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"WORKING TOWARDS BEING THE BEST"

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Unit-1 Topic- 3

Pharmaceutical and Formulation Considerations

Dosage Form Design

- ***Pharmaceutics***

  - study on the: formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms

- ***Pharmaceutical ingredients or excipients***

  -Selective use of these non medicinal agents

  - Uses

solubilize	thicken	stabilize	flavor
suspend	dilute	preserve	efficacious
suspend	emulsify	color	appealing closure forms.

Requirements of a proper design & formulation of dosage form

Consideration of drug substances:

- Physical, chemical & biological characteristics

*compatible with one another - stable, efficacious, attractive, easy to administer & safe

*manufactured under appropriate measures of quality control & packaged in containers to make product stable

*labeled to promote correct use & stored under conditions to maximize shell life

The Need for Dosage Forms

- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity. **(Coated tablets)**

- To protect the drug substance from the destructive influence of gastric acid after oral administration. **(Enteric-coated)**

The Need for Dosage Forms

- To conceal the bitter, salty or offensive taste or odor of a drug substance. **(Capsules, Flavored syrups)**

- To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle. **(Suspension**

The Need for Dosage Forms

- To provide clear liquid dosage forms of substances. **(Syrups, Solutions)**
- To provide rate-controlled drug action. **(Controlled-release tablets)**
- To provide optimal drug action from topical administration sites. **(Ointments,Creams, Transdermal patches)**

The Need for Dosage Forms

- To provide for insertion of a drug into one of the body's orifices **(Suppositories)**
- To provide placement of drugs directly in the bloodstream or body tissues **(Injections)**
- To provide for optimal drug action through inhalation therapy **(Inhalants, Inhalation aerosols)**

General Considerations in Dosage Form Design

- Determine desired product type - framework for product development.

- develop and examine initial formulations of the product:

  - desired features: drug release profile bioavailability clinical effectiveness
  - pilot plant studies and production scale-up.

- master formula

  - formulation that best meets the goals of the product

- Factors to consider before formulation of a medicinal agent in one or more dosage forms
  - Therapeutic matters (nature of the illness)
  - manner it is treated (locally or through systemic action)
  - age and anticipated condition of the patient.

Preformulation Studies

- drug be chemically and physically characterized
- define the nature of the drug substance.

Three ways liquid drug be given in solid form

Liquid substance:

- Sealed in soft gelatin capsule
- Developed into a solid ester or salt form suitable for tablets or drug capsules
- Mixed with a solid or melted semisolid material

  - melted mixtrue is poured into hard gelatin capsules to harden & capsules sealed

Preformulation Studies
1. Physicochemical Description

- **physical description** of particle size, crystalline structure, melting point solubility etc.
- **Chemical properties** of structure form reactivity
- **purity** of the chemical substance for: identification and for evaluation of its chemical, physical, and biologic properties

Preformulation Studies
2. Microscopic Examination

- indication of **particle size and size range** of the raw material along with the crystal structure.
- **information generated in formulation processing** attributable to changes in particle or crystal characteristic changes of the drug molecules or particles.

Preformulation Studies
3. Melting Point Depression

- Determines the: purity of the substance
  compatibility of various subs before inclusion in the dosage form
  - pure subs: sharp melting point
  - impure subs: depressed melting point

Preformulation Studies
4. Phase Rule

- Phase diagrams constructed determines:

  - existence & extent of the presence of solid and liquid phases in binary, ternary & other mixtures

Particle Size

- affects : physical–chemical properties of drug subs's:

*dissolution rate bioavailability content uniformity

stability taste texture

flow properties absorption sedimentation rate

Preformulation Studies
Polymorphism

- substances can exist in more than one crystalline form

- Polymorphic forms – diff. physical-chemical properties (incl. melting pt. & solubility)
- Evaluation of:

*crystal structure (microscopy, IR spectroscopy, thermal analysis, x-ray diffraction)

*polymorphism & *solvate form

Preformulation Studies
Solubility

- Determined by equlibrium solubility method

  - excess amount of drug + solvent = shaken at constant temp. over a prolonged period of time until equilibrium is obtained

- Drug possess **aqueous solubility** - for therapeutic efficacy.
- Insoluble compounds: incomplete/erratic absorption

Preformulation Studies Solubility

- Solubility & particle size
- Solubility & pH

  - drug formulated to liquid product:

  adjustment of pH of solvent where drug is dissolved to adjust solubility

  - Weak acidic or basic drugs - require **extremes in pH** outside or accepted physiologic limits or that may cause stability problems with formulation ingredients.

