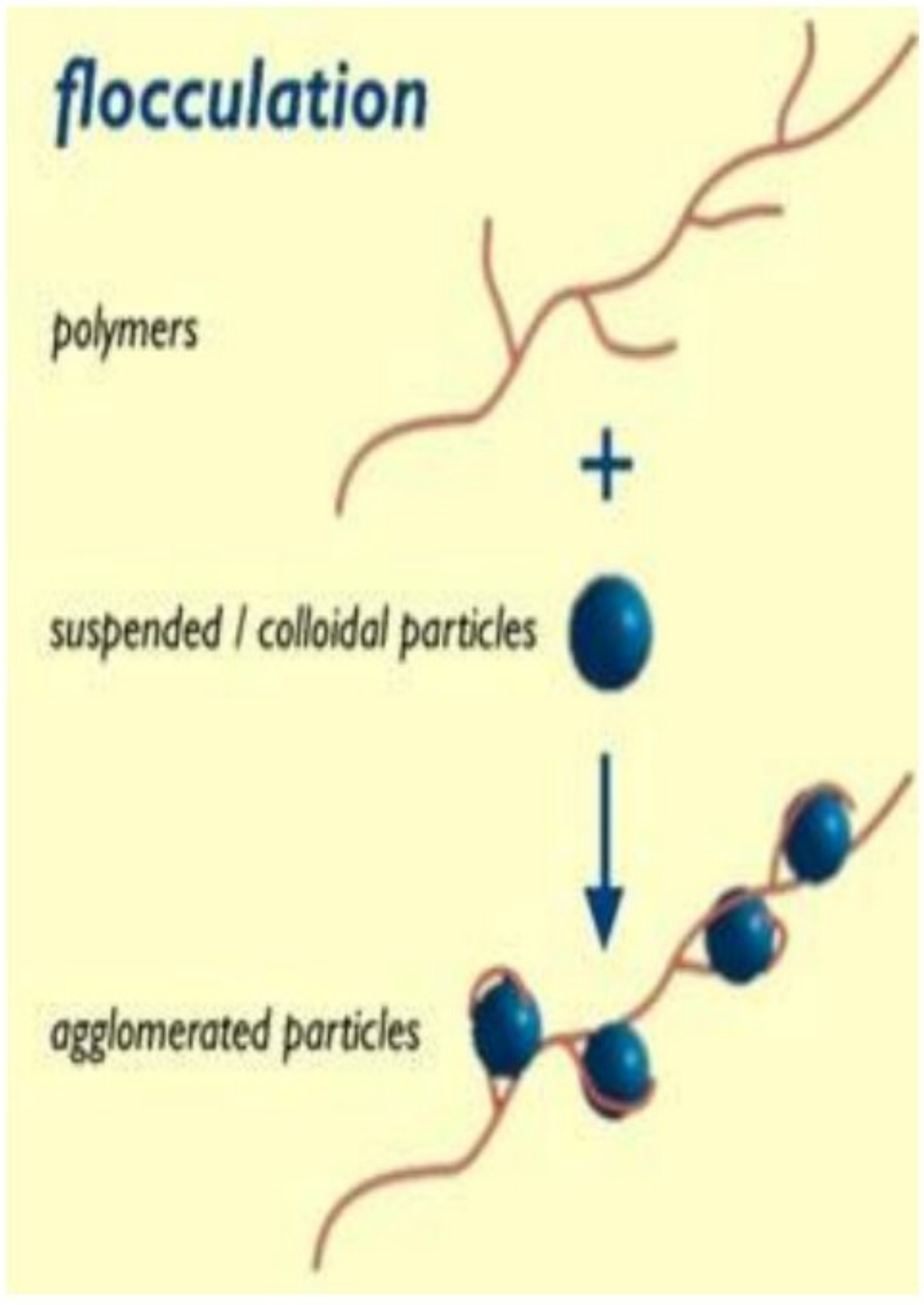
- The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of negatively charged phosphate anion.
- With continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in negative directions.
- Only when zeta potential becomes sufficiently negative to affect potential does the sedimentation volume start to fall.

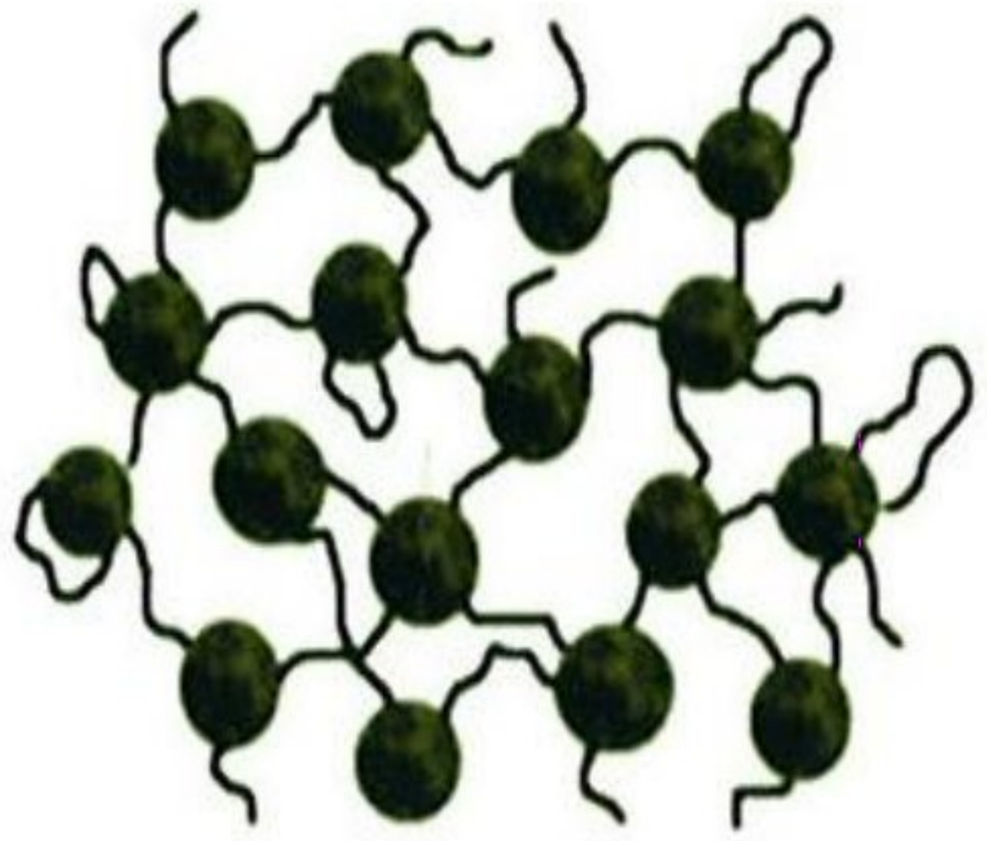
18.15.1.2 SURFACTANTS

- Both ionic and non-ionic surfactants can be used to bring about flocculation of suspended particles.
- Optimum concentration is necessary because these compounds also act as wetting agents to achieve dispersion.
- At optimum concentrations they reduce the surface tension between liquid medium and solid particles.
- The particles are attracted towards to each other by van der-waals forces and forms loose agglomerates.

18.15.1.3 POLYMERS

- Polymers possess long chain in their structures.
- Starch, alginates, cellulose derivatives, carbomers, tragacanth
- The part of the long chain is adsorbed on the surface of the particles and remaining part projecting out into the dispersed medium.
- Bridging between these later portions, also leads to the formation of flocs.





FLOCCULATION
(polymeric flocculant)

18.16 Flocculation in Structured Vehicles

Structured vehicles are those containing thickening or suspending agents.
These are used to increase the viscosity of the suspension.
These structured vehicles entrapped the particle and reduces the sedimentation of flocculated suspension.

Too high viscosity is not desirable as:

- It causes difficulty in pouring and administration.
- It may affect drug absorption since they adsorb on the surface of particle and suppress the dissolution rate.

Structured vehicle is not useful for Parenteral suspension because they may create problem in syringeability due to high viscosity.

18.17 Applications

- Suspension is usually applicable for drug which is insoluble or poorly soluble. E.g. Prednisolone suspension
- To prevent degradation of drug or to improve stability of drug. E.g. Oxytetracycline suspension
- To mask the taste of bitter of unpleasant drug. E.g. Chloramphenicol palmitate suspension
- Suspension of drug can be formulated for topical application e.g. Calamine lotion.
- Suspension can be formulated for parentral application in order to control rate of drug absorption, E.g. penicillin procaine
- Vaccines as a immunizing agent are often formulated as suspension. E.g. Cholera vaccine
- X-ray contrast agent are also formulated as suspension. E.g. Barium sulphate for examination of alimentary tract

18.18 Route of Administration

- Orally
- As injectable form -- I/M, S/C
- Drug reservoir as transdermal patches
- Aerosol

Chapter 19 ADSORPTION

Adsorption consists of two components:

ADSORBENT

Kaolin, pectin, altpulgite, talc, Magnisum trisilicate, $Al(OH)_3$, Simithicone, $CaCO_3$ (Activated Charcoal), $Mg(OH)_3$ etc.

19.1.1.1.1 ADSORBATE

Toxins, Strychnine HCl, Digoxin and many other drugs

19.2 ADSORPTION

It is an accumulation of substance at the interface or boundary between two and heterogeneous phases. For example, Solid-Gas, Oil- H_2O, Gas- Liquid, or Solid – Liquid.

"It is essentially a surface phenomenon".

19.3 ABSORPTION

It implies the penetration one component throughout the body of a second. The distinction between adsorption and absorption is not always clear.

19.4 SORPTION

When there is not any distinction between adsorption and Absorption, then a non-committal word "Sorption" is used.

19.5 TYPES OF ADSORPTION

Two Types:

19.5.1.1.1 PHYSICAL ADSORPTION

It is an adsorption at the surface through weak "van der waal" forces.

19.5.1.1.2 CHEMICAL ADSORPTION

It involves stronger valence forces; it is more potent and usually involves "Ion Exchange Process"

- ❖ Frequently both physical and chemical adsorption may be involved.
- ❖ For example, in adsorption of "Toxins" in the stomach by "Attapulgite" and "Kaolin" Chemisorption involves cation exchange with the basic group of Toxins and physical adsorption of the remainder of the molecule.

19.6 OTHER EXAMPLE OF ADSORPTION

- Stychinine HCl onto Activated Charcoal (Solid – Liquid)
- Activated Charcoal used in Respirators for civilian and forces (Solid- Gas)
- Decrease in surface tension is due to surface active agent for example liquid-gas bonding.
- Emulsifying agent as emulsion stabilizers in case of liquid- liquid bonding.

- ❖ Langmuir regarded adsorption phenomenon as function of unsaturated valencies and sharing of electrons. Sometimes bonds are strong and sometimes weak.

19.7 POSITIVE ADSORPTION

Solution of Strychnine HCl shaken with activated charcoal resulted into different concentration of strychnine HCl at surface of charcoal than in the bulk. (Volume Concentration)

If surface concentration is greater than volume concentration adsorption is called positive adsorption

19.8 NEGATIVE ADSORPTION

If surface concentration is less than the bulk (volume concentration) the adsorption is called negative adsorption.

