Chapter-4

Pharmaceutical dosage form design and drug delivery

5th Stage

Lec. Ashti M.H. Saeed

Msc Drug Delivery

Mustansiriyah University

College of pharmacy

Dosage Form Design & Drug Delivery

✖ Pharmaceutical and Formulation Considerations

Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialised pharmaceutical functions.

Selective use of these non-medicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types.

Each type of dosage form is unique in its physical and pharmaceutical characteristics. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed pharmaceutics.

The proper design and formulation of a dosage form requires

1. Consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product.
2. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe.
3. The product should be manufactured with appropriate measures of quality control and packaged in containers that should be labelled to promote correct use and be stored under conditions that contribute to maximum shelf life.

The need for dosage forms

The potent nature and low dosage of most drugs in use today precludes (not permits) any expectation that 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 lay person accurately obtain from a bulk supply the 325 mg of aspirin found in the common tablet? Not possible.
Yet compared with many other drugs, for example, the dose of ethinyl estradiol, 0.05 mg, is 1/6,500 the amount of aspirin in an aspirin tablet. To put in another way, 6,500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one standard tablet. When the dose of the drug is minute, as with ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with filler 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:

1. To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampoules)
2. To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric coated tablets)
3. To control the bitter, salty, or offensive taste or odour of a drug substance (capsule, coated tablets, flavoured syrups)
4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (suspensions)
5. To provide clear liquid dosage forms of substances (syrups, solutions)
6. To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)
7. To provide optimal drug action from topical administration sites (ointments, creams, trans-dermal patches, and ophthalmic, ear, and nasal preparations)
8. To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories)
9. To provide for placement of drugs directly in the bloodstream or body tissues (injections)
10. To provide for optimal drug action through inhalation therapy (inhalation aerosols).

✖ **General considerations in dosage form design**

Before formulating a drug substance into a dosage form, the desired product type must be determined, 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 meet the goals for the product is selected to be its master formula. Each batch of product subsequently prepared must meet the specifications established in the master formula. Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease.

Before medicinal agent is formulated into one or more dosage forms, among the factors considered are such therapeutic matters as

1. the nature of the illness,
2. the manner in which it is treated (locally or through systemic action),
3. the age and anticipated condition of the patient.

The Age of The Intended Patient Also Plays a Role in The Dosage Form Design??

For infant and children younger than 5 years of age, pharmaceutical liquids rather than solid forms preferred for oral administration. These liquids which are flavoured aqueous solutions, syrups, or suspensions, are usually administered directly into infant's or child's mouth by drop, spoon, or oral dispenser or incorporated into child's food.

Single liquid paediatric 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 simple rebellious, there may be some questions as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instance, injections may be required. Infant-size suppositories may also be employed, although drug absorption from the rectum is often erratic.

How to solve the difficulty of swallowing especially a solid dosage form (uncoated): 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 pleasant-tasting creamy material.

Newly available tablets dissolve in 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 gelatine desert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowed them. Additionally, if a person has difficulty swallowed a capsule; the contents may be emptied 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 liquid 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.

- **multiple medication therapy**

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and colour of solid dosage forms, the easiest is proper identification 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.

Per-formulation Studies

Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterised.

1. Physical Description

It is important to understand the physical description of a drug substance prior to dosage form development. Most drug substances in use today are solid materials, pure chemical compounds of either crystalline or amorphous constitution. The purity of the chemical substance is essential for its identification and for evaluation of its chemical, physical, and biologic properties.

Chemical properties include structure, form, and reactivity. Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point, and solubility.

Biologic properties relate to its ability to get to a site of action and elicit a biologic response. Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs; gases, even less frequently.

Liquid drugs pose an interesting problem in design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from atmosphere to prevent evaporation loss.

Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is kept for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilatation.

Propylhexedrine is another volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylinder roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually plastic, sealed nasal inhaler. The inhaler's cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited time because of the volatility of the drug.

Another problem associated with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form, the most popular form of oral medication.
An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after replacement under the tongue. However, because the drug is volatile, it has a tendency to escape from the tablets during storage, and it is critical that the tablets be stored in a tightly sealed glass container.

For the most part, when a liquid drug is to be administered orally and a solid form is desired, one of two approaches is used.

- First, the liquid substance may be sealed in a soft gelatine capsule. Vitamins A, D, and E, cyclosporine and ergoloid mesylates are liquids commercially available in capsule form.
- Second, the liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules. For instance, scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets.
- Another approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high-molecular-weight polyethylene glycol. The melted mixture is poured into hard gelatine capsules to harden and the capsules sealed.

For certain liquid drugs, especially those taken orally in large doses or applied topically, they may have some advantage in the therapy:
For example, 15-mL doses of mineral oil may be administered conveniently as such. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin, However, for the most part, pharmacists prefer solid materials in formulation work because they can easily form them into tablets and capsules.

✖ Solid dosage forms are preferred

Formulation and stability difficulties arise less frequently with solid dosage form than with liquid preparations, and for this reason many new drugs first reach the market as tablet or dry-filled capsules.

Later, when the pharmaceutical problems are resolved, a liquid form of the same drug may be marked. This procedure is doubly advantageous, because for the most part physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms. Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

2. Microscopic Examination

It gives an indication of particle size and size range of the raw material along with the crystal structure.

Photomicrographs of the initial and subsequent batch lot of the drug substance can provide important information in case of problems in formulation processing attributable to changes in particle or crystal characteristics of the drug.

4. Heat of Vaporization

The use of vapour pressure is important in the following situations:

1. The operation of implantable pumps delivering medication as well as aerosol dosage forms
2. The use of nasal inhalants (propylhexedrine with menthol and lavender oil-benzedrex) or treating nasal congestion. Some volatile drugs can even migrate within a tablet dosage form so the distribution may not be uniform any longer. This may have an impact in tablet that are scored for dosing where the drug in one portion may be higher or lower than in the other portion.
3. Exposure of personal to hazardous drugs due to handling, spilling, or aerosolizing of the drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapour pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil).
4. Particle size affects the vapor pressure; the smaller the particle size, the greater the vapor pressure.

4. **Melting Point Depression**

The melting point, or freezing point, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium. If not pure, the substance will exhibit a change in melting point. (A pure chemical is ordinarily characterised by a very sharp melting peak). An altered peak or a peak at a different temperature may indicate an adulterated or impure drug – measured by DSC instrument.

Differential scanning calorimetry (DSC) is a technique used to measure thermodynamics of solid or liquid phase transitions that produce or absorb heat.

- This phenomenon is commonly used to determine the purity of a drug substance and in some cases the compatibility of various substances before inclusion in the same dosage form.

5. particle size

Certain physical and chemical properties of drug substances, including dissolution rate, bioavailability, content uniformity, taste, texture, colour, and stability, are affected by the particle size distribution

In addition, flow characteristics and sedimentation rates, among other properties, are important factors related to particle size. It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and efficacy of special interest is the effect of particle size on absorption. Particle size significantly influences the oral absorption profiles of certain drugs, including griseofulvin, nitofurantoin, spironolactone, and procaine penicillin.

Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation.

- Particle size is analysed using special instrument like Mastersizer 2000E particle size analyzer

THANK YOU DEARS