Preformulation Studies
Dissolution Rate

- **time for the drug to dissolve** in the fluids at the absorption site (rate-limiting step in absorption).
- Dissolution rate of drugs - increased by decreasing the particle size.
- for higher dissolution rate
  - use a highly water soluble salt of the parent substance.

2 methods in determining dissolution rates of chemical compounds

1.Constant surface method

- **intrinsic dissolution rate** of the agent
- Characteristic of compound & solvent under fixed experimental conditions
- mg dissolved/min/cm square

2.**Particulate dissolution**

- Weighed amount of powdered sample + dissolution medium in constant agitation system

- to study the influence of particle size, surface area, and excipients upon the active agent

Fick's law (law of diffusion)

- describes the:

  * relationship of diffusion & dissolution of the active drug in the dosage form & when administered in the body

- 1st law

  *relates to a steady state flow

- 2nd law

  *relates to a change in conc. of drug with time, at any distance, or a nonsteady state of flow

Preformulation Studies
Membrane Permeability

- Everted intestinal sac
  - determines degree & rate of passage of drug through the membrane sac by passive & active transport
- early assessment of passage of drug molecules across biologic membranes
- To produce a biologic response - drug molecule must first cross a biologic membrane
- The biologic membrane (lipid barrier) - permits absorption of lipid soluble substance by passive diffusion
- Molecules' lipophilic character – measured by the oil-water coefficient

Basis of pH-partition coefficient

Interrelationship at the absorption site & absorption characteristics of various drugs:

- Dissociation constant
- lipid solubility
- pH

Indication of absorption expectations:

- Data from basic physicochemical studies: pKa, solubility & dissolution rate

Preformulation Studies
Partition Coefficient

- selection of appropriate extraction solvents, drug stability, use of salting-out additives and environmental concerns.

Preformulation Studies
pKa / Dissociation Constants

- extent of ionization of drug - strong effect on formulation & pharmacokinetic parameters of the drug
- determined by potentiometric titration

  - for the pharmacist important:

    *predicting precipitation in admixtures

    *calculating solubility of drugs at certain pH values

Stability

-**extent a product retains** within specified limits and through its period of storage and use

Stability studies conducted in the preformulation phase:

- Solid-state of the drug alone
- Solution phase
- with the expected excipients

Drug and Drug Product Stability

- Evaluation of:
  - physical and chemical stability of pure drug substances -important for preformulation.

Drug Stability : Mechanisms of Degradation

-Chemically drug substances with different susceptibilities toward chemical instability:

alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides and others.

most frequently encountered destructive process:

- **Hydrolysis** (solvolysis process)

- (drug) molecules interact with water molecule to yield breakdown product.

- susceptible to the hydrolytic process: esters, substituted amides, lactones, and lactams

most frequently encountered destructive process:

- **OXIDATION**
  - loss of electrons from an atom or molecule;
  - involves **free radicals (** molecules or atoms containing one or more unpaired electrons).
  - destructive to: aldehydes, alcohols, phenols, sugars, alkaloids & unsaturated fats & oils

Drug and Drug Product Stability: A. Kinetics and Shelf Life

Five types of stability

1. Chemical –active ingredient retains chemical integrity and labeled potency within the specified limits.

- important for selecting:

*storage conditions (temp., light, humidity)

*proper container for dispensing

*anticipating interactions when mixing drugs & dosage forms

- must know reaction order & rate

2. Physical - original physical properties, appearance, palatability, uniformity, dissolution and suspendability are retained.
3. Microbiologic –sterility/resistance to microbial growth
4. Therapeutic –therapeutic effect remains unchanged
5. Toxicologic - no significant increase in toxicity occurs.

