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SOLUBILITY ENHANCEMENT TECHNIQUES - A REVIEW

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Abstract:
Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution but also because of a chemical reaction Solubility is the phenomenon of dissolute on of solid in liquid phase to give a homogenous system. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for drugs. This is true for parenterally, topically and orally administered solutions. Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects, but poorly solubility of drug is major challenge for formulation scientist. About 40% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. On the basis of solubility, drugs are classified into four classes of the BCS classification. We may define a drug as 'poorly soluble' when its dissolution takes longer than the transit time past its absorptive sites, resulting in incomplete bioavailability. The aqueous solubility of a drug is a prime determinant of its dissolution rate and in the case of poorly soluble drugs Solubility challenges are faced in the Class II and Class IV of the BCS system. The method is suitable for thermo labile materials.

Keywords: *Solubility Enhancement, bioavailability, poorly water soluble, Dissolution, solid dispersion,*

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1. INTRODUCTION:

Solubility is defined here as the concentration of the solute in a solution when equilibrium exists between the pure solute phase and the solution phase. At low concentrations, solubility is difficult to measure analytically, and at high concentrations, solubility is not an issue in the discovery process (Johnson and Zheng, 2006). Knowledge of the solubility of a drug in water can be critical in formulating products, developing analytical methods, and evaluating drug transport or distribution problems. The approaches presented in this chapter are ideal solution theory, regular solution theory, and the Hansen solubility approach. Of these three, the only one that was developed to describe solutions involving polar species was the Hansen approach. As the reader will discover, however, the Hansen approach is principally based on regular solution theory, which, in turn, was derived from ideal solution theory. Thus, one cannot consider the Hansen solubility approach without some

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration. In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration, which can detract from the drug's inherent efficacy. Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing small absorption window. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, one of the major current challenges of the Pharmaceutical industry is related to strategies that improve the water solubility of drugs. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects (Teo filo Vasconcelos et al., 2007).The lack of ability of a drug to go into solution is sometimes a more important limitation to its rate of absorption than its ability to permeate intestinal mucosa. For many drugs that cross the intestinal mucosa easily, the onset of drug levels will be dictated by the time required for the dosage form to release its contents, and for the drug to dissolve.

We may define a drug as 'poorly soluble' when its dissolution takes longer than the transit time past its absorptive sites, resulting in incomplete bioavailability. The aqueous solubility of a drug is a prime determinant of its dissolution rate and in the case of poorly soluble drugs (as defined above); the aqueous solubility is usually less than 100 µg/ ml. A further parameter that is useful for identifying 'poorly soluble' drugs is the dose: solubility ratio of the drug. The dose: solubility ratio can be defined as the volume of gastrointestinal fluids necessary to dissolve the administered dose. When this volume exceeds the volume of fluids available, one may anticipate incomplete bioavailability from solid oral dosage forms (Dressman and Horter, 2001).

2. DISSOLUTION

2.1 Introduction:

Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.

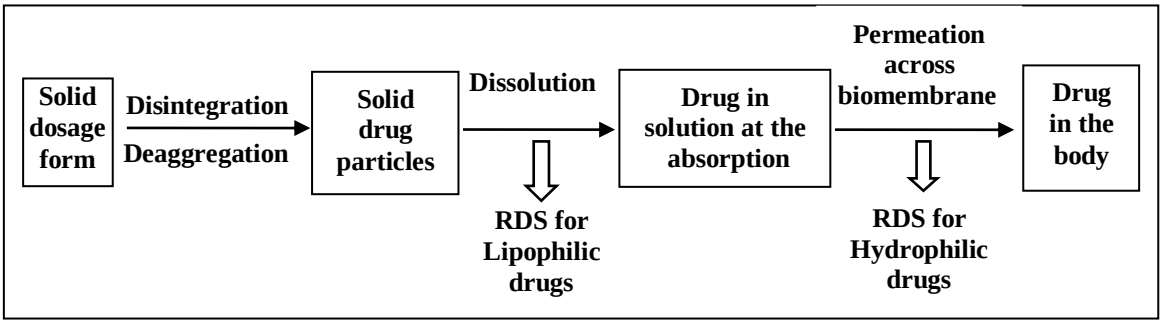

Figure 1.1: Two rate determining steps (RDS) in the absorption of drugs from orally administered formulations.

