PHARMACEUTICS-I (BP103T)

UNIT: 2

CLASS: 9

TOPIC: Solubility Enhancement

DEFINITION: Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

• Solubilization can be defined as a preparation of thermodynamically stable isotropic solution of a substance normally insoluble or slightly soluble in a given solvent by introduction of an additional component or components.

The biopharmaceutical classification system (BCS): I High solubility High permeability II Low solubility High permeability III High solubility Low permeability IV Low solubility Low permeability

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. The Indian pharmacopoeia provides general terms to describe a given range.

These descriptive terms are given as: Very soluble <1, Freely soluble 1 – 10, Soluble 10 – 30, Sparingly soluble 30 – 100, Slightly soluble 100 – 1000, Very slightly soluble 1000 – 10,000, Insoluble >10,000

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

• Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.

• Currently only 8% of new drug candidates have both high solubility and permeability.

D NEELIMA
Assistant Professor

• Nearly 40% of the new chemical entities currently being discovered are poorly water soluble.

• More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories.

• Low aqueous solubility is the major problem encountered with formulation development of new chemical entities.

• Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

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.

Steps involved are: 1: Holes opens in the solvent 2. Molecules of the solid breaks away from the bulk. 3. The freed solid molecule is integrated into the hole.

I. Physical Modifications

A. Particle size reduction

1. Micronization

2. Nanosuspension

3. Sonocrystalisation

4. Supercritical fluid process

B. Modification of the crystal habit

1. Polymorphs

2. Pseudopolymorphs

C. Drug dispersion in carriers

1. Eutectic mixtures

2. Solid dispersions

3. Solid solutions

D. Complexation: Use of complexing agents

E. Solubilization by surfactants

II. Chemical Modifications

1. Change in the pH

2. Use of buffer

3. Derivatization

III. Other methods

1.co-crystallisation

2. co-solvency

3. Hydrotrophy

4.Solubilizing agents

5. Selective adsorption on insoluble carrier

6. Solvent deposition

7. Using soluble prodrug

8. Functional polymer technology

9. Precipitation Porous

10. microparticle technology

11. Nanotechnology approaches

A. Particle size reduction: Particle size reduction can be achieved by

a. Micronization b. nanosuspension c. Sonocrystalisation d.Supercritical fluid process.

1. Micronization: Micronization increases the dissolution rate of drugs through increased surface area.

• Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc.

• Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

• The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods. The process is also called micro-milling.

2. Nanosuspension: Nanosuspensions are sub-micron colloidal dispersion of pure particles of the drug, which are stabilized by surfactants. Nanosuspension technology is used for efficient delivery of hydrophobic drugs. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Advantage: Increased dissolution rate due to larger surface area exposed. Eg, Nanosuspension approach has been employed drugs like paclitaxel, tarazepide, amphotericin B which are still on research stage.

3. Sono crystallisation: Particle size reduction on the basis of crystallisation by using ultrasound is Sono crystallisation. Sono crystallisation utilizes ultrasound power for inducing crystallisation. It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz 5 MHz.

4. Supercritical fluid process:

• Supercritical fluids are dense non-condensable fluid whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp) allowing it to assume the properties of both a liquid and a gas.

• Through manipulation of the pressure of SCFs, the favourable characteristics of gases – high diffusivity, low viscosity and low surface tension may be imparted upon the liquids to precisely control the solubilisation of a drug with a supercritical fluid.

• Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes.

• A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels.

B. Modification of the crystal habit: Polymorphs Enantiotropic One polymorphs form can change reversibly into another at a definite transition temperature below the melting point. Monotropic No reversible transition is possible.

• Metastable forms are associated with higher energy and thus higher solubility. Similarly, the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increased surface area.

• The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates.

• They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is Amorphous > metastable polymorph > stable polymorph

• Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

C. Drug dispersion in carriers: The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the

• Hot melt mehod

• Solvent evaporation method

• Hot melt extrusion method

1. Hot melt method: Drug + vehicle (m.p low, organic solvent – insoluble) A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process. (heating) Melting. Freezing quickly Dosage forms Important requisites: 1. Miscibility of the drug & carrier in the molten form, 2. Thermostability of the drug & carrier. Suitable to drugs and vehicles with promising heat stability.

2. Solvent evaporation method: Drug + vehicle (both soluble in solvent) organic solvent solution evaporates the solvent coprecipitates dosage forms. The solvent evaporation can be done by spray drying or freeze drying. Temperatures used for solvent evaporation generally lie in the range 23-65 C. suitable to drugs with volatility or poor stability suitable to drugs with volatility or poor stability.

3.Hot-melt Extrusion: Hot melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

2 MARKS QUESTIONS

1. Define solubility.
2. What is mechanism involved in solubility?

5 MARKS QUESTIONS

1. Explain any two methods for improving the solubility of poorly soluble drugs.

10 MARKS QUESTIONS

1. What is solubility? How can you enhance the solubility of poorly soluble drugs?