Drug and Drug Product Stability:

B. RATE REACTIONS

- description of the **drug concentration** with respect to time.

C. Q_{10} METHOD

- **estimate the shelf life** of a product that has been stored or to be stored under a different set of conditions.

ENHANCING STABILITY

- drugs subjected to hydrolysis

  *water reduced or eliminated from the system.

  *water-liable drugs - waterproof protective coating applied in the tablet.

  *in liquid formulation - water replaced by substitute liquids.

***suspending them in nonaqueous vehicle**

***for injectable products – anhydrous vegetable oils may be used as solvent**

ENHANCING STABILITY

- For unstable antibiotic drugs (aq. prepn desired)

  - supplied in dry form for reconstitution before dispensing

- For unstable prepns: storage under refrigeration
- pH – major determinant in stability

  - optimum stability: pH 5 & 6
  - buffering agents increases stability

ENHANCING STABILITY

- oxygen sensitive drugs

  * prepared in dry state

  *packaged in sealed containers with air replaced by inert gas (Nitrogen, carbon dioxide).

  * **add antioxidants (for stability):**

    - **in aq. Prepns:**

      Na2SO3, NaHSO3, H3PO2, ascorbic acid

    - **in oleaginous/ unctous prepns:**

      alpha tocopherol, butylhydroxyanisole & ascorbyl parmitate

ENHANCING STABILITY

- trace metals in drug, solvent, container or stopper

- source of difficulty in preparing stable solns of oxidizable drugs

- eliminated by:

*purification of source of contaminant

*complexing or binding metal by using specialized agents (chelating agents- Ca disod edetate & EDTA)

ENHANCING STABILITY

- Light

  - catalyst to oxidation reactions

  -prepns packaged in light resistant or opaque containers

In summary : easily oxidizable drugsmay be stabilized in formulation by:

- selective exclusion from the system of:
  oxygen oxidizing agents trace metals
  light heat other chemical catalysis
- add to create and maintain a favorable pH:
  antioxidants chelating agents
  buffering agents

Other destructive process in pharmaceutical preparations

- Polymerization

  - reaction between two or more identical molecules with resultant formation of new & generally larger molecule (formaldhyde)

Process where one or more active chemical groups removed:

- Chemical decarboxylation
- deamination

- Decarboxylation

  - decomposition of RCOOH & release of CO_2

- Deamination

  -removal of nitrogen containing group from organic amine (ex. Insulin)

Importance of Drug Stability

- in preclinical testing and in clinical (human) trials

  - for a true and accurate assessment of the drug/drug prod evaluated

- marketed drug product

  - for the safety and effectiveness when distributed and during the entire course of its shelf-life and use

Product stability assessed before marketing:

- Formulation
- Influence of:
  - pharmaceutic ingredients present
  - container & closure
- Manufacturing & processing conditions
- Packaging components & conditions of warehousing/storage
- Conditions of shipping, temp., light & humidity
- Shelf life & patient utilization

stability testing considerations

- product containers, closures, and other packaging features
- parenteral and other sterile prods must meet sterility test stds

  - to ensure protection against microbial contamination

Drug instability detected

- Change in:

  physical appearance, color, odor, taste or texture of the formulation

Scientific data pertaining to the stability of a formulation

- leads to:
  - *prediction of the expected shelf-life of the proposed product
  - *redesign of the drug (to more stable salt or ester form)
  - *reformulation of the dosage form.

