3.6 PHARMACEUTICAL FORMULATIONS (THEORY)

Subject code: T3106

UNIT I: Pharmaceutical dosage form- concept and classification

Dosage form: In order to make a drug administrable to the patient, it is converted into a dosage form by mixing it with some non drug components called as Excipients or additives. The form in which the drug substances are presented in the market are called the dosage forms.

CONCEPT OF DOSAGE FORMS:

The desirable properties of dosage forms are:

1. It should be convenient to handle, use and store. For better compliance it should not disturb his routine lifestyle as far as possible and should be acceptable aesthetically, organoleptically, therapeutically and from economic standpoint.

2. It should be stable during storage and use. During storage the physical, chemical and therapeutic integrity of the dosage form should be maintained by assuring freedom from interaction between components, with packaging materials and environmental factors (heat, humidity, oxygen, light). It should also withstand mechanical shock during transportation. The dosage form should retain its shape, size, appearance, taste, flavor and therapeutic effect during the stipulated half life.

3. The dosage form should be represented in different dosage form strengths providing flexibility of dose to suit different age groups (50, 100,200mg etc)

4. It should provide anticipated therapeutic effect. The extent and pattern of drug release from the dosage form should be predictable.

5. It should protect the drug substance and conceal the disagreeable taste or odour.

6. It should be economical and presentation should be elegant.

7. Finally it should permit easy identification through distinct colour, shape or identification marking.

THE NEED FOR DOSAGE FORMS

The potent nature and low dosage of most of the drugs in use today precludes any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance. For instance, how could the lay person accurately obtain from a bulk supply the Not possible. Yet compared with many other drugs, the dose of aspirin is formidable.

When the dose of the drug is minute, as with ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the dosage unit is large enough to

pick up with the fingertips. Besides providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for additional reasons:

• To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampoules)

• To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric-coated tablets)

• To conceal the bitter, salty, or offensive taste or odor of a drug substance (capsules, coated tablets, flavored syrups)

• To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (suspensions)

• To provide clear liquid dosage forms of substances (syrups, solutions)

• To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)

• To provide optimal drug action from topical administration sites (ointments, creams, transdermal patches, and ophthalmic, ear, and nasal preparations)

• To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories)

• To provide for placement of drugs directly in the bloodstream or body tissues (injections)

• To provide for optimal drug action through inhalation therapy (inhalants and inhalation aerosols)

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Before formulating a drug substance into a dosage form, the desired product type must be determined in so far as possible to establish the framework for product development. Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up.

The formulation that best meets the goals for the product is selected to be its *master formula*. Each batch of product subsequently prepared must meet the specifi cations established in the master formula.

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease. Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are such therapeutic matters as the nature of the illness, the manner in which it is treated (locally or through systemic action), and the age and anticipated condition of the patient.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are usually prepared because they are easily handled by the patient and are most

convenient in the self-administration of medication. If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment.

The age of the intended patient also plays a role in dosage form design. For infants and children younger than 5 years of age, pharmaceutical liquids rather than solid forms are preferred or oral administration. These liquids, which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser or incorporated into the child's food. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When a young patient has a productive cough or is vomiting, gagging, or simply rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated.

In such instances, injections may be required. Infant-size rectal suppositories may also be employed, although drug absorption from the rectum is often erratic. During childhood and even adulthood, a person may have difficulty swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant-tasting creamy material.

Newly available tablets dissolve in the mouth in about 10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water. Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, if a person has difficulty swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed. Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identifi cation of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the *preformulation* work needed before actual product formulation begins.