19.9 FACTOR AFFECTING ADSORPTION

19.9.1.1 SOLUBILITY OF THE ADSORBATE

$$Adsorption \propto \frac{1}{Solubility}$$

Highly soluble substance has poor/less adsorption on adsorbent surface due to more firm solute – solvent bonds. This empirical rule is known as **Lundeliu's Rule.**

Example, I_2 adsorption on carbon from its solution into CCl_4, $CHCL_3$ and CS_2 was 1:2:4.5 respectively. It is close to inverse ration for solubility of I_2 into these solvents.

- ❖ Phobic substances adsorb more than philic.
- ❖ Keeping philic moiety constant Ć hydrocarbons chains vary, adsorption increases as the series ascended.

19.9.1.2 pH

- Ionization is effected by pH which actually affects the solubility of drugs.
- In drugs with single molecules, adsorption increases when ionization is suppressed. It is maximum when drug is completely unionized.
- Amphoteric Compound (Ć +ve and –ve Charge)

- Adsorption is maximum at isoelectric point.
- pH and solubility act in concert
- Unionized form of drugs in aqueous soln. has low solubility.
- Of the two i.e. pH and Solubility, Solubility has more pronounced effect

Example:

- Adsorption of hyoscine and Atropine on Magnesium Trisilicate.
- Hyoscine is completely unionized but has less adsorbed than atropine which is 50% ionized. Because Hyoscine is highly soluble (1:9.5 parts of H_2O) than atropine (1:400 parts of H_2O). So solubilization is inversely proportion to adsorption.

19.9.1.3 Nature of Adsorbent

- Physio-chemical nature of adsorbent plays significant role on the rate and capacity of adsorption.
- Finely divided particles have more adsorption capacity because of more surface area.
- Adsorbents can be converted into activated form to increase the capacity of adsorption.

Example: Activated Charcoal

i. Special treatment to remove surface impurities
ii. To convert into small particles

Activated charcoal is prepared from coco-nut shells.

- Dust particles removed by steam and air.
- Then converting into small particles.

19.9.1.4 Temperature

Adsorption is an exothermic process and an increase in temperature will decrease adsorption.
Small variation may not have much influence.

19.9.1.5 Pressure

At solid-gas interface amount adsorbed is

$$\text{Amount Adsorbed} = \frac{x}{m} = KP^n$$

Where P = Pressure and K and n were constant.

19.9.1.6 Concentration

At solution solid particle it can be given as

$$\text{Amount Adsorbed} = \frac{x}{m} = KC^n$$

Where C = concentration, K & n = constants.

19.10 Chromatography

Separation of components solutes in a solution exploits the principle of adsorption. Smallest difference in their absorbability or differences in their distribution/ partition between two phases.

19.10.1.1 Types of Chromatography

19.10.1.2 Adsorption Chromatography

Adsorbents like Kreselgur, charcoal, cellulose, MgO, CaO, PO_4, CO_3, etc are packed in column (Stationary or Fixed Phase)
Water, alcohol, chloroform etc as mobile phase.

19.10.1.3 Partition Chromatography

Two immiscible liquids are used
H_2O and CH_3Cl (liquids) with silica gel which acts support for liquid as fixed phase and CH_3Cl or other liquids as mobile phase.

19.10.1.4 Paper Chromatography

Normally filter paper is used. Two types:

- Ascending
- Descending

When mobile phase is at bottom or at the top respectively

19.10.1.5 Working of Chromatography

1. Preparation of sample and its injection
2. Sample goes to column (Fixed phase)
3. It comes across and mobile phase and separation of components solutes complete
4. Separated components is taken to detector and recorded.

19.11 Application of Adsorption

Adsorption has the application in:

1. Preparative and Analytical Chromatography
2. Heterogeneous catalysis
3. Water purification
4. Solvent recovery

19.12 Medical and Pharmaceutical Applications

19.12.1.1 Adsorption of noxious substance from alimentary canal

Universal and antidote (activated charcoal, MgO and Tannic acid) when used orally, reduces toxic levels of poisoning.

19.12.1.2 Removal of Toxic Elements from Blood

Some adsorbents are used to remove toxic elements by subjecting its dialysis through "hemodialysis" membrane over charcoal and adsorbents (chlorpheniramine, colchicine, Phenytoin, aspirin etc.)

19.12.1.3 Treatment of severe drug overdoses

- Extracorporeal method has been developed named "Haemoperfusion"

- Microencapsulation of activated charcoal by Arcylic Hydrogel, a biocompatible material preventing Embolism and removal of platelets.
- In vivo – In vitro relationship regarding adsorptive capacity of adsorbents.
- No relationship exists.

Reason:

- GIT and biological system have many other things which alter the adsorption ratio.

Example:

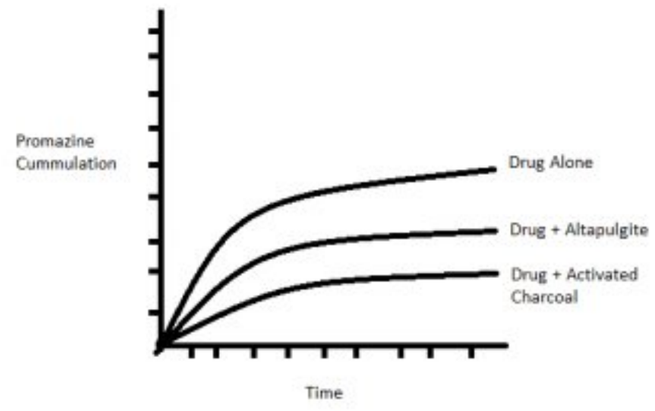
- In vitro – 5g activated charcoal bin 8g of Aspirin
- In vivo – 30g of activated charcoal inhibits the GIT adsorption of 3g of Aspirin by 50%.

19.12.1.4 Adsorption problems in Drug Formulation

Drugs containing antacids and other drugs, when given, the above problem results. Adsorbents are non-specific nutrients, drugs and enzymes when given orally.

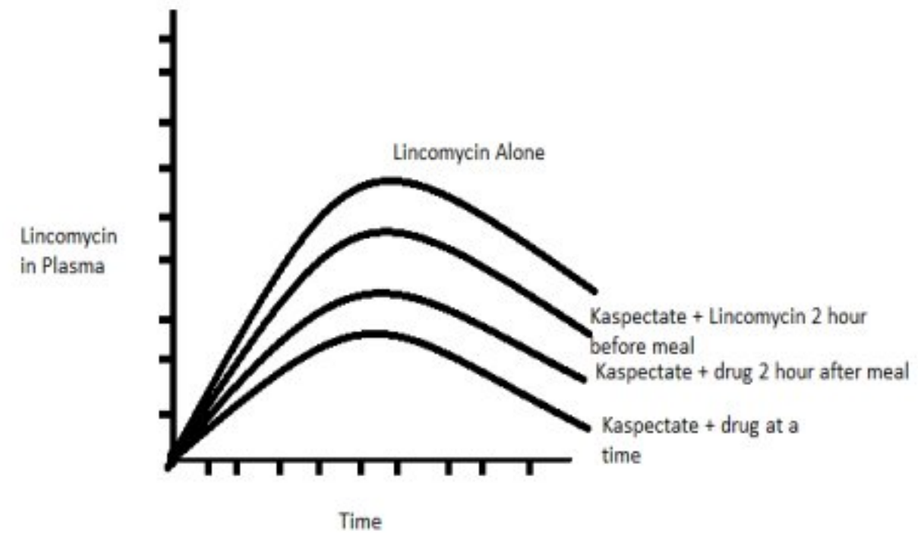
Example:

19.12.1.5 Promazine given above or Ć adsorbents



19.12.1.6 Lincomycin

Kaopectate is a combination of Kaolin and Pectinic acid.



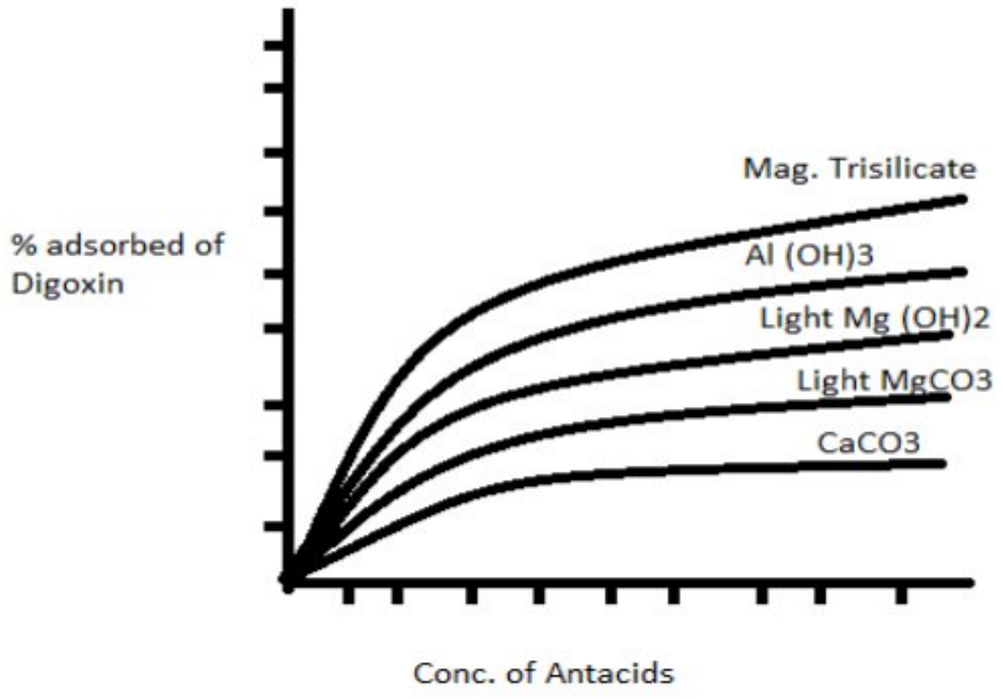
19.12.1.7 PAS (para- aminosaliculic acid) and Rifampicin

Availability of rifampicin is reduced due to bentonite used as an excipient. Bentonite is naturally occurring mineral (montmorillonite) and hydrated aluminum silicate.

19.12.1.8 B.P.C mixture of Mag.trisilcate and belladonna.

Complete adsorption hyoscine onto magnisum trisilicate which is an adsorbent.

19.12.1.9 Cardioactive Glycosides (Digoxin, Digitoxin, Digitonin etc) adsorb onto antacids.



19.13 Other Uses of Adsorption Phenomenon

19.13.1.1 Decolourization

During purification (by partitioning, crystallization and precipitation) chemical is tinted so colour is removed by adding activated charcoal or other appropriate adsorbents

Precaution: Adsorption active principle like alkaloid drugs on kieselguhr, adsorption is decreased.

19.13.1.2 Adsorption of water Vapors:

Alumina and silica gel remain in solid forms even after 40% adsorption of H_2O. $CaCl_2$ and P_2O_5 also adsorb H_2O but liquefy after water adsorption.

Alumina and silica gel are preferred.

19.13.1.3 Adsorption of Pyrogens

Pyrogen are low molecular weight drugs (glucose, sodium citrate, calcium gluconate etc.) can be pyrogen free but high molecular weight drugs get adsorbs highly on adsorbents so cannot be pyrogen free.

19.13.1.4 Surface Area Determination

Properties of powders are highly influenced

E.g. rate of soln. rate of oxidation, hygroscopic, sedimentation behavior, resistance to gas flow, bulk density and associated packing problems.

19.13.1.5 Monitoring of Pore Size of Filter Papers

Membrane filtration for sterility pore size decreases to 450 nm.