Frequently, dissolution is the limiting or rate controlling step in the absorption of drugs with low solubility because it is often the slowest of the various stages involved in the release of the drug from its dosage form and passage into systemic circulation.

Dissolution is a kinetic process and the rate of dissolution reflects the amount of drug dissolved over a given time period. The rate at which a solid dissolves in a solvent was proposed by Noyes and Whitney in 1897 and elaborated subsequently by other workers. The equation can be written as (Patrick JS, 2006):

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C) \qquad OR \qquad \frac{dC}{dt} = \frac{DS}{Vh}(C_s - C)$$

Where, M is the mass of solute dissolved in time t, dM/dt is the mass rate of dissolution (mass/time), D is the diffusion coefficient of the solute in solution, S is the surface area of the exposed solid, h is the thickness of the diffusion layer, Cs is the solubility of the solid (i.e., concentration of saturated solution of the compound at the surface of the solid and at the temperature of the experiment), and C is the concentration of solute in the bulk solution and at time t. The quantity dC/dt is the dissolution rate, and V is the volume of solution. In dissolution or mass transfer theory, it is assumed that an aqueous diffusion layer or stagnant liquid film of thickness h exist at the surface of a solid undergoing dissolution. The saturation solubility of a drug is a key factor in the Noyes and Whitney equation. The driving force for dissolution is the concentration gradient across the boundary layer (Patrick JS, 2006).

2.2. Different roles of In-vitro dissolution testing

- In the investigation of drug release mechanisms, especially for extended-release formulations.
- In formulation development to reach a predefined target release profile and robust drug release properties with respect to influence of physiological factors (e.g., pH and food)
- To generate supportive data for interpretation of bioavailability studies
- To validate the manufacturing processes
- In storage stability studies
- In Batch quality control
- As a surrogate for bioequivalence studies

3. SOLUBILITY:

31. Introduction:

Absolute Solubility or intrinsic solubility is defined as the maximum amount of solute dissolved under standard conditions of temperature, pressure, and pH.The simplest definition of solubility is that the solubility of a substance is the molarity of that substance (counting its entire solution species) in a solution that is at chemical equilibrium with an excess of the undissolved substance at constant temperature. The Biopharmaceutics Classification System (BCS) was introduced by the US Food and Drug Administration (FDA) to assess oral drug products. In this system, drugs are classified into four groups based on the ability of a given drug substance to permeate biological membranes and aqueous solubility (Wei-Qin and Hong, 2008).For a drug to be called “soluble,” the Food and Drug Administration (FDA) biopharmaceutical classification system (BCS) requires that the human dose of drug be soluble in 250 ml throughout the gastrointestinal pH range of 1–7.5. For drugs with moderate permeability, when the projected doses are about 1 mg/kg, the effects of different solubility of drugs can be roughly estimated as in Table 1.2 (Wei-Qin and Hong, 2008).

Table 1.1: Descriptive Terms of approximate Solubility as per IP 1996

Descriptive Term	**Approximate volume of solvent in milliliters per gram of solute**
Very soluble	Less than 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble or Practically Insoluble	More than 10,000

Table 1.2: Solubility data interpretation (Chemical Sciences, 2001)

Solubility (µg/ml)	Classification	Comments
≤ 20	Low	Will have solubility problems
20–65	Moderate	May have solubility problems
≥ 65	High	No solubility problem

Table 1.3: Classification of Effective Permeability (Chemical Sciences, 2001)

Effective Permeability (cm/s)	Classification	Comments
$\leq 0.1\times 10^{-6}$	Low	Will have permeability problems
$0.1–1\times 10^{-6}$	Moderate	May have permeability problems
$\geq 1\times 10^{-6}$	High	No permeability problem

Table 1.4: BCS Classification (Dressman JB, 2004)

Sr. No.	Classes	Parameter
1.	Class I	High soluble and High permeability
2.	Class II	Low soluble and High permeability
3.	Class III	High soluble and Low permeability
4.	Class IV	Low soluble and Low permeability

3.2. Approaches to improve the solubility or to increase the available surface area for dissolution of the poorly water soluble drugs.