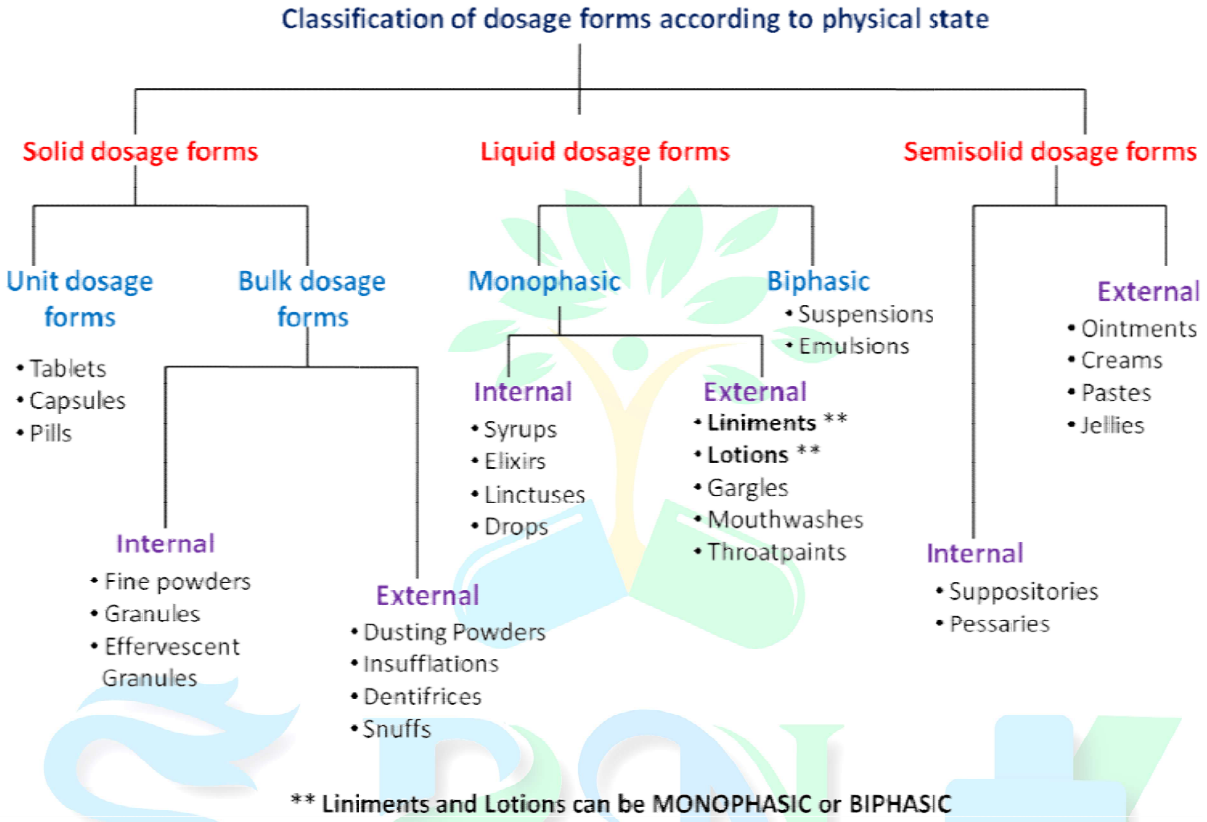
CLASSIFICATION OF DOSAGE FORMS:

According to physical state: Solid, semi solid, liquid, gaseous.

Route of administration: Oral, Parenteral, rectal, nasal, Transdermal etc.

Site of application: Skin, eye, tooth, hand, foot, hair, nose etc

Use: External, Internal



Definitions:

Tablets: Tablets are unit solid dosage form of medicament or medicaments with or without suitable diluents. They are prepared by moulding or usually by compression. Tablets are generally meant for oral administration but may be used by other routes of administration. Examples are Aminophylline tablets, Chloroquine sulphate tablets, paracetamol tablets

Capsules: Capsules are the solid unit dosage form of medicament in which the drug or drugs are enclosed in a practically tasteless, hard or soft soluble container or shell made up of a suitable form of gelatin. Hard capsules are used for filling the solid substances. Soft gelatin capsules are used for enclosing the solids, liquids and semi liquids. Ex. Amoxycillin capsules, Ampicillin capsules

Powders: Powders are solid dosage form of medicament meant for internal and external use. The powders meant for internal use are known as oral powders whereas those meant for external use are known as dusting powders. The powders may be simple or compound. Examples are Compound rhubarb powder, compound sodium chloride and dextrose oral powder, talc dusting powder.

Pills: Pills are an old dosage form of prescribing solid medication. Inconvenience associated with the administration of powders led to the use of pills by converting the powder into spherical shape which facilitate swallowing. Pills may be considered as predecessor of tablets in the process of evolution of unit dosage forms.

Granules: Granules are the solid dosage form of medicament in which the powdered drug or drugs are mixed with sweetening, flavoring and coloring agents. A suitable granulating agent is added to moisten the powder and mixed thoroughly. The wet mass is passed through a sieve and granules are dried at a temperature of 60^0C. They are supplied in glass containers and the patient is asked to add sufficient freshly boiled and cooled water to constitute a liquid preparation.