Accelerated stability testing

- Use of exaggerated conditions of temp., humidity, light & others
- accelerated temp

  - 6 mons study at 40 ºC with 75% relative humidity

Short term accelerated studies

- Determines most stable of the proposed formulations for a drug product
- lesser temp and humidity

  - 30ºC and 60% humidity

- Stress testing

  -temp. elevations in 10^{o} increments higher than used in accelerated studies

  - employed until chem.. or phy. Degradation

Long term stability studies

- product is subjected to different climatic zones (temp. & humidity)nationally & internationally
- predicted from the data generated from continuing stability studies
- 12 months minimum and conducted at 25°C +/- 2°C and at a relative humidity of 60% +/- 5%

PACKAGING & STORAGE of PHARMACEUTICALS

- labeling is essential for:

  *prod. stability

  *efficacious use

- **CONTAINERS**

  - stds for packaging of pharmaceuticals by manufacturers are contained in the CGMP

Tests performed depending on the intended use and type of container:

- physicochem. tests
- light-transmission tests for glass or plastic
- drug compatibility
- leaching and or migration tests,
- vapor-transmission test for plastics, moisture barrier tests, toxicity studies for plastics,
- valve, actuator, metered-dose, partical size, spray characteristics, leak testing for aerosols,
- sterility and permeation tests for parenteral containers
- drug stability for all packaging

According to USP:

- CONTAINER

  -holds the article and is or may be in direct contact with the article

- IMMEDIATE CONTAINER

  - in direct contact with the article at all times

- Closure

  - part of the container

- Closure & container

  - clean and dry prior to its being filled with the drug

CLASSIFICATION OF CONTAINERS BY THE BP according to their ability to protect their contents from external conditions:

- well-closed container

  - protects the contents from extraneous solids and from:

    *loss of the article under ordinary conditions of handling, shipment, storage & distribution

- tight container

  - protects the contents from contamination by extraneous liqs., solids, or vapors, from:

    * loss of the articles, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage and distribution and is capable of tight re-closure

CLASSIFICATION OF CONTAINERS BY THE USP according to their ability to protect their contents from external conditions:

- hermetic container

  -impervious/resistant to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution

  -those sterile are generally used to hold prepns intended for injection or parenteral adm

- single-dose container

  -quantity of drug contained is intended as a single dose and when opened cannot be resealed with assurance that sterility has been maintained

  - includes fusion-sealed ampules, pre-filled syringes and cartridges

CLASSIFICATION OF CONTAINERS BY THE USP according to their ability to protect their contents from external conditions:

- single-dose container

- designed to hold a quantity of drug intended for adm as a single dose promptly after the container is opened

  -single-unit package is termed a unit-dose package when dispensed to a patient

  -may be performed on a large scale by a manufacturer or distributor or on a smaller scale by the pharmacy dispensing the medication

CLASSIFICATION OF CONTAINERS BY THE USP according to their ability to protect their contents from external conditions:

- multiple-dose container

  -hermetic container that permits withdrawal of successive portions of the contents without changing the strength or endangering the quality or purity of the remaining portion

  - referred as vials

  - contain more than a single unit or dose of the medication

- Tablets, capsules & oral liquids

  - packaged in single-unit or multiple-unit containers

Single-unit packages

- convenient & sanitary means of maintaining and utilizing the medication
- advantages:

*positive ID of each dosage unit and reduction of medication errors

*reduced contamination of the drug due to its protective wrapping

*reduced dispensing time

*greater ease of inventory control in the pharmacy or nursing station

*elimination of waste through better medication management with less discarded medication

- Packaging materials
  - may be combinations of paper, foil, plastics or cellophane

- Packaging of solid dosage forms in:
  *clear plastic or aluminum blister wells
    - most popular method of single-unit packaging

- Oral liquids

  - may be single-unit dispensed in:

  *paper *plastic *foil cups

  *pre-packaged and dispensed in glass containers (with threaded caps or crimped aluminum caps)

Light resistant containers

- required by many pharmaceutical prods to protect them from photochem. deterioration
- amber glass or light resistant opaque plastic will reduce light transmission sufficiently to protect a light-sensitive pharmaceutical
- UV absorbers may be added to plastic to decrease the transmission of short UV rays
- must meet the USP stds w/c define the acceptable limits of light transmission at any wavelength of light between 290 and 450 nm

Classification of glass used in packaging pharmaceuticals depending upon the chem.. constitution of the glass and its ability to resist deterioration:

- Type I highly resistant, borosilicate glass
- II treated soda-lime glass
- III soda-lime glass
- NP gen. purpose soda-lime glass