I. Physical modifications

- Particle size modulation
  - Micronization
  - Nanosuspensions
- Modifications of the crystal habit
- Polymorphs
- Pseudopolymorphs (including solvates)
- Complexation/Solubilization
  - Use of surfactants
  - Use of cyclodextrins
- Drug dispersion in carriers
  - Eutectic mixtures
  - Solid dispersions (non-molecular)
  - Solid solutions

II. Chemical modification

- Soluble prodrugs
- Salts

The second approach of chemical modification has a number of drawbacks of being very expensive and time consuming, require repetition of clinical study and long time for regulatory aspects. Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drug. However, these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical. Moreover, the salts that are formed may convert back to their original acid or base forms and lead to aggregation in the gastrointestinal tract. Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced for very fine powders. To overcome these drawbacks, various other formulation strategies have been adopted including the use of cyclodextrins, nanoparticles, solid dispersions and permeation enhancers. Solid dispersions and cyclodextrin complexations are one of the most successful strategies to improve drug release profile of poorly water soluble drugs (Teo filo Vasconcelos et al., 2007).

Micronization:

The process involves reducing the size of the solid drug particles ranging from 1 to 10 microns commonly by spray drying or by use of air attrition method. Examples of drug whose bioavailability have been increased by micronization include griseofulvin and several steroidal and sulfa drugs. Micronization has several disadvantages; the most important disadvantage is limited opportunity to control important characteristics of final particles formed such as size, shape, morphology. Beside this micronization is a high energy process which causes disruptions in drug's crystal lattice.

Use of surfactants:

The surface active agents enhance dissolution rate primarily by promoting wetting and reducing the surface tension between liquid and particle surface. They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC the drug entrapped in the micelle structure fails to partition in the dissolution fluid. Non ionic surfactants like polysorbates are widely used. Surfactants have been added to solid dispersions to improve the dissolution rate of poorly water-soluble drugs (Aungst BJ et al., 1977). They have also been used to improve miscibility between drug and polymer or simply to inhibit drug crystallization during storage. In one study, the miscibility of griseofulvin was increased from 3%w/w to 40%w/w in PEG6000 by adding 5%w/w of sodium dodecyl sulfate (Wulff M, 1996).1.2.2.3. Use of salt formsThe aqueous solubility of a poorly soluble drug can be improved by the selection and preparation of an appropriate salt. The formulation scientist must then determine the resulting physicochemical properties and assess the sensitivity of the product to the environmental and chemical conditions likely to be encountered in handling and storage. In addition, formation of the salt may also reduce the toxicity and modify the pharmacological activity of the drug. Therefore, it is recommended that salt forms be screened early in the preformulation investigations to allow clinical evaluation of those candidates deemed suitable by virtue of their physicochemical properties (Steven HN, 2008).

Alteration in pH of the drug microenvironment:

The aqueous solubility of some drugs can be increased by adjusting the pH.

This can be achieved by addition of the suitable buffers to the formulation e.g. buffered aspirin tablets.

Use of metastable polymorphs:

Polymorphism describes the existence of a drug in two or more crystalline forms, each of which possesses a different space lattice arrangement but is chemically identical. There are two types of polymer:

1. Enantiomeric polymorph is the one which can be reversibly changed into another form by altering the temperature or pressure
2. Monomeric polymorph, which is unstable at all temperature and pressure.

Metastable polymorphs is more soluble than the stable polymorph of a drug that exhibits polymorphism e.g. B form of chloramphenicol palmitate is more water soluble than the A and the C forms (Paul BM and Michael JJ, 2008).

Pseudopolymorphs:

The stochiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates. The solvates can exist in different crystalline forms called as Pseudopolymorphs. When the solvent in association with the drug is water, the solvate is known as hydrate. Generally, the anhydrous form of a drug has greater aqueous solubility than the hydrates. On the other hand, the organic (nonaqueous) solvates have greater aqueous solubility than the nonsolvates for example the n-pentanol solvate of fludrocortisones and succinylsulfathiazole are more water soluble than their nonsolvated forms. In case of organic solvates, if the solvent is toxic, they are not of therapeutic use (Brahmankar and Jaiswal, 2006).

Selective adsorption on insoluble carriers:

A highly active adsorbent such as the inorganic clay like bentonite can enhance the dissolution rate of poorly water soluble drugs like indomethacin, griseofulvin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are: the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media (Brahmankar and Jaiswal, 2006).