19.13.1.6 Stability of Colloids

Protective colloids (lyophilic colloids for lyophobic colloid's stability)

19.13.1.7 Stability of Emulsions

By using emulsifying agents of appropriate HLB no. (Hydrophilic – lipophlic balance)
Pharmacological Activity due to Adsorption at Receptor Sites.

19.13.1.8 Rheological Properties of Suspensions

Heterogenous system behave differently than homogenous system behave differently than homogenous systems.
Adsorption at walls of container also adsorption into the container's wall.

Chapter 20 RHEOLOGY

20.1 RHEOLOGY

- Rheology is derived from two Greek work "Rheo" means to flow and "Logos" means science so Rheology is *the study of flow properties of liquids and deformation of solids.*
- Science concerned with the deformation of matter under the influence of stress.
- The flow of simple liquids can be described by viscosity, an expression of the resistance to flow; however, other complex dispersions cannot be simply expressed by viscosity.

20.2 SHEAR STRESS

- The force per unit area F/A required to bring about flow is called SHEAR STRESS.
- Since the units of force are Newtons and the units of area are m^2 it follows that the units of Shear Stress are N/m^2
- This is referred to as the PASCAL (i.e. 1 N/m^2 = 1 Pascal) and is denoted by the symbol σ (in older textbooks you may see it denoted as τ).

20.3 SHEAR RATE

- The difference of velocity (dv) between two planes of liquid separated by an infinitesimal distance (dr) is called velocity gradient rate of shear.
- G=dv/ dr
- Directly proportion to F
- Directly proportion distance b/w layers

20.4 ABSOLUTE VISCOSITY (DYNAMIC VISCOSITY)

- The resistance to flow encountered when one layer or plane of fluid attempts to move over another identical layer or plane of fluid at a given speed. Absolute viscosity is also called dynamic viscosity
- The Shear Rate obtained from an applied Shear Stress will be dependent upon the material's resistance to flow i.e. its VISCOSITY.
- Since the flow resistance =force / displacement it follows that:

VISCOSITY = SHEAR STRESS / SHEAR RATE $\eta = \sigma/G$

$\eta = (F/A) / (dv/dr)$

$\eta = (F\,dr / A\,dv)$

$\eta = N\,m / m^2\,m/sec$

$\eta = N\,sec / m^2$

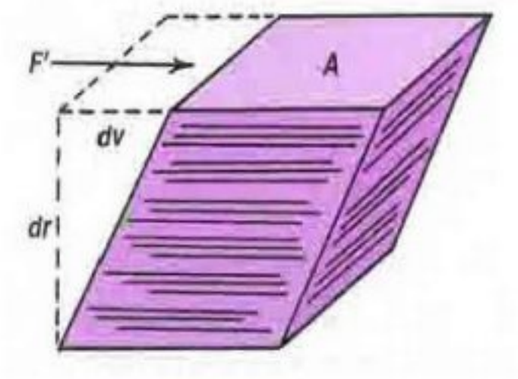
$\eta = dyne\,cm / cm^2\,cm/sec$

$\eta = dyne\,sec / cm^2$

20.4.1.1 BASIC UNIT IS POISE - JEAN LOUIS MARIE POISEUILLE

Poise (force of 1 dyne per square centimeter maintains a difference in velocity of 1 centimetre per second between two parallel planes 1 centimetre apart)

- 1 Pa.s = 1 N s/m^2
- 1 Poise = 100 centipoises
- Poise = 1 centipoises



20.4.1.2 INTERCONVERSION

- P = 0.1 Pa·s
- cP = 0.001 Pa·s.= 1 mPa·s

20.5 KINEMATIC VISCOSITY

Kinematic viscosity is the ratio of absolute or dynamic viscosity to density - a quantity in which no force is involved

Kinematic viscosity = η/ρ

Units are Stock / centistokes (cS) – George Gabriel Stokes

20.6 NEWTON

The SI unit of force, equal to the force that produces an acceleration of one meter per second per second on a mass of one kilogram.

20.7 DYNE

The standard centimeter-gram-second unit of force, equal to the force that produces an acceleration of one centimeter per second per second on a mass of one gram.

20.8 PASCAL

The SI unit of pressure or stress, equal to one newton per square meter.

20.9 RELATIVE VELOCITY

Relative velocity is a measurement of velocity between two objects moving in different frames of reference

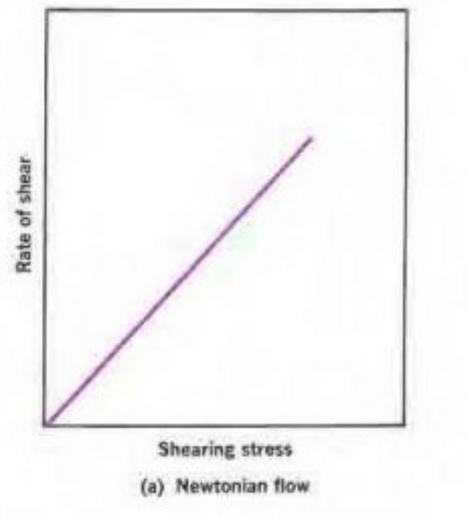
20.10 FLUIDITY

Reciprocal of viscosity is called fluidity.

$$\Phi = 1/\eta$$

20.11 Newton's Law of Flow

- The rate of flow (D) is directly proportional to the applied stress (τ).
- Fluids that obey Newton's law of flow are referred to as *Newtonian fluids and fluids which deviate are known as non-Newtonian fluids.*



(a) Newtonian flow

- *Newtonian fluids e.g* Water, benzene

20.12 Non-Newtonian fluids

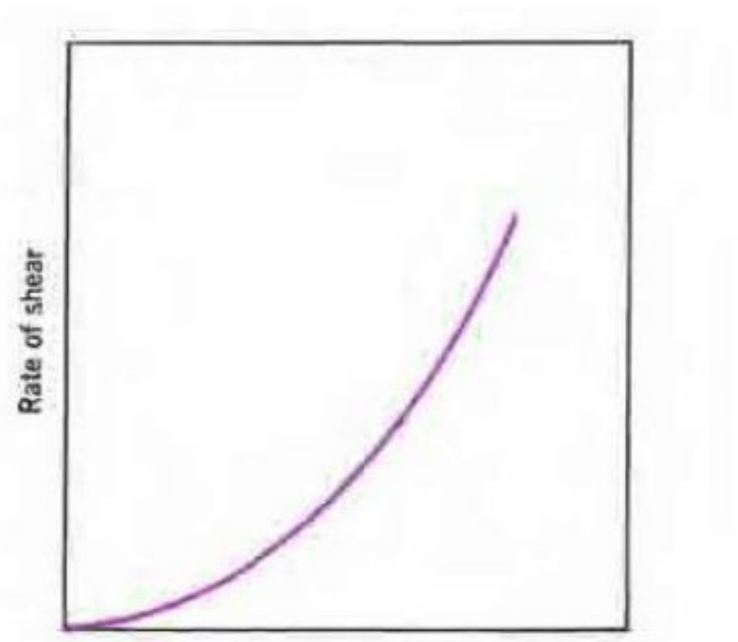
- Most pharmaceutical fluids (including colloidal dispersions, emulsions, and liquid suspensions) do not follow Newton's law of flow, and the viscosity of the fluid varies with the rate of shear.
- There are three types of non-Newtonian flow:
  - *plastic,*
  - *pseudoplastic*
  - *dilatant.*

20.12.1.1 Plastic flow

(b) Simple plastic flow

- Substances that undergo plastic flow are called *Bingham bodies.*
- Require force to bring about flow
- Do not flow till shear stress exceed Yield value
- Plastic flow is associated with the presence of flocculated particles in concentrated suspensions.
- Plastic flow does not begin until a shearing stress, corresponding to a *yield value, is exceeded.*
- The curve intersects the shearing stress axis but does not cross through the origin.
- The materials are said to be "elastic" at shear stresses below the yield value.
- *Flocculated solids are light, fluffy conglomerates of* adjacent particles held together by weak van der Waals forces.
- The yield value exists because a certain shearing stress must be exceeded in order to break up van der Waals forces.
- A plastic system resembles a Newtonian system at shear stresses above the yield value.
- Yield value, is an indicator of flocculation (higher yield value, greater degree of flocculation).