- Types I, II & III for parenteral prods
- Type NP – for non-parenteral

Newer plastic materials used:

- PET – polyethylene terephthalate
- amorphous PET (APET)
- PET glycol (PETG)

- APET & PETG

  - excellent transparency, luster and can be sterilized with gamma radiation

Problems encountered in the use of plastics in packaging:

- permeability of the containers to atmospheric oxygen and to moisture vapor
- leaching of the constituents of the container to the internal contents
- absorption of drugs from the contents to the container
- transmission of light through the container
- alteration of the container upon storage

properties of plastics may be altered

- addition of:

  -plasticizers, stabilizers, antioxidants, antistatic agts, antimold agts, colorants, and others

drug subs's subjected to oxidative degradation

-may undergo a greater degree of degradation when packaged in plastic as compared to glass

LEACHING

- movement of components of a container into the contents
- Cpds leached from the plastic containers:

  polymer additives as the plasticizers, stabilizers or antioxidants
- occurs when liq. or semi-solid dosage forms are packaged in plastic
- little leaching occurs for tabs or caps packaged in plastic
- Influenced by:

  *temp *excessive agitation of the filled container

  *solubilizing effect of liq. contents on one or more of the polymer additives

- Soft-walled plastic containers of PVC – polyvinyl Cl

  - used to package IV solns and blood for transfusion

SORPTION

- binding of molecules to polymer materials
- absorption and adsorption are considered
- occurs through chem. or phy. means due to:
  - *chem.. structure of the solute molecules
  - *phy. and chem. properties of the polymer
- occurs with active pharmacologic agts or with pharmaceu. excipients thus, ings must be examined in the proposed plastic packaging to determine its tendency

- Pharmacist should dispense medication to patients in:

  - same type & quality of container used by the manufacturer of the product.

Child-Resistant/Adult-Senior Use Packaging

- **Child-resistant container**

  - defined as:

  *significantly difficult for children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time

  *not difficult for “normal adults” to use properly.

- Child-proof closures

  - initial regulations called for its use for

  *aspirin products *certain household chemical products

  - shown to have a significant potential for causing accidental poisoning in youngsters

Drugs intended for oral use

- dispensed by the pharmacist to the patient in containers having child-resistant closures unless the prescriber or the patient specifically requests otherwise, or unless the product is specifically exempt from the requirement

- Adults, particularly the elderly or those with arthritis or weakened hand-strength (with difficulty opening child-resistant packages)

  - the regulations were amended and (1998) to require that child-resistant containers be capable of being readily opened by senior adults

STORAGE

- product must be stored under proper conditions

  - to ensure the stability of a pharmaceutical prepn for the period of its intended shelf life

- Labeling of each product

  - includes the desired conditions of storage

Terms employed for the desired conditions as defined by the USP:

- Cold
  - any temp not exceeding 8°C (46°F)
  - a refrigerator is a cold place where the temp. is maintained bet. 2o and 8oC (36o and 46oF)
- Cool
  - any temp bet. 8° and 15°C (46° and 59°F)

Terms employed for the desired conditions as defined by the USP:

- Room Temp.

  - temp prevailing in a working area

  -20°to 25°C (68°F to 77°F) but also allows for temp variations bet 15° and 30°C (59° and 86°F) experienced in pharmacies, hospitals, and drug warehouses

- Warm

  - any temp bet 30° and 40°C (86° and 104°F)

- Excessive Heat

  - any temp above 40°C (104°F)

Protection from Freezing

- protects the product from:
  - *freezing
  - *risk of breakage of the container
  - *loss of strength or potency
  - *destructive alteration of the dosage form

Stability Testing

Signs of degradation of the specific dosage forms must be observed and reported.

- Tablets : Apperance (cracking, chipping, mottling), friability, hardness, color.
- Capsules: Moisture tackiness, color appearance, shape, brittleness and dissolution
- Oral Solutions and Suspensions: Appearance, precipitation, pH, color, odor, dispersibility (suspension) and clarity (solutions)

- Oral Powders: Appearance, color, odor, moisture
- Metered–dose inhalation aerosols delivered dose per activation, number of metered doses, color, particle size distribution, loss of propellant, pressure, valve corrosion, spray pattern, absence of pathogenic microorganism
- Topical creams: ointments, lotions, solutions, and gels. Appearance, color, homogeneity, odor, pH, resuspendability (lotions), consistency, particle size, distribution strength, weight loss.