Drug dispersion in carriers:

The drug can be dispersed in the hydrophilic carriers as:

- Eutectic mixtures
- Solid dispersions (non-molecular) or
- Solid solutions

A Solid solution is a binary system comprising of a solid solute molecularly dispersed in solid solvent. Since the two components crystallize together in a homogeneous one phase system, solid solution are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to the molecular level, solid solution show greater aqueous solubility and faster dissolution than eutectic and solid dispersions. They are generally prepared by fusion method whereby a physical mixture of a solute and solvent are melted together followed by rapid solidification. Such system, prepared by fusion is often called as melts (Vasanthavada M et al., 2008).

Eutectic mixture:

These systems are also prepared by fusion method. Eutectic melts differ from solid solution in that the

fused melt of solute-solvent show complete miscibility but negligible solid-solid solubility. When the eutectic mixture is exposed to water, the soluble carrier dissolved leaving the drug in a microcrystalline state which solubilize rapidly. The method however cannot be applied to the drugs which fail to crystallize from the mixed melt, thermolabile drugs and Carriers such as succinic acid that decompose at their melting point (Leuner and Dressman, 2000).

Solid dispersion:

These are generally prepared by solvent or co-precipitation method whereby both the guest solute and the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohols. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier. The basic difference between solid dispersion and solid solution is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter (Leuner and Dressman, 2000).

Molecular encapsulation with Cyclodextrin:

Cyclodextrins have been used extensively in pharmaceutical research and development, and there are currently over 30 marketed cyclodextrin-containing pharmaceutical products worldwide. Cyclodextrins possess a special ability to complex with drugs enabling them to increase solubility, reduce bitterness, enhance stability and decrease tissue irritation upon dosing. In addition, cyclodextrins have been utilized for a number of different drug delivery routes, and there has been a large amount of recent investigation into cyclodextrin polymers and cyclodextrins conjugated to other delivery vehicles e.g., Nanoparticles, liposomes (Carrier RL, 2007).

CYCLODEXTRIN COMPLEXATION

Definition:

A complex is a species of definite substrate (S)-to-ligand (L) stoichiometry that can be formed in an equilibrium process, in solution, and also may exist in the solid state (Connors KA, 1990).

Types of Complexes:

On the basis of the type of chemical bonding, complexes can generally be classified into two groups (Connors KA, 1990).

a) Coordination complexes: These complexes are formed by coordinate bonds in which a pair of electrons is, in some degree, transferred from one interactant to the other. The most important examples are the metal-ion coordination complexes between metal ions and bases.

b) Molecular Complexes: These species are formed by noncovalent interactions between the substrate and ligand. Among the kinds of complex species included in this class are small molecule-small molecule complexes, small molecule–macromolecule species, ion-pairs, dimers and other self-associated species, and inclusion complexes in which one of the molecules, the "host", forms or possesses a cavity into which it can admit a "guest" molecule. The classifications of complexes into various types are somewhat arbitrary.

Structures and physicochemical properties of CDs:

Cyclodextrins are cyclic oligosaccharides consisting of a variable number of glucose residues attached by α-(1, 4) linkages. The three most important of these are α-, β- and γ-CDs, which respectively consist of six, seven, and eight glucose units. Their conformation and numbering are presented in Figure 1.2 (Wei-Qin and Hong, 2008).

As a consequence of the $^4C_1$ conformation of the α-d-glucose residues and lack of free rotation about glycosidic bonds, the compounds are not perfectly cylindrical molecules, but are somewhat cone shaped, with all of the secondary hydroxyl groups situated at one end of the annulus and the primary hydroxyl groups at the other. The cavity is lined by a ring of hydrogen atoms (bonded to C-5), a ring of glucosidic oxygen atoms, and another ring of hydrogen atoms (bonded to C-3), thus making the cavity relatively apolar. The shape of the molecule is stabilized by hydrogen bonds between secondary hydroxyl groups of adjacent α-d-glucose residues. Figure 1.3 shows the physical shape of the CD molecule.