20.13 Pseudoplastic Flow



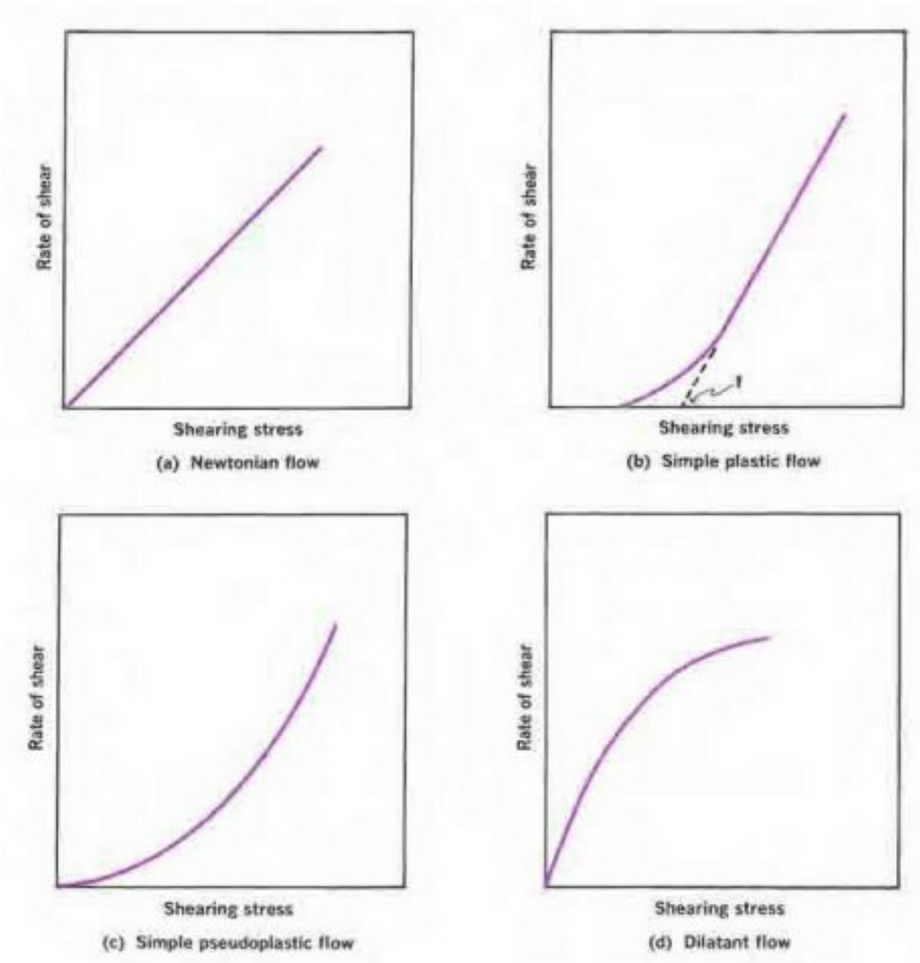
(c) Simple pseudoplastic flow

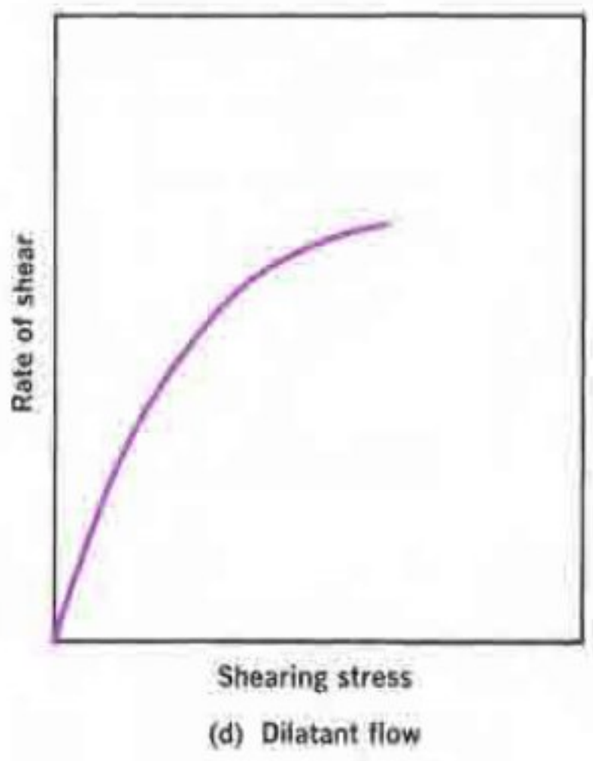
- *Pseudoplastic flow is exhibited by polymers in solution.*
- A large of number of pharmaceutical products, including natural and synthetic gums (eg, liquid dispersions of tragacanth, sodium alginate, methyl cellulose, and sodium carboxymethylcellulose) exhibit *pseudoplastic flow properties.*
- Pseudoplastic substances begin flow when a shearing stress is applied, ie, there is no yield value (it does cross the origin).
- Viscosity of a pseudoplastic substance decreases with increasing shear rate.
- With increasing shearing stress, the rate of shear increases; these materials are called *shear-thinning* systems.

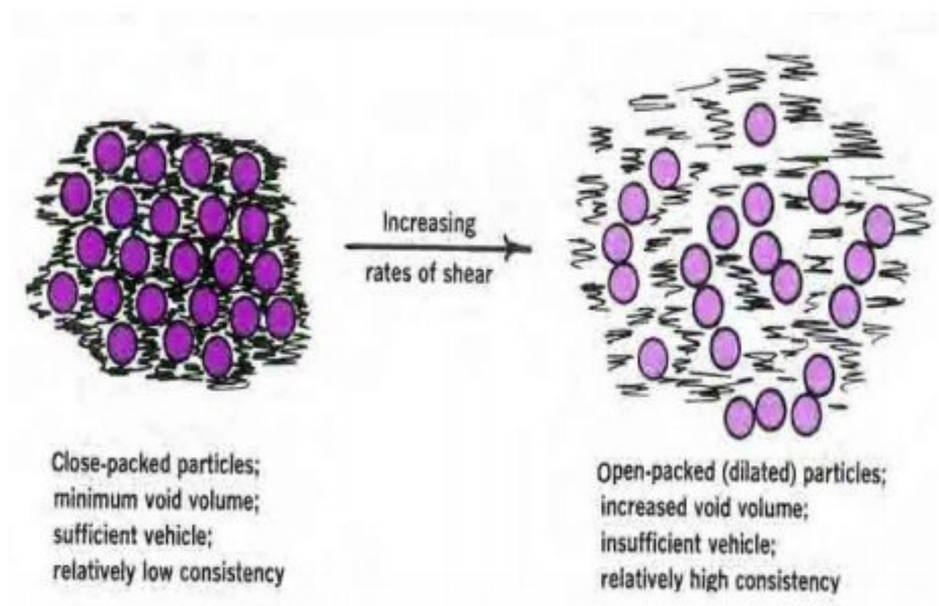
- Shear thinning occurs when molecules (polymers) align themselves along their long axes and slip and slide past each other.

20.14 Dilatant Flow

- Certain suspensions with a high percentage of dispersed solids exhibit an increase in resistance to flow with increasing rates of shear.
- This type of behavior may be exhibited by dispersions containing a high percentage (≥50%) of small, deflocculated particles.
- Dilatant materials *increase in volume when sheared.*
- They are also known as *shear-thickening systems* (opposite of pseudoplastic systems).
- When the stress is removed, the dilatant system returns to its original state of fluidity.
- Viscosity increases with increasing shear rate.
- Dilatant materials may solidify under conditions of high shear.







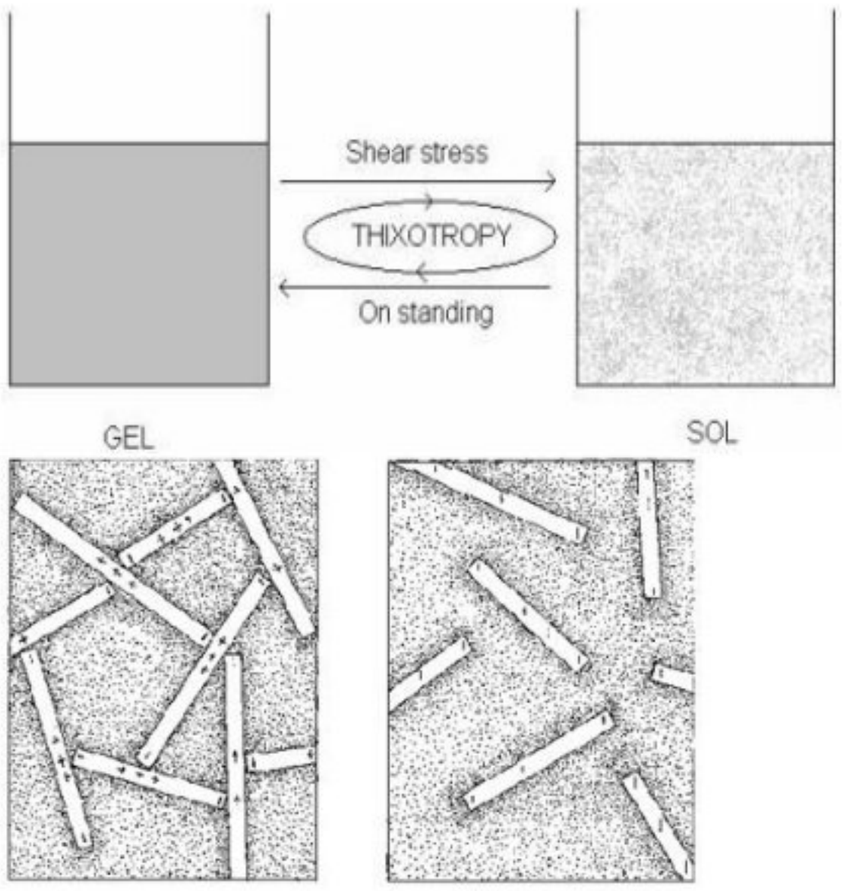
20.15 Thixotropy

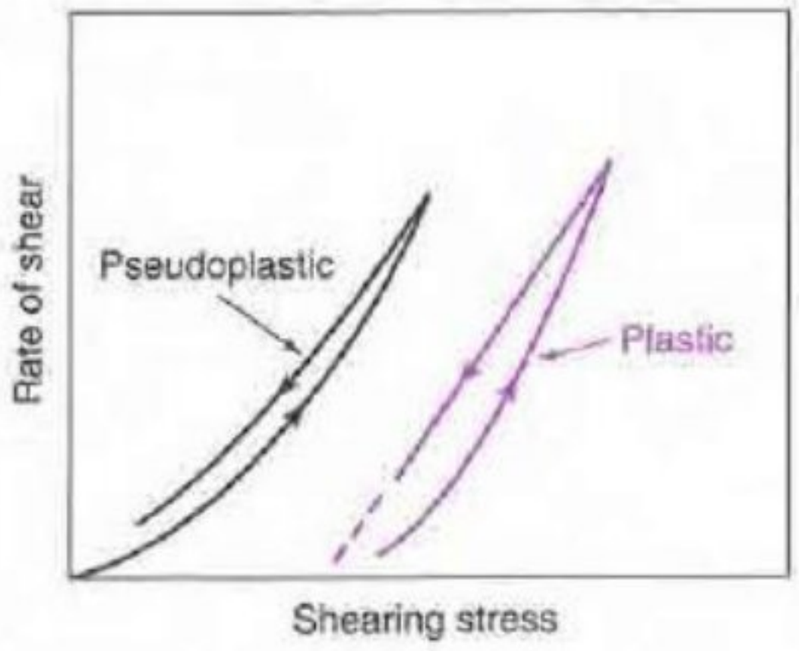
- An isothermal and comparatively slow recovery, on standing the material, of a consistency lost through shearing.
- Change by touch
  - Thixis ---- touch
  - Tropos ---- change
- As shear stress increases viscosity decreases
- On removing stress viscosity is regained after lag time.
-

stress application stress removal

Gel ----------> Sol ----------> Gel

- Thixotropy is a nonchemical isothermal gel-sol-gel transformation.
- If a thixotropic gel is sheared (by simple shaking), the weak bonds are broken and a lyophobic solution is formed.
- On standing the particles collide, flocculation occurs, and the gel is reformed.
- Bentonite gel





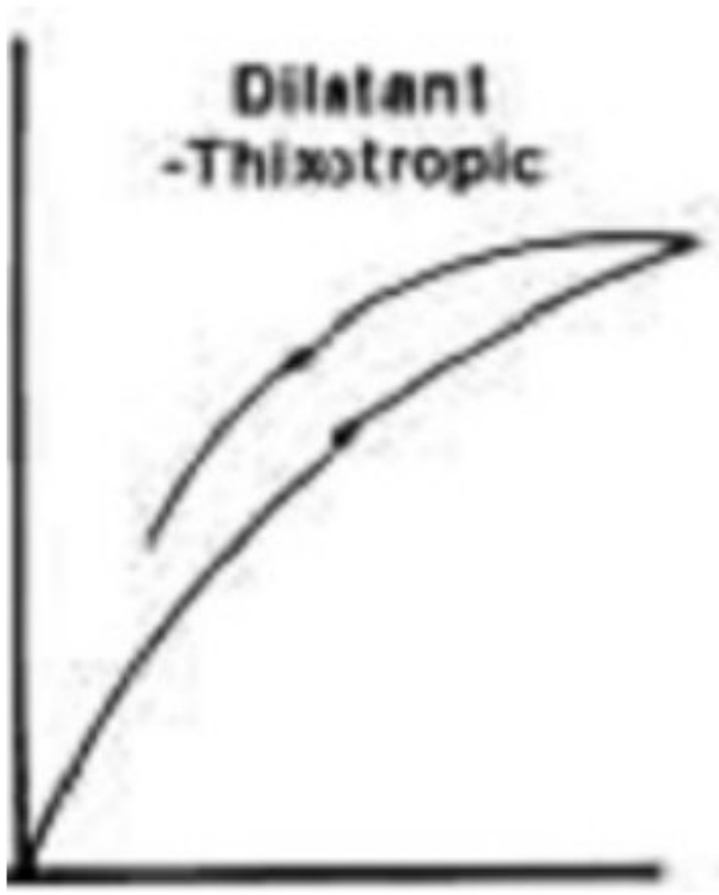
20.16 Rheograms/Flow Curves /Consistency Curve