- Opthalmic and Nasal and Oral inhalation preparations: Appearance, color consistency, pH, clarity (solutions), particle size, and resuspendability (suspensions, ointments), strength and sterility.
- Small Volume Parenterals: Appearnace, color, clarity, particulate matter, pH volumes and extractables (when plastic containers are used), sterility, pyrogenicity and closure integrity.

- Suppositories: Softening range; appearance and melting.
- Emulsions: Appearance (such as phase separation) color, odor, pH, and viscosity.
- Controlled release membrane drug delivery systems: seal strength of thr drug reservoir, decomposition products, membrane integrity, drug strength and drug release rate.

FDA guidelines on stability for extemporaneous compounding

- Nonaqueous liquids & solid formulations (source of active ingredient)'s
  - not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier
- Nonaqueous liqs & solid formulations in w/c USP or NF substance (source of ing)
  - beyond-use not later than 14 days in storage at cold temperatures

FDA guidelines on stability for extemporaneous compounding

- Other formulations beyond-use date of the intended duration of therapy or 30 days whichever is earlier

PHARMACIST:

- oral aq. liq prepns made from existing tab or cap formulation

  -pharmacist should make up only at most a 14 days supply and must be stored in a ref.
- must dispense the medication in a container conducive to stability and use

  -advise the patient of the proper method of use and conditions of storage of the medication
- when compounding on the basis of extrapolated or less than concrete information

  - should keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription

Stability testing

- manufactured products - shelf life of 2 or more years to ensure stability at the time of consumption.
- expiration date - limits the time during which the product may be dispensed by the pharmacist or used by the patient.

PHARMACEUTIC INGREDIENTS (PIs)

- required in preparing the drug subs. into a final dosage form
- for each dosage form:

  *establish the primary features of the prod

  *contribute to the physical form, texture, stability, taste and over all appearance

Pharmaceutical Ingredients and Excipients

Definition of terms

- Solvents are used to dissolve the drug substance.
- Flavors and sweeteners are used to make the product more palatable
- Colorants are added to enhance appeal
- Preservatives may be added to prevent microbial growth

Pharmaceutical Ingredients and Excipients

- Stabilizers (antioxidants and chelating) - to prevent decomposition.
- Diluents or fillers - to increase the bulk of the formulation.
- Binders – to cause adhesion of the powdered drug and pharmaceutical substances.
- Antiadherents or lubricants to assist smooth tablet information.

Pharmaceutical Ingredients and Excipients

- Disintegrating agents - promote tablet break up after administration and coatings to improve stability, control disintegration or enhance appearance.

Sweetening Pharmaceuticals

- used in foods and pharmaceuticals:
  *sucrose
  *artificial sweetening agents
- **SWEETENING PHARMACEUTICALS**
  - mask unwanted taste
  - commonly used - **sucrose**
  -**Delaney Clause:** no new food additives may be used if animal studies/appropriate tests showed that it caused cancer

Sweetening Pharmaceuticals

- Saccharin & cyclamate - used in foods
  - -“generally recognized as safe” (before the amendment’s passage)
  - - use on rats: developed incidence of bladder tumors (cancer)
  - - continued availability but warning labels be used

  - -**cyclamates (**banned) - possible carcinogenicity, genetic damage, testicular atrophy

Sweetening Pharmaceuticals

- Aspartame –
  - 1st artificial sweetener (1958 amendment) w/ requirement for pre-marketing proof of safety.
- **Acesulfame potassium (nonnutritive sweetener)**
  - structurally similar to saccharin (USP approved)
  - 130 times as sweet as sucrose, excreted unchanged in the urine;
  - more stable than aspartame
- **Stevia** (Stevia rebaudiana Bertoni)
  – new sweetening agent: natural, nontoxic, safe, 30x sweeter than cane sugar/sucrose