Effervescent Granules: Effervescent Granules are specially prepared solid dosage form of medicament, meant for internal use. They usually contain a citric acid, tartaric acid, sodium bicarbonate and medicament, a sweetening agent such as saccharin or sucrose may be incorporated. When these granules are added to the water, the acids react with sodium bicarbonate to liberate CO_2 and the preparation is taken while effervescing or immediately afterwards. These preparations act as antacids

$$3NaHCO_3 + C_6H_8O_7.H_2O \xrightarrow{\Delta} C_6H_5Na_3O_7 + 3CO_2 + 3H_2O$$

$$2NaHCO_3 + C_4H_6O_6 \xrightarrow{\Delta} C_4H_4Na_2O_6 + 2CO_2 + 2H_2O$$

Dusting powders: Dusting powders are meant for external application to the skin. They are usually mixtures of two or more than two ingredients in fine powder e.g. starch, kaolin, talc, zinc oxide etc. They must be homogeneous and in a very fine state of subdivision to enhance effectiveness and minimize local irritation, for this purpose they may be passed through sieve no. 120. Dusting powders may be medicated or non-medicated. Dusting powders are applied to the skin for antiseptic, antipruritic, astringent, antiperspirant, absorbent, protective and lubricant purposes. Dusting powders should not be applied to open wounds or to raw surfaces. Examples are dicophane dusting powder, zinc and salicylic acid dusting powder, zinc, starch and talc dusting powder.

Insufflations: These are finely divided powders meant for introduction into the body cavities such as ears, nose, toot h sockets and vagina with the help of an apparatus known as insufflators, to which it would be difficult to apply the powder directly. Insufflators suffer from the drawback that uniform dose delivery cannot be regulated. Intranasal insufflations can produce systemic effects in addition to local action. Most of the drawbacks of the insufflators have been overcome through the usage of aerosol packages.

Dentifrices: Dentifrices are the substances or preparations which are generally used with or without the help of tooth brush for cleaning the surface of the teeth. They are available in the form of tooth powders and pastes. They usually contain soap or detergent (for cleaning action), mild abrasive and an anti-cariogenic agent.

Snuffs: Snuffs are finely divided solid dosage forms of medicament which are inhaled in to the nostrils for its anti septic, bronchodilator and decongestion action. Example: Maxeran - Metoclopramide snuffs

Liniments: Liniments are the liquid and semi liquid preparations meant for applications to the skin by friction or rubbing of the skin but should not be applied to the broken skin. The liniments may be alcoholic or oily solutions or emulsions. They should be dispensed in colored fluted

bottles in order to distinguish from preparations meant for external use. The bottle should be labeled "FOR EXTERNAL USE ONLY" and "SHAKE THE BOTTLE BEFORE USE". Examples are Soap liniment and white liniment

Lotions: Lotions are monophasic/ biphasic liquid preparations meant for external applications without friction. These are liquid suspensions or dispersions. They usually contain alcohol or glycerin because alcohol hastens drying and produces cooling sensation whereas glycerin keeps the skin moist for a sufficient long time. Lotions may be used for local actions as cooling, soothing or protective purposes. They are generally prescribed for antiseptic action. They should be dispensed in colored fluted bottles in order to distinguish from preparations meant for external use. The bottle should be labeled "FOR EXTERNAL USE ONLY" and "SHAKE THE BOTTLE BEFORE USE". Examples are Calamine lotion and Salicylic acid lotion.

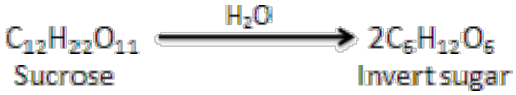
Gargles: Gargles are aqueous solutions used for the prevention or treatment of throat infections. Usually they are concentrated solutions and should be diluted with warm water before use. In using gargles they are brought into intimate contact with the mucous membrane of the throat and are allowed to remain there for a few moments after which they are thrown out of the mouth. Some of the analgesic preparations like aspirin gargles may be swallowed afterwards. Gargles should be dispensed in white fluted bottles.

Mouthwashes: Mouthwashes are usually aqueous solutions in concentrated form with a pleasant taste and flavor used for rinsing, deodorant, refreshing out antiseptic action. Medicated mouthwashes may contain astringents, anti bacterial agents, protein precipitants or other agents. They are generally used after dilution with warm water on the mucous membrane of the mouth. Ex. Compound Sodium chloride and zinc sulphate mouthwash, zinc chloride mouthwash.

Spirits: Spirits are the liquid preparations of medicaments in alcohol (90 percent). Ex. Chloroform spirit, lemon spirit, compound orange spirit.

Throat paints: Throat paints are viscous liquid preparations used for mouth and throat infections. Glycerin is commonly used as a base because of viscous nature and agreeable taste. Examples are boroglycerin, phenol glycerin and compound iodine paint(Mandles Paint).

Syrups: Syrups are sweet, viscous, concentrated aqueous solutions of sucrose or other sugars in water or any other suitable aqueous vehicle. They are used as sweetening and flavoring agents. Syrup I.P is a 66.7%w/w solution of sucrose whereas Syrup U.S.P consists of 85%w/w solution of sucrose in purified water. Both the concentrations give stable syrups resistant to microbial growth. Syrups containing lesser concentrations of sucrose require preservatives. Heat employed during the preparation of syrups causes an inversion of a slight portion of the sucrose.