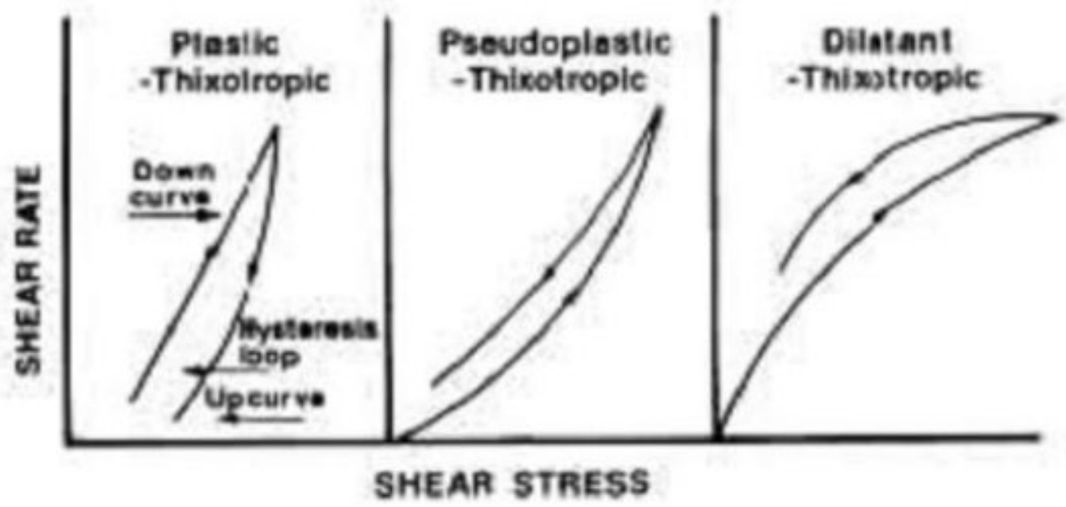
- Rheograms is plot of shear stress as a function of shear rate.
- for thixotropic materials, rheograms are highly dependent on the rate at which shear is increased or decreased and the length of time a sample is subjected to any one rate of shear.
- A hysteresis loop is obtained.
- A up-curve
- A down-curve
- Both not superimposable

20.17 Dilatant system

stress application stress removal

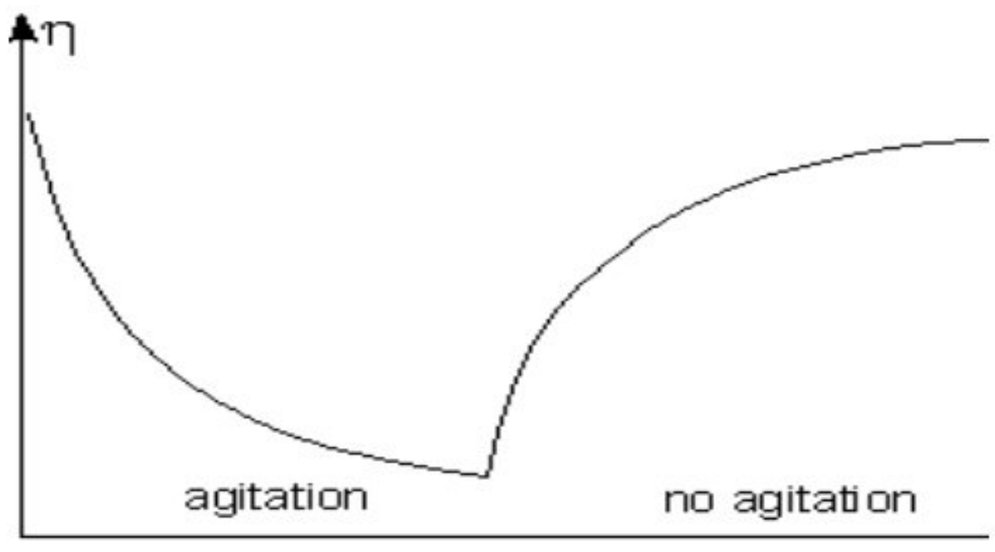
Sol ----------> Gel ----------> Sol





The advantage that thixotropic preparations have is that the particles remain in suspension during storage, but when required for use, the pastes are readily made fluid by tapping or shaking.

- The shearing force on the injection as it is pushed through the needle ensures that it is fluid when injected; however, the rapid resumption of the gel structure prevents excessive spreading in the tissues, and consequently a more compact depot is produced than with nonthixotropic suspensions.



20.18 Irreversible Thixotropy

- Structure does not reform
- Lag time is so long (LAG TIME is the period of time between two closely related events or phenomena e.g., time between stimulus & response or between cause & effect)
- Gel of higher mol wt polysccharides

20.19 Rheopexy

- Rheo ---- flow
- Pexia --- solid
- A property of certain sols which set to gel form more quickly when mechanical means are used to hasten the orientation of the particles.
- time-dependent change
- Non-newtonian fluids – gypsum pastes and printers ink.

20.20 Negative Thixotropy

- Negative thixotropy is also known as antithixotropy, which represents an increase rather than a decrease in consistency on the down-curve (an increase in thickness or resistance to flow with an increased time of shear).
- It may result from an increased collision frequency of dispersed particles (or polymer molecules) in suspension, which causes increased interparticle bonding with time.
- At rest the large floccules break up and gradually return to the original state of small floccules and individual particles.
- Observed in magnesia magma

20.21 Antithixotropy

- flocculated
- 1-10%

20.22 Dilatancy

- Deflocculated
- >50%

20.23 Instruments – Viscometers

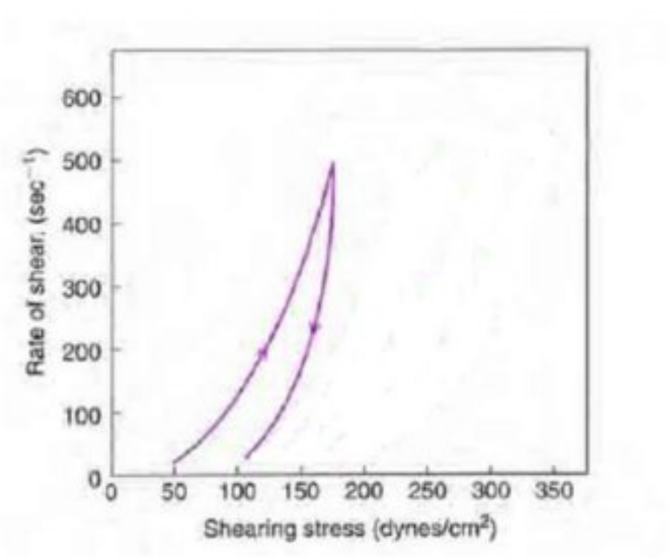
A viscometer (also called *viscosimeter*) is an instrument used to measure the viscosity and flow parameters of a fluid.

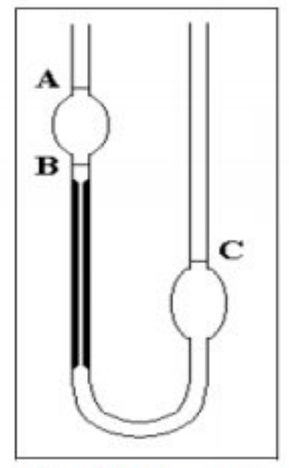
- Capillary viscometer
- Falling or rising body viscometer
- Rotational viscometer

20.23.1.1 Capillary Viscometer

- Involve measuring the time for a fluid to flow through a capillary tube.
- Oswald viscometer is common used
- Refined by Cannon, Ubbelohde
- The viscosity of water is 0.890 mPa·s at 25 degrees Celsius, and 1.002 mPa·s at 20 degrees Celsius.

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1\ t_1}{\rho_2\ t_2}$$





Ostwald Viscometer

20.23.1.2 E

XAMPLE

Viscosity of water = 0.89 cP
Density of water = 1 g/ml
Flow time of water = 48 sec
Density of liquid = 0.85 g/ml
Flow time of liquid = 20 sec
Viscosity of liquid = ?

20.23.1.3 Solution

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1\ t_1}{\rho_2\ t_2}$$

$0.89/\eta 2 = 1 \times 48 / 0.85 \times 20$
$\eta 2 = 0.89 \times 0.85 \times 20 / 48$
$\eta 2 = 0.315$ cP or mPa s

20.23.1.4 Falling Sphere Viscometer

Stockes' law: the force that retards a sphere moving through a viscous fluid is directly

proportional to the velocity of the sphere, the radius of the sphere, and the viscosity of the fluid.

- Stockes' law is the basis of the falling sphere viscometer
- Fluid is stationary in a vertical glass tube.
- A sphere of known size and density is allowed to descend through the liquid.
- Measure the time it takes to pass two marks on the tube.
- Electronic sensing can be used for opaque fluids.
- Knowing the terminal velocity, the size and density of the sphere, and the density of the liquid, Stokes' law can be used to calculate the viscosity of the fluid

- Formula

$$\eta = d^2 g (\rho_s - \rho_l) / 18 v$$

η = viscosity
d= diameter
g= acceleration due to gravity
ρ_s = density of sphere
ρ_l= density of liquid
V = terminal velocity

20.23.1.5 Rotational Viscometers

- Rotational viscometers use the force required to turn
  an object in a fluid which can indicate the viscosity of that fluid.
- The viscometer determines the required force for rotating a disk or bob in a fluid at known speed.
  - "Cup and Bob" viscometers
  - "Cone and Plate" viscometers

20.23.1.6 "Cup and Bob" Viscometers

- Couette type viscometer (cup is rotated)
- Searle type viscometer (bob is rotated)
- Sample is placed in the space between
- outer wall of bob and inner wall of cup
- Cup/bob is driven by motor
- Sample is sheared
- Torque is measured
- Torque is proportional to viscosity

20.23.1.7 "Cone and Plate" viscometers

- Consists of stationary "plate" and revolving "cone"
- Sample is placed at the centre of plate
- Plate is raised into position under cone
- Cone is driven by motor
- Sample is sheared in the narrow gap b/w cone and plate
- Torque is measured

- Torque is proportional to viscosity

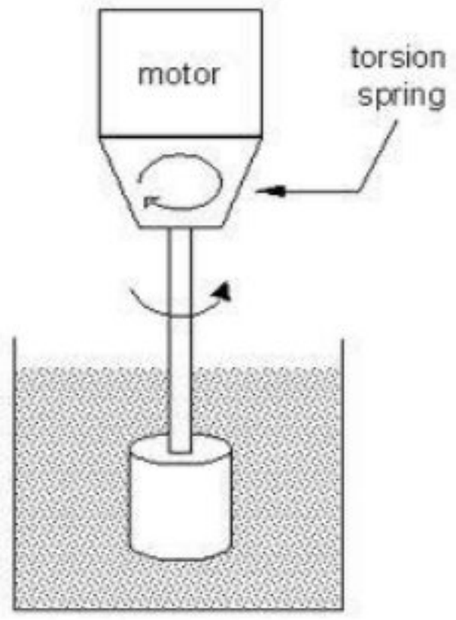
20.24 Applications of Rheology

20.24.1.1 Emulsion

- Emulsion (lotion and creams) exhibit non-newtonian behavior
- Lotions – pseudo-plastic
- Cream (semi solid) – plastic
- Different rheological behaviors can be conferred by varying the conc. of dispersed phase and conc/nature of emulsifying agents.
- Shear-thinning emulsion are preferred as cream
- Thixotropic lotion exhibit considerable consistency when allowed to stand at rest in bottle. Once the bottle is shaken they lose their consistency and easily pour from bottle.
- Stability and release of drug may also depend on rheological characteristics

20.24.1.2 Suspensions

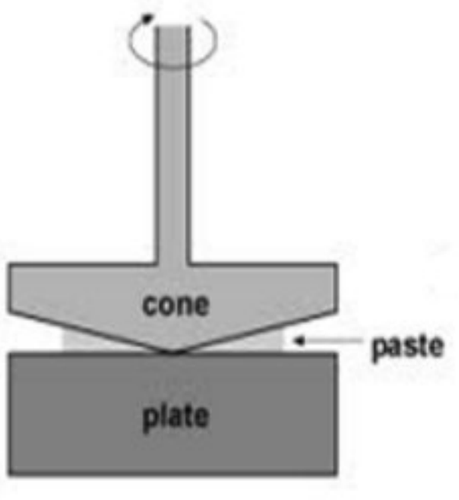
- Most of suspensions exhibit plastic or pseudo-plastic characteristics along with thixotropy
- Rheological properties depend on the degree of flocculation of dispersed phase, type/quantity of suspending agent/thickening agents added.