	Sucrose	Saccharin	aspartame
Source	Sugar cane; sugar beet	Chemical synthesis; phthalic anhydride	Methyl ester dipeptide of phenylalanine and aspartic acid
Relative sweetness	1	**300**	180-200
Bitterness	None	**Moderate to strong**	none
After taste	None	Moderate to strong metallic to bitter	none
Calories acid stability	4/g	0	4/g
Acid stability	good	Excellent	fair

Coloring Pharmaceuticals

- for esthetics.
- Coal tar (pix carbonis)

  - thick black viscid liquid

  - by product of destructive distillation of coal.

  -source of synthetic coloring agents in pharm. products in the middle of the 19th century
- Dyes – added to pharmaceutical prens in the form of diluted solutions
- Lakes - commonly used in the form of fine dispersions or suspensions.

Coloring Pharmaceuticals

- 90% of the dyes used in the products - synthesized from derivative of benzene (**aniline**)
- FDA - **regulates use color additives** in foods, drugs, and cosmetics (Federal Food, Drug, and Cosmetic Act of 1938)
  - **FD&C color additives** - foods, drugs, and cosmetics
  - **D&C color additives -** drugs, some in cosmetics & medical devices
  - **external D&C color additives -** restricted to external parts of the body (not including the lips and other parts that are covered by mucous membrane)

Factors in selecting dyes

- Solubility of prospective dye
- pH & pH stability of the preparation to be colored
- Dyes must be photostable

Preservatives

- liquid and semisolid preparations
  - must be preserved against microbial contamination.

Sterilization and Preservation

- some types of pharmaceutical products (ex. Ophthalmic and injectable preparations)

- **sterilized by physical methods** :
  - ***autoclaving** (20min at 15 lb. press. & 121°C, dry heat at 180°C for 1 hr)
  - ***bacterial filtration**.

Sterilization and Preservation

- Preparations that provide excellent growth media for microbes
  - **aqueous preparations**: syrups, emulsions, suspensions
  - **semi solid preparations** particularly creams.
  - **hydro-alcoholic & most alcoholic preparation**
    *may not require addition of chemical preservative

Sterilization and Preservation

- **prevent** microbial growth:
  - *15% alcohol in acid media
  - *18% alcohol in alkaline media.

- Alcohol-containing pharmaceuticals (elixirs, spirits, and tinctures) - **self sterilizing** and do not require additional preservation.

Preservative Selection

- **Considerations in selecting preservative in pharmaceutical preparations:**

1. **prevents the growth** of the type of microorganisms (contaminants of the preparations)
2. **soluble enough in water** to achieve adequate concentrations in aqueous phase with two or more phase systems
3. proportion of preservative remaining undissociated at the pH of preparation (**can penetrate** the microorganism & **destroy** its integrity).

Preservative Selection

4. concentration of the preservative **does not affect** the safety/comfort of the patient
5. with adequate stability and **not reduced in concentration** by chemical decomposition/volatilization
6. **compatible** with all other formulative ingredients and **does not interfere** with them
7. **does not adversely affect** the preparation's container or closure.

Mode of action

Mechanisms preservative interfere with microbial growth, multiplications, and metabolism:

1.Modifications of cell membrane permeability and leakage of cell constituents (partial lysis)

2. Lysis and cytoplasmic leakage

3. Irreversible coagulation of cytoplasmic constituents

4.Inhibition of cellular metabolism by interfering with enzyme systems/inhibition of cell wall synthesis

5. Oxidation of cellular constituents

6. Hydrolysis

PRESERVATIVE UTILIZATION

PRESERVATIVES:

- suitable substances added to enhance its permanency or usefulness
- examples: commonly employed:

benzoic acid	alcohol
sodium benzoate	phenylmercuric nitrate and acetate
phenol	benzalkonium chloride

PRESERVATIVE UTILIZATION

- IV prepns in large volumes as blood replenishers/nutrients

  - no bacteriostatic additives

- Injectable prepns in small volumes

  -can be preserved with suitable preservatives

END