Elixirs: Elixirs are clear, pleasantly flavored, sweetened hydro alcoholic liquid preparations for oral administration. The main ingredients of elixirs are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, sugar and preservatives may be incorporated to the preparation. The elixirs may be medicated or non medicated. The medicated elixirs usually contain very potent drugs such as antibiotics, antihistaminics and sedatives. The non medicated elixirs are used as flavored and vehicles. Ex. Chlorpheniramine elixir, Diphenhydramine elixir, Ephedrine elixir etc

Linctuses: Linctuses are sweet viscous liquid preparations usually containing medicinal substances which have demulcent, sedative or expectorant properties. They are used for the treatment of cough. Linctuses are swallowed slowly in small doses without addition of water. Ex. Codeine Linctus, Noscapine linctus.

Nasal Drops: Nasal drops are usually aqueous solutions intended for instillation into the nostrils by means of a dropper. They are commonly used for their antiseptic, local analgesic or vasoconstrictor properties. Ex. Ephedrine Nasal drops

Eye drops: Eye drops are sterile aqueous or oily solutions or suspensions for instillation into the eye. They are usually applied to the space between the eyeball and eye lids or on to the corneal surface. The main requirement of eye drops is that they should be sterile, usually isotonic, buffered and free from foreign particles to avoid irritation to the eye. They usually contain substances having antiseptic, anesthetic, anti inflammatory, mydriatic or miotic properties or substances used for diagnostic purposes.
Eye drops shoulder be dispensed b in glass or suitable plastic containers with a screw cap fire with a rubber teat and glass dropper for easy application of the drops or the containers may be fitted with a nozzle from which drops can be directly instilled into the eye.
Ex. Atropine eye drops, Chloramphenicol eye drops, pilocarpine eye drops

Suspensions: Suspensions are the biphasic liquid dosage form of medicament inwhich finely divided solid particles ranging from 0.5 to 5 microns are suspended or dispersed in a liquid or semifluid vehicle. Suspensions are mainly used for oral administration, external application or parenteral use. Ex. Barium sulphate suspension, Chalk- Kaolin Suspension.

Emulsions: Emulsions are the biphasic liquid dosage form of medicament in which two immiscible liquid are made miscible by the addition of a third substance known as emulgent or emulsifying agent. Emulsions are pleasant to take than to take an oil as such. Emulsions are of two types a. Oil in water type (O/W) b. Water in oil type(W/O). The former is generally for oral administration whereas the latter is generally for application to the skin. Emulsions should be supplied in wide mother containers labeled with "Shake the bottle before use" Ex. Castor oil emulsion, Liquid paraffin emulsion.

Ointments: Ointments are soft semi solid preparations meant for external application to the skin or mucous membranes. They usually contain a medicament dissolved, suspended or emulsified in the base. Ointments are used for their emollient and protective action to the skin. Ex. Compound Bendix acid ointment, cetrimide ointment etc

Creams: Creams are viscous semi solid emulsions intended for application to the skin. Creams differ from ointments that they have lighter body than ointments. Moreover due to the presence of water soluble bases they can be easily removed from skin and clothings. Creams may be of oil in water type or water in oil type. The aqueous creams have a tendency to bacterial and mold growth, therefore a preservative must be added in their formulation. Ex. Cetomacrogol cream, Chlorhexidine cream, Hydrocortisone cream.

Pastes: Pastes are semi solid preparations meant for external application to the skin. They differ from ointments in that they generally contain a large amount of finely powdered solids such as starch, zinc oxide, calcium carbonate etc. They provide a protective coating over the areas to which they are applied. Ex. Magnesium sulphate paste, Zinc and coal tar paste.

Jellies: Jellies are transparent or translucent non greasy semi solid preparations meant for external application to the skin or mucous membrane. They are used for medication or lubrication purposes. Some of them are also used as contraceptive jellies. Ex. Proflavin jelly, icthammol jelly etc

Suppositories: Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects. The word suppository is derived from the Latin word "supponere" which means "to place under". Thus, suppositories are meant for placing under the body cavities such as rectum, vagina, urethra etc. The shape and size of a suppository must be such that it can be easily inserted into the intended orifice without causing undue distension, and once inserted, it must be retained for the appropriate period.

Pessaries: Pessaries are the solid unit dosage form of medicament meant for introduction into the vagina. The bases used for the manufacture of pessaries are such that at room temperature they retain the original shape but when inserted into the cavity either melt or dissolve in the cavity fluids to release the medicament. They may be prepared either by moulding or by compression. Ex. Lactic acid pessaries, Nystatin pessaries