- Pseudoplasticity along with thixotropy is preferred.
- Proper selection of rheological characteristics also improve the physical stability of suspensions

20.24.1.3 Ointment and Gel

- Rheological characteristics directly affect stability, elegance and extrudability from tube
- Capacity to take up solid/liquids,



adherence/spreadability on the skin and release of drug from base, are also affected

- Most of topical semisolid show plastic flow (hydrocarbon bases). Dilatancy and pseudoplastic behaviors with thixotropy is also observed.
- Flow behaviors ranges from plug flow to stream line flow
- Powder and granules
- Good Rheological characteristics of granules/powder are required to ensure uninterrupted flow from hopper to die cavities
- Also important during encapsulation.
- Stickiness and roughness of surface should be reduced for adequate flow.

20.24.1.4 PROCESSES

20.24.1.5 MIXING

Large impeller at low shear rate is required for shear thinning system. To ensure effective mixing.

Semisolid exhibiting dilatant properties should be processed with a low shear mixer to prevent a consistency build up.

20.24.1.6 TRANSFER

Rheology is also important during fluid transfer from one site to another.

Chapter 21 RATE AND ORDER OF REACTION

21.1 STABILITY

"The ability of a Pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life").

"The capacity of a drug product to remain within specifications established to ensure its identity, strength, quality and purity"

The extensive chemical degradation of the active ingredient can cause:

- Substantial loss of active ingredient from the dosage form
- Can produce a toxic product that has undesirable effects
- Instability of the product can cause decreased bioavailability.

21.2 KINETICS

Kinetics is the study of the rate at which processes occur.

The kinetic studies are useful in providing information that:

- Gives an insight into the mechanism of the changes involved, and
- Allows prediction of the degree of change that will occur after a given time

21.3 RATE OF REACTION/ PROCESS

- The velocity with which a reaction or process occurs is called RATE of Reaction.
- It is expressed as dC/dt (the change in concentration, or C; within a given time interval, or dt).
- Reaction rates depend on certain conditions (e.g. reactant conc., temperature, pH, presence of solvents or additives). Radiation and catalytic agents (e.g. polyvalent cations) also have an effect.

21.4 ORDER OF A REACTION / PROCESS

- The way in which the concentration of the drug or reactant in a chemical reaction affects the rate is called order of a reaction or process.
- The rate of a reaction is proportional to the concentration to the nth power, where n is the order of the reaction. That is,

$$dC/dt \ \alpha \ C^n$$

  - dC/dt is the rate of a reaction,
  - C is the concentration of reactants, and
  - n is the order of the reaction.
- Usually, pharmaceutical degradation can be treated as a Zero-order or first-order.
- The first step of the example reaction,

$$N_2O_5 = 2NO_2 + \frac{1}{2}O_2$$

- The rate of reaction = *k1 [N2O5], i.e. there is only one* concentration term and the reaction is known as *first order.*
- In the second step,

$$\text{rate of reaction} = k_2 [\tfrac{1}{2}O_2][\tfrac{1}{2}O_2] = k_2 [\tfrac{1}{2}O_2]^2$$

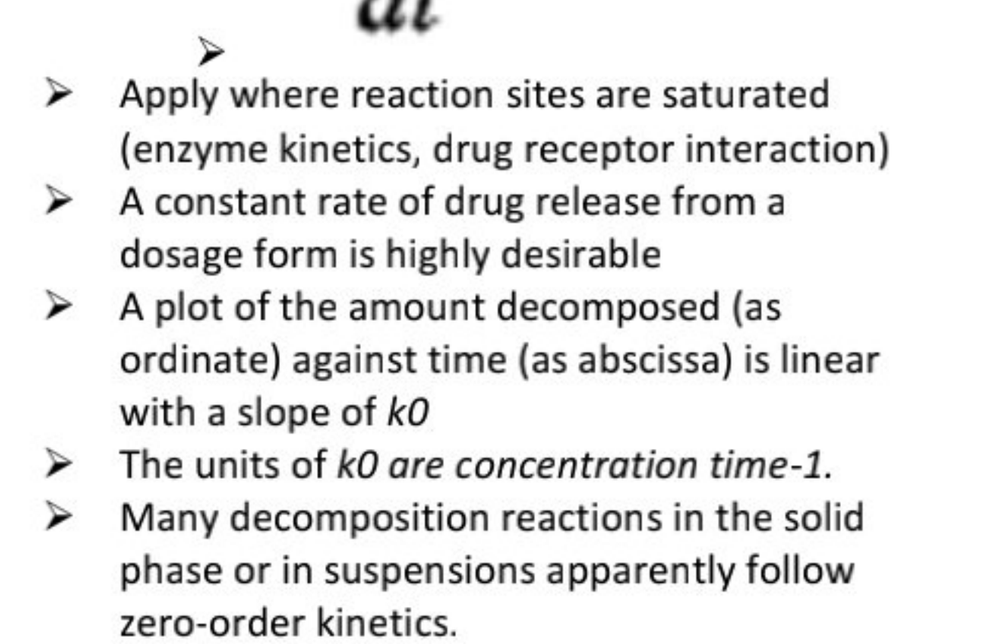
- where *k1 and k2 are the reaction rate constants. Thus* there are two concentration terms and the reaction is known as *second order.*

21.4.1.1 ZERO ORDER

- In a zero-order reaction, the rate is independent of the concentration of the reactants (rate is constant)
- Other factors, such as absorption of light in certain photochemical reactions, determine the rate.
- Zero-order reaction can be expressed as

$$\frac{dc}{dt} = -k_0$$

- Apply where reaction sites are saturated (enzyme kinetics, drug receptor interaction)
- A constant rate of drug release from a dosage form is highly desirable
- A plot of the amount decomposed (as ordinate) against time (as abscissa) is linear with a slope of *k0*
- The units of *k0 are concentration time-1.*
- Many decomposition reactions in the solid phase or in suspensions apparently follow zero-order kinetics.



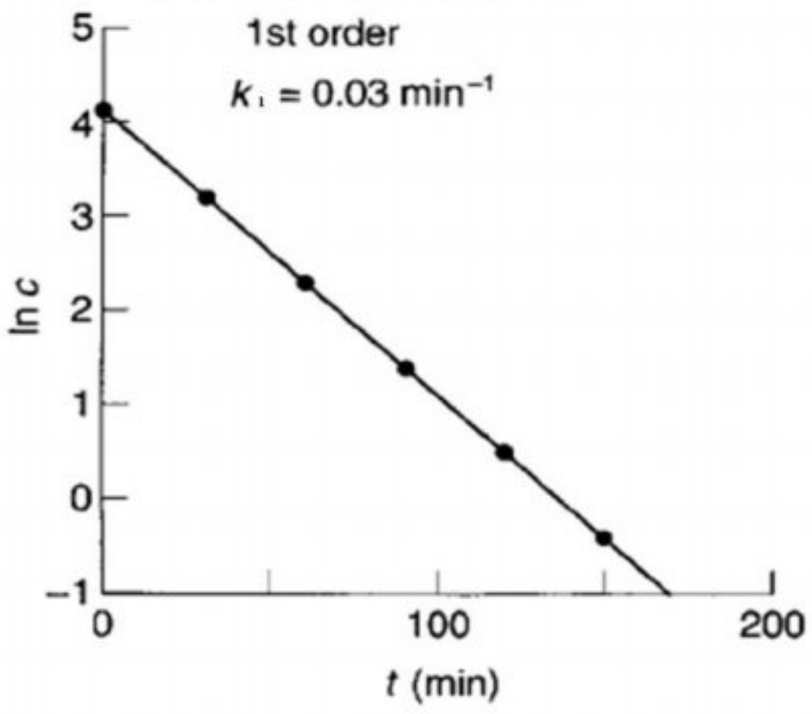
- If there are two reactants and one is in large excess, the reaction may still follow first-order kinetics because the change in concentration of the excess reactant is negligible. This type of reaction is a PSEUDO FIRST-ORDER REACTION.
- Consider the hydrolysis of ethyl acetate:
- CH3COOEt + H2O ---> CH3COOH + EtOH
- Strictly the reaction is second order and the rate of
- reaction is expressed as:
- Rate = *k2 [CH3COOEt] [H2O]*

21.4.1.2 First Order

- In a first order reaction, the rate depends on the concentration of a single reactant
- In first order reaction, drug concentration decreases exponentially with time

$$\frac{dc}{dt} = -k_1 C$$

- A plot of time (as ordinate) against the logarithm of the amount remaining (as abscissa) is linear.
- The units of *k1 are time–1.*



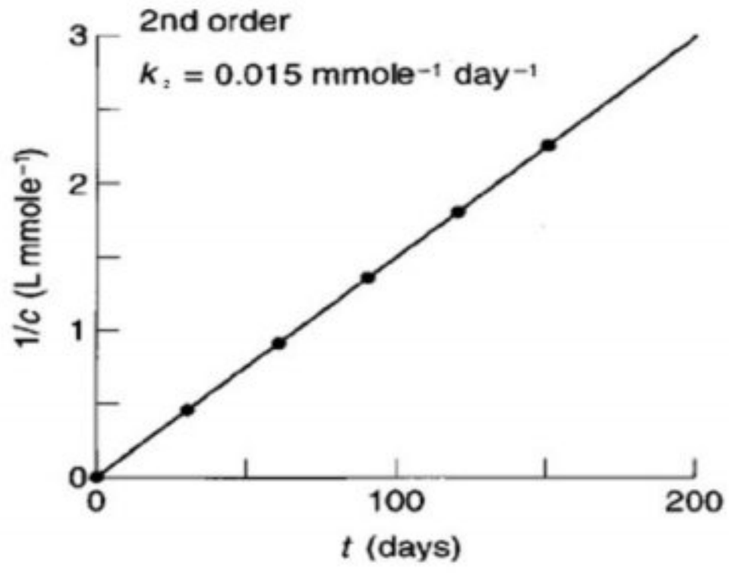
- If there are two reactants and one is in large excess, the reaction may still follow first-order kinetics because the change in concentration of the excess reactant is negligible. This type of reaction is a *pseudo first-order reaction.*
- Consider the hydrolysis of ethyl acetate:
  CH3COOEt + H2O ---> CH3COOH + EtOH
- Strictly the reaction is second order and the rate of reaction is expressed as:
  Rate = *k2 [CH3COOEt] [H2O]*
- In a dilute aqueous solution of ethyl acetate, [H2O] is very large compared to [CH3COOEt] and hardly alters during the course of the reaction.
- [H2O] can be taken as a constant and incorporated into the second-order rate constant, *k':*
  Rate = *k' [CH3COOEt]*
- Thus the reaction is, in effect, first order with a rate constant *k'. This applies to many drug decompositions* by hydrolysis in aqueous solution.