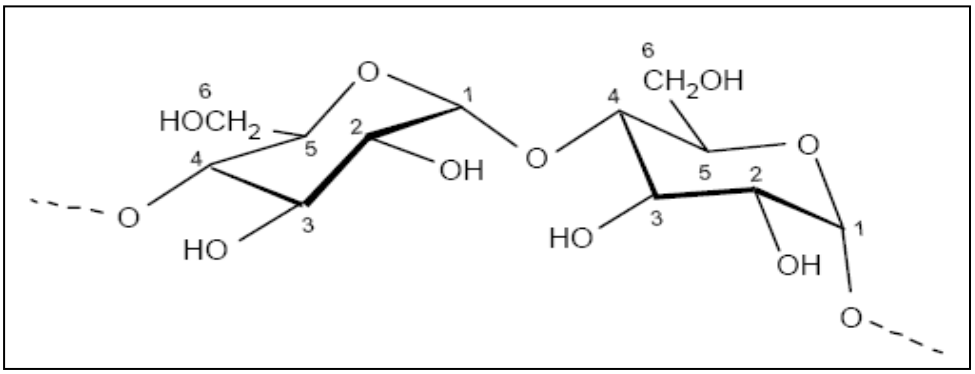

Figure 1.2: Conformation and numbering of the CDs (Wei-Qin and Hong, 2008)

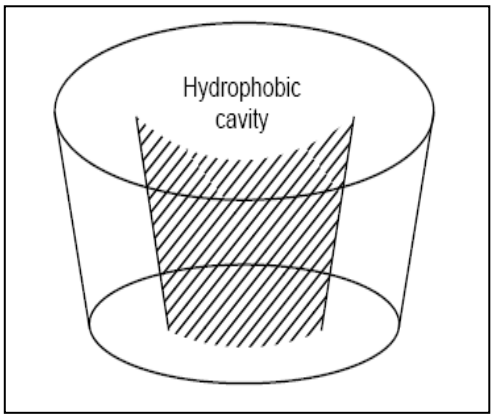

Figure 1.3: Physical shape of the CD molecule (Wei-Qin and Hong, 2008)

Solid preparations:

- Oral bioavailability of poor water-soluble drugs can be improved by enhancement of the dissolution rate and/or apparent solubility (via supersaturation in the gastrointestinal fluids).
- Physical stability of compounds in their metastable forms (such as amorphous) can be enhanced by the inhibition or prevention of crystal growth.
- Content uniformity of a small amount of a drug in bulky diluents can be ensured by an increase in dispersibility and fluidity.
- Shelf life of drugs can be extended by increasing their stability.

1. **Liquid preparations:**

- Solubility and/or stability of the drug in water can be improved.

2. **Suspensions and emulsions**

- Caking, creaming, and phase transitions can be suppressed by the protective sheath of CDs.
- Thixotropic nature of suspensions can be controlled.
- Physical stability of the dispersed system can be improved.

3. **Semisolid preparations:**

- Topical bioavailability can be improved by the enhanced release of a drug from ointment or suppository bases.
- Water-absorbing capacity of oleaginous and water-in-oil bases can be improved by hydrophilic CDs.

4. **Injectable Preparations:**

- Solubility and/or stability of the drug in water can be improved.
- Drug-induced hemolysis and muscular tissue damage can be reduced.
- Solubilized products can be prepared by freeze-drying CD complexes if needed for enhanced stability.
- Suspensions for parenteral use can be prepared by reducing the drug to a fine

powder containing the CD complex by use of ball milling.

4.SOLID DISPERSION:

- **Solid dispersion**— is a system in which the concentration of the drug is in excess of its saturation solubility at room temperature. The excess drug separates as solid phase, which is dispersed in the vehicle in crystalline or amorphous forms. The term refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the solid dispersion techniques. The dispersion of drug or drugs in solid diluent or diluents by traditional mechanical mixing is not included in this category (Godfried OA, 2001).
- **Solid solution—** is a system in which the drug remains dissolved in the vehicle in at room temperature and upon aging (Godfried OA, 2001).
- **Coevaporates—** Solid dispersion is prepared by solvent removal processes (Godfried OA, 2001).
- **Coprecipitates—** Solid dispersion is obtained when a precipitate of the drug and carrier is obtained by treating the solution containing the drug and the carrier with another solvent (Godfried OA, 2001).

The advantage of solid dispersion compared with conventional capsules and tablet formulations is shown in (Figure 1.6).

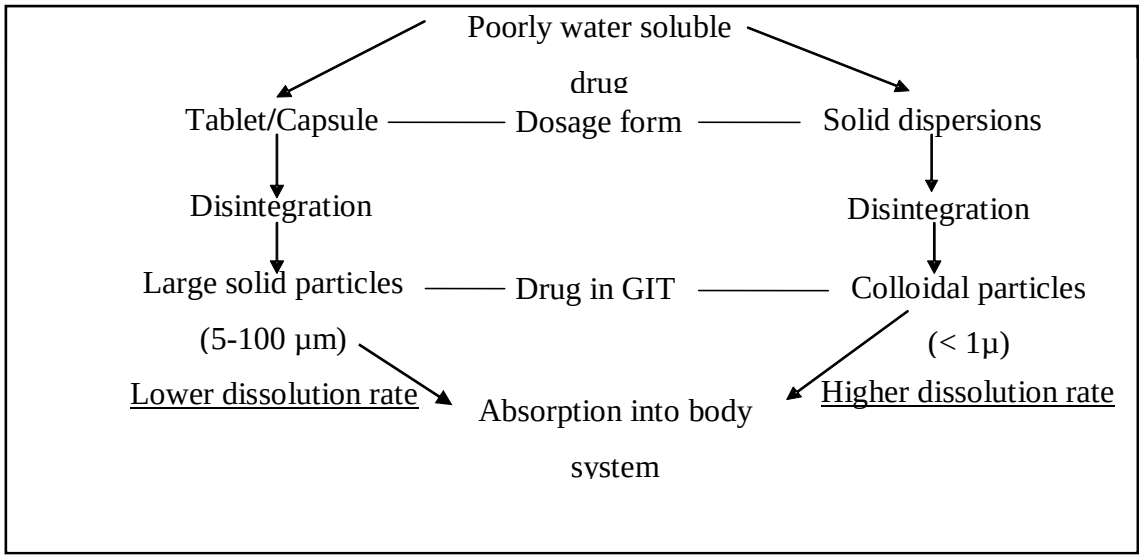

Figure 1.4: Schematic representation of the bioavailability enhancement of poorly water soluble drug by solid dispersion **technique (Serajuddin ATM, 1999)**

The mechanism suggested for enhanced solubility and rapid dissolution of dispersion is when the dispersion is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles. For conventional capsules and tablets, the dissolution rate is limited by size of primary particles formed after the disintegration of dosage form. In this case an average particle size of 5um is usually the lower limit, although higher particle size is preferred for ease of handling, formulation and manufacturing. On the other hand, if a solid dispersion is used, a portion of drug dissolves immediately to saturate the gastrointestinal fluid and excess drug precipitates out as colloidal particles or oily globules of submicron size. Because of such early promises in bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in pharmaceutical field (Leuner and Dressman, 2001).

4.1. The basic mechanisms responsible for increasing solubility of the drugs (Ford JL, 1986):

- Wetting of drug improved by direct contact of the drug with the hydrophilic matrix.
- Polymorphic forms.
- Reduced particle size or particle agglomeration.
- Formation of higher energy states.
- Formation of amorphous states-the drug has higher energy in the amorphous state

than crystalline state, through which the saturation concentration is increased.
- Soluble complex formation in microenvironment.
- Super saturation phenomenon

4.2. Methods of preparing Solid Dispersion:

Three basic methods used to prepare solid dispersions are:

- Melting (fusion) method
- Solvent evaporation method
- Fusion-solvent method

4.3 Melting (fusion) method

The drug and carrier should be miscible in the molten state is the basic requirement of this method. In this method physical mixture of drug and carrier is heated directly until it melts. The molten mixture is then cooled and solidified rapidly in an ice bath. The resulting solid mass is then crushed, pulverized and sieved. Several mechanisms could operate during the process of dispersion. If the drug has high degree of solubility in the carrier, the drug could remain dissolved in the solid state, yielding what is known as a solid solution. Particle size reduction under these conditions proceeds to the ultimate level leading to molecular dispersion of the drug of the drug in the carrier matrix. These systems show very high dissolution rates compared to control samples. If, on the other hand, the solubility of the drug in solid state is not so high, crystallites of the drug become dispersed in the matrix. Such system show only moderate increases in dissolution rates. A third mechanism is the conversion of a drug to an amorphous form in the presence of the matrix, again exhibiting different dissolution rates and solubility. Other factors that may play role include solubilizing effect conferred by the carrier itself, improved wetting or decreased hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties. The basic reason for increase in solubility is that, as the melt is rapidly quenched there is supersaturation of the drug where the drug molecules are arrested in solvent matrix by instantaneous solidification, usually rapid solidification is achieved by cooling on stainless-steel plates as it favors rapid heat loss.

Advantages:

1) The fusion process technically the less difficult method of preparing dispersions, provided the drug and carrier are miscible in the molten state.
2) The process is not time consuming.
3) The method is also advantageous for compounds, which do not undergo significant thermal degradation.

Limitations:

1) Thermal degradation, sublimation, and polymeric transformation, which can affect the physicochemical properties of the drug including its rate of dissolution
2) The temperature at which the dispersion solidifies affects crystallization rates and may alter both the size of the crystals and the hardness of the dispersion. This may result in tacky or glassy and unmanageable dispersions.
3) If the drug and carrier display a miscibility gap, there may be only moderate increase in dissolution rate.

However, various modifications are being done in the basic process due to the thermal instability and immiscibility. They are as follows (Leuner and Dressman, 2000):

1) Hot melt extrusion:

Drug carrier mix is typically processed with twin–screw extruder; the drug carrier mix is simultaneously melted, homogenized, extruded and shaped as tablets, granules, pellets, sheets or powders (Figure 1.7).

Advantage:

Drug carrier mix is only subjected to an elevated temperature for about 1 minute which enables drug that are somewhat thermo labile to be processed.

This method has already been used successfully to prepare Solid Dispersion of itraconazole and hydroxypropylmethylcellulose (HPMC), indomethacin, lacidipine, nefidipine, piroxicam, tobutamide and polyvinylpyrrolidone (PVP), itraconazole and HPMC, Eudragit E 100 or a mixture of Eudragit E 100-PVP vinyl acetate to improve solubility and dissolution rate of poor water soluble drugs.

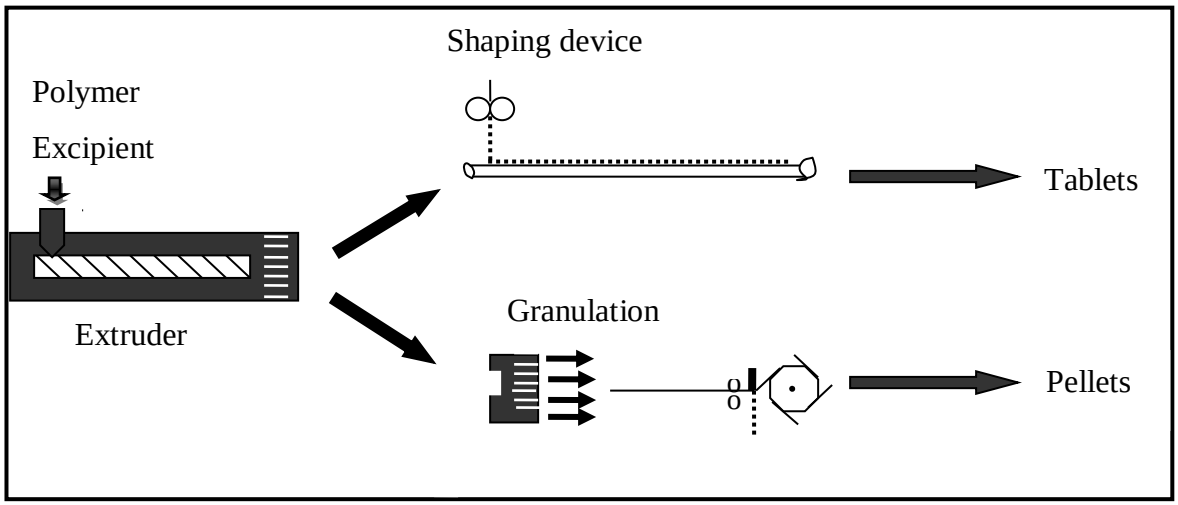

Figure 1.5: Scheme of hot melt extruder (Leuner and Dressman, 2000)

2) Hot-spin-melting:

A further alternative for processing thermolabile substances is by hot-spin-melting. Here, the drug and carrier are melted together over an extremely short time in a high speed mixer and, in the same apparatus, dispersed in air or an inert gas in a cooling tower. Some drugs that have been processed into solid dispersions using hot-spin-melting to date include testosterone, progesterone and dienogest.

3) Meltrex™

Meltrex™ is a patented solid dispersion manufacturing process, also on the basis of the melting process. The crucial elements in the Meltrex™ technology is the use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad temperature range. This process permits a reduced residence time of the drug in the extruder, allowing a continuous mass flow and avoiding thermal stress to the drug and excipients. Additionally, it is possible that the application of this technique to protect drugs susceptible to oxidation and hydrolysis by complete elimination of