21.4.1.3 Second-order Reaction

- The rate depends on the concentration of two reacting species, A and B.
- For the usual case where the initial concentrations of A and B are different, the rate equation is:

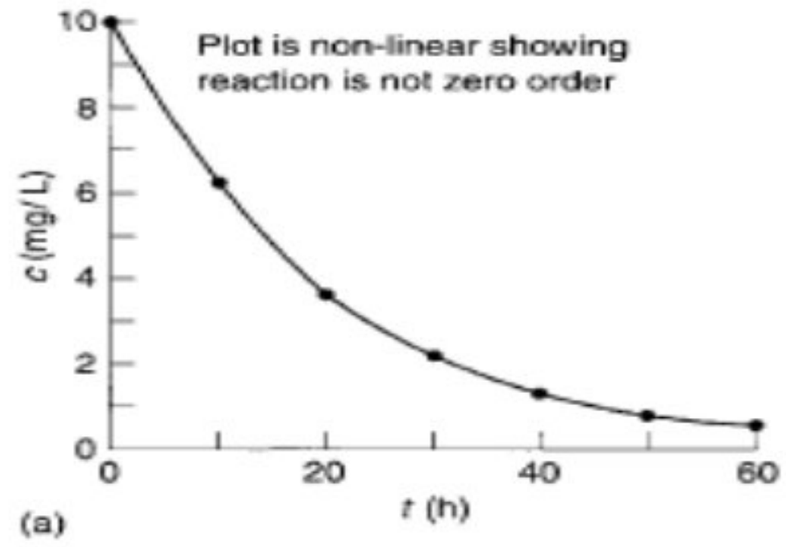
$$\frac{dc}{dt} = -k_2\, c^2$$

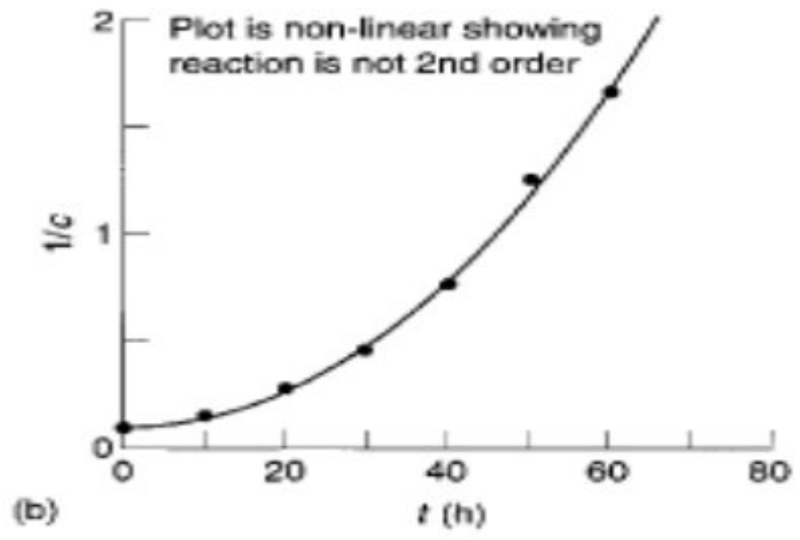
- A plot of time (as ordinate) against the 1/c *(as abscissa) is linear.*
- The units of *k2 are concentration–1 time–1.*

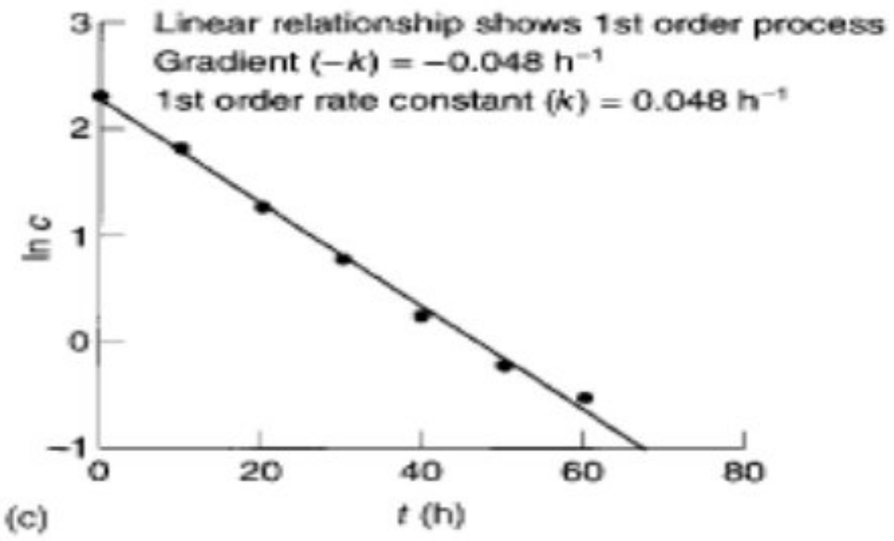


21.5 Determination of Order and Rate Constant from Experimental Data

Substituting the data into the integrated equations and observing which plot is a straight line.







21.6 Factors that Affect Reaction Rates

21.6.1.1 Temperature

- An increase in temperature causes an increase in reaction rate, as expressed in the equation first suggested by Arrhenius.

$$k = A e^{-Ea/Rt} \text{ or}$$

$$\log k = \log A - (Ea/2.303\ \ 1/RT)$$

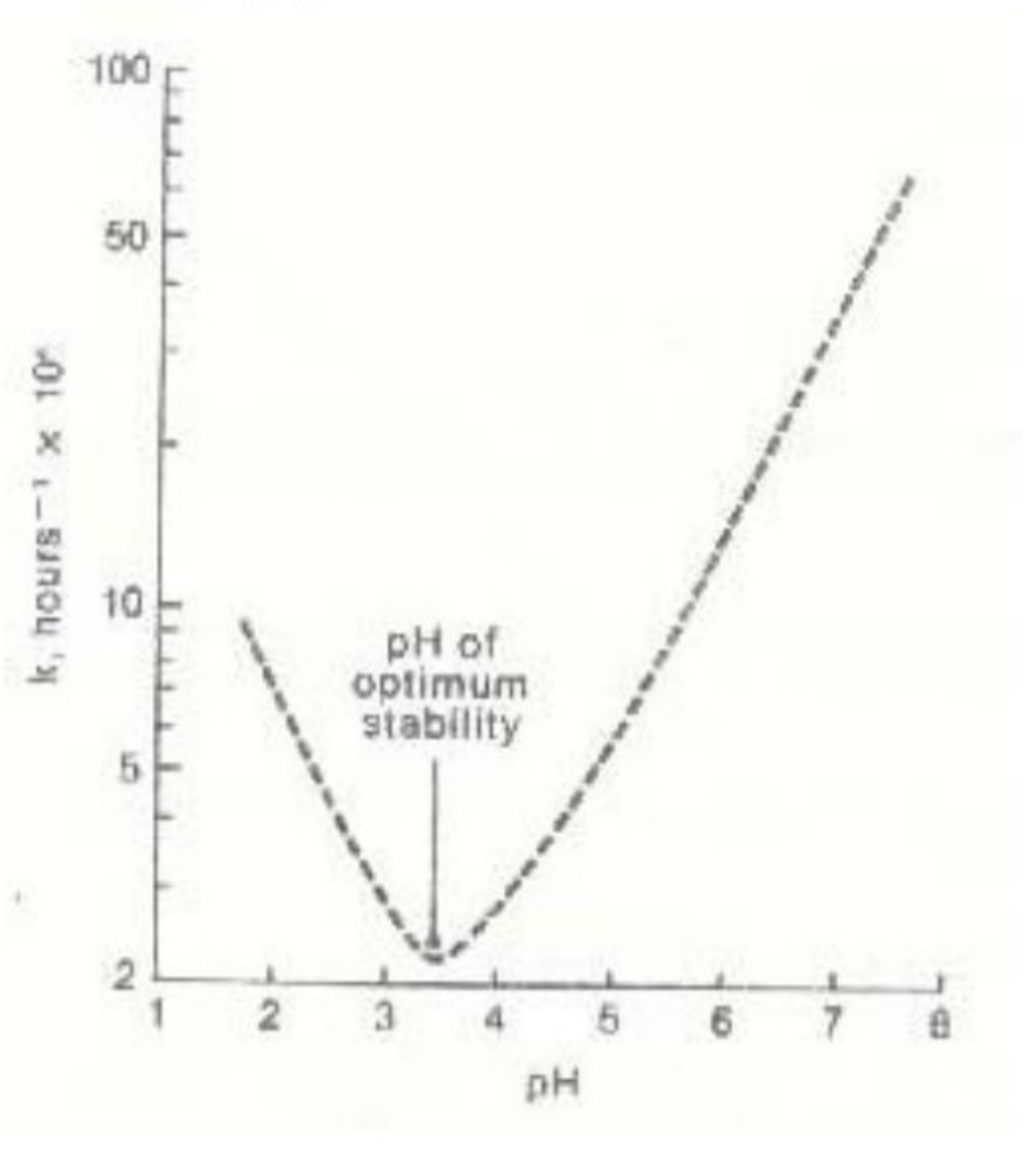
  - k is the specific reaction rate constant.
  - A is a constant known as the frequency factor.
  - Ea is the energy of activation,
  - R is the molar gas constant, and
  - T is the absolute temperature.

21.6.1.2 Presence of Solvent.

- Many dosage forms require the incorporation of a water miscible solvent (e.g. low molecular weight alcohols, such as the polyethylene glycol (PEGs) to stabilize the drug.
- Rate is altered because:
  1. Alters the transition state
  2. The activity coefficients
  3. pka
  4. Surface tension
  5. Viscosity
- In some cases, additional reaction pathways are generated. For example, with an increasing concentration of ethanol in an aqueous solution, aspirin degrades by an extra route and forms the ethyl ester of acetylsalicylic acid.

21.6.1.3 Change in pH

- H^+ catalysis predominates at lower pH, whereas OH^- catalysis operates at higher pH.
- At intermediate pH, the rate may be pH independent or may be catalyzed by both H^+ and OH^-.
- Effect of pH on degradation kinetics is determined



21.6.1.4 Presence of Additives

- Buffer affects the rate of degradation, primarily as a result of salt increasing the ionic strength.
- Increasing salt concentrations (e.g.,. citrate, phosphate), can substantially affect the magnitude of pka. In this way, they change the rate constant.

- Buffer salts can also promote drug degradation through general acid or base catalysis.
- Surfactants may acceralate or decelerate drug degradation.
- Acceleration of degradation is common and is caused by miceller catalysis.
- Stabilization of a drug through the addition of a surfactant is less common.

Chapter 22 STABILITY STUDIES

22.1 STABILITY

- "The ability of a Pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life"

(WHO GUIDANCE, 1996)

- "The capacity of a drug product to remain within specifications established to ensure its identity, strength, quality and purity"

(FDA GUIDANCE, 2006)

- The extent to which a product retains, within specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging.

22.2 STABILITY STUDIES

- Stability studies provide the evidences on how the quality of a drug substance/ product varies with time under the influence of a variety of environmental factor such as temperature humidity and light.
- Stability data is used to determine:
  - shelf life
  - storage conditions
  - packaging

22.3 SHELF LIFE

- The time period during which a pharmaceutical product is expected to remain within the approved shelf life specifications, provided that it is stored under the labeled storage conditions.

22.4 SPECIFICATIONS

- The combination of physical, chemical, biological, and microbiological tests and acceptance criteria for these tests.

22.5 PURPOSE

- Evaluation of influence of product related factors on stability of Dosage Form
- physical and chemical properties of excipients,
- dosage form and its composition,
- the nature of container-closure system
- packaging material
- Manufacturing conditions

22.6 TYPE/NATURE

- Long term (real time)
  To claim shelf life
- Accelerated
  Product development

22.7 STORAGE CONDITIONS

General case

- Accelerated 40 °C + 2 °C / 75%RH + 5% RH
- Long term 25 ° C+ 2 °C / 60 %RH + 5% RH

22.7.1.1 DRUG PRODUCTS INTENDED TO BE STORED IN A REFRIGERATOR

- Accelerated 25 ° C+ 2 °C / 60%RH + 5% RH
- Long term 5 °C + 3 °C

22.8 CLIMATIC ZONES

Four climatic zones have been defined based on characteristic prevalent annual climatic conditions:

- Climatic Zone I
- Climatic Zone II
- Climatic Zone III
- Climatic Zone IV

22.8.1.1 CLIMATIC ZONE I

- Temperate Climate
  - 20 °C and 42RH
- Canada, Germany
- Long term (real time)
  - 25 °C / 60%RH
- Accelerated
  - 40 °C / 75%RH

22.8.1.2 CLIMATIC ZONE II

- Subtropical & Mediterranean climate
  - 21.6 °C and 52RH
- Iraq, Jordan
- Long term (real time)
  - 25 °C / 60%RH
- Accelerated
  - 40 °C / 75%RH

22.8.1.3 CLIMATIC ZONE III

- Hot & Dry
  - 26.4 °C and 37RH
- France, Korea
- Long term (real time)
  - 30 °C / 65%RH
- Accelerated
  - 40 °C / 75%RH

22.8.1.4 CLIMATIC ZONE IV

- Very hot/Humid
  - 26.7 °C and 76RH

- Pakistan, India
- Long term (real time)
  - 30 °C / 65%RH
- Accelerated
  - 40 °C / 75%RH

22.9 Testing Parameters

22.9.1.1 Tablets

- Dissolution
- Friability / hardness
- Water content

22.9.1.2 Hard Gelatin Capsules

- Dissolution
- Water content
- Brittleness

22.9.1.3 Emulsions

- Phase separation
- Mean size and distribution of dispersed globules
- pH
- Viscosity
- Level of microbial contamination

22.9.1.4 Oral Suspensions

- pH
- Viscosity
- Formation of precipitates
- Redispersibility
- Mean size and distribution of particles
- Level of microbial contamination

22.9.1.5 Oral Solutions

- Clarity for solution
- pH
- Level of microbial contamination
- Specific gravity
- Color change

22.9.1.6 Powders for Oral Suspensions

- Water content
- Reconstitution time

22.9.1.7 Topical Products

- Homogeneity
- pH
- Redispersibility (for lotions)
- Viscosity
- Particle / globule size distribution

22.9.1.8 Ophthalmic Products

- Sterility
- Particle size distribution (for suspensions)

22.10 Stability Protocols

1. Type, size and number of batches
2. Type, size and source of container and closure
3. Container storage orientation test time point
4. Sampling time points
5. Sampling plan
6. Test storage conditions
7. Test parameters
8. Test methods
9. Acceptance criteria

22.10.1.1 Type, Size and Number of Batches

- 1-3
  - research
  - production batch
- First three batches

22.10.1.2 Laboratory Scale Batch

- early stage of development
- 100-1000 time less
- helps in suitable manufacturing process

22.10.1.3 Pilot Scale Batch

- A batch of an active substance or pharmaceutical product manufactured by a procedure that is fully representative of and simulating that to be applied to a full production scale batch.
- Not < 10 time

22.10.1.4 Primary Batch

- A batch of an active substance or pharmaceutical product used in a formal stability study, from which stability data is submitted in a registration application for the purpose of establishing a re-test period or shelf life respectively.

22.10.1.5 Production Batch

- A batch of an active substance or pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

22.10.1.6 Type, Size and Source of Container and Closure

- Same as proposed for marketing
- May include secondary pack but not shipper
- Separate testing f available in different containers
- Container storage orientation test time point
  - Upright
  - Inverted or on-the-side position

22.10.1.7 Sampling Time Points (Frequency)

- At the accelerated storage conditions, a minimum of three time points for sampling, including the initial and final time points from a 6 month study period are recommended.
  - Accelerated 0, 15, 30, 60 and 90 days
  - Long term 0, 3, 6, 9 12, 18, 24 and 36 months
- If available in different strength then reduced testing plan are adopted
  - Bracketing design
  - Matrixing design

22.10.1.8 Bracketing design

Highest and lowest strength/size is tested

Strength		50			100			150		
Batch		1	2	3	1	2	3	1	2	3
size	15	√	√	√				√	√	√
	30									
	60	√	√	√				√	√	√

22.10.1.9 Matrixing design

All strength are tested at all point

Strength		50			100			150		
Batch		1	2	3	1	2	3	1	2	3
Time points	0	√.	√.	√.	√	√	√	√.	√.	√.
	3	.	√.	.	√			.	.	√.
	6	.	.	√.		√		√.	.	.
	9	√.	.	.			√	.	√.	.
	12	√.	√.	√.	√	√	√	√.	√.	√.
	18	√.	.	.		√		.	.	√.
	24	.	√.	.	√			.	√.	.
	36	√.	√.	√.	√	√	√	√.	√.	√.

22.10.1.10 Sampling Plan

- Number of samples
- Plan of sampling
  - Represent whole batch
  - Unbiased
  - nth container

22.10.1.11 Test Storage Conditions

- Product
- Zone

22.10.1.12 Test Parameters

- Type of dosage form
- API and sometime degradation products

22.10.1.13 Test Methodology

- Test and its method follow Official compendia
- If not given in compendia the validate it
- Validate for specificity, precision, linearity, reproducibility and range

22.10.1.14 Acceptance Criteria

- Fixed numerical limits when result is in quantitative terms (Moisture, viscosity, particle size, assay etc)
- For qualitative tests (color, ordour, phase separation etc) it may be PASS or FAIL

22.11 Stability Chambers /Rooms

- Specially designed equipment used in the stability testing of pharmaceutical products.
- Used to maintain specified environmental conditions of temperature, humidity and light.
- Range in size from the smallest 182 liter (6.5 cu.ft) when demand for test space is small, to the largest standard Walk-in Room.
- Stability chambers are used for accelerated and long-term testing.
- A stability test chamber must perform reliably and accurately throughout this time.
- Fitted with recording, safety and alarm devices
- Maintenance or service interventions during the testing are disruptive and costly
- For photostability: Combination of visible light and near UV, on separate shelves (important for maximum light uniformity)
- Provide circulation of air for more uniform distribution of temperature and humidity.

22.12 Modes of Pharmaceutical Degradation

The decomposition of active ingredient in a dosage form occurs through several pathways

22.12.1.1 Chemical degradation

- Solvolysis
- Oxidation
- Photolysis
- Dehydration
- Isomerization
- Racemization
- Decarboxylation

22.12.1.2 Physical degradation

- Loss of volatile components
- Loss of H2O
- Absorption of H2O
- Crystal growth
- Polymorphic changes
- Colour changes

22.13 Chemical Degradation

22.13.1.1 Solvolysis (Hydrolysis)

- Hydrolysis is the most common type of degradation because many medicinal compounds are esters, amides or lactams.
- eg Aspirin, sulphonamide, spiranolactone, penicillin
- Esters usually undergo hydrolytic reactions that cause drug instability.
- Formulators are reluctant to incorporate drugs that have ester functional groups into liquid dosage forms.

22.13.1.2 Prevention

- Replace water
- Prepare suspension
- Prepare dry powder

22.13.1.3 Oxidation

- Oxidation is usually mediated through reaction with atmospheric oxygen under ambient conditions (auto- oxidation).
- Also due to reversible loss of electron
- Both water and oil soluble drug are degraded
- Aldehyde, alcohol, alkaloids, unsaturated fats
- Riboflavin, adrenaline

22.13.1.4 Prevention

- Pack in an inert atmosphere (e.g. nitrogen) to exclude air from their containers.
- Fill the container completely
- Use sod bisulfite, butylated hydroxy toluene, ethylene diamine tetra acetic acid

22.14 Photoiysis

- Photolysis is the degradation of drug molecules by normal sunlight or UV.
- Activation energy is needed. Molecules may absorb the proper wavelength of light and acquire sufficient energy to undergo reaction.
- Photolytic degradation occurs on exposure to light of wavelengths less than 400nm. Shorter wavelength are more dangerous
- Once started -- continue even light source is removed
- Chlorpromazine, morphine, codeine

22.14.1.1 Prevention

- An amber glass bottle or an opaque container acts as a barrier to this light, thereby preventing or retarding photolysis. For example, sodium nitropruside in aqueous solution has a shelf life of only 4 hours if exposed to light. When protected from light, the solution is stable for at least 1 year.
- Avoid direct light

22.15 Physical degradation

22.15.1.1 Loss of Volatile Components

- Volatile components such asAlcohol, ether, Iodine, volatile oils, Camphor, menthol, Nitroglycerine evaporates.

22.15.1.2 PREVENTION

- Such product should be placed in well closed container
- Place at low temperature

22.15.1.3 LOSS OF H_2O

- Loss of water from o/w emulsions thus its stability changes.
- Water evaporates causing the crystalline growth.
  This will result into ↑ in potency & ↓ in weight.
- This tendency depends on temp. and humidity of surrounding environment.
  e.g. water evaporates from efflorescent salts such as Na2SO4, borax

22.15.1.4 PREVENTION

- Such product should be placed in well closed container
- Use glass containers

22.15.1.5 ABSORPTION OF H_2O

- Hygroscopic drugs absorb the water from external atmosphere causing the physical degradation.
- Depends on temp and humidity of surrounding material
  e.g.
  · Glycerin suppositories may become opaque
  · Gelatin capsule may soften
  · Some deliquescent salts calcium chloride, potassium citrate.

22.15.1.6 PREVENTION

- Such product should be placed in well closed container
- Use moisture absorbent

22.15.1.7 CRYSTAL GROWTH

- In solutions after super saturation crystal growth occurs
- Reason may be the fall in temp and a consequent ↓ in solubility of solute
  e.g.
  · Injection of calcium glucconate
- In suspensions crystals settle down and caking occurs and suspension becomes unstable.
  e.g. Ophthalmic preparations.

22.15.1.8 PREVENTION

- Minimum temp. flocculation should be managed
- Incorporation of surface active agent
- By increasing viscosity of suspending material

22.15.1.9 POLYMORPHIC CHANGES

- In polymorphic changes crystal forms are changed. A stable crystal form loosens.
  This may cause alteration in solubility and possibly crystalline growth in aqueous suspensions

22.15.1.10 PREVENTION

- Formulated products should contain a stable crystalline form of the drug.

22.15.1.11 COLOUR CHANGES

- Colour changes is due to
  - pH change
  - Presence of reducing agent
  - Exposure to light

22.15.1.12 PREVENTION

- PH should not be changed
  Exposure to light should be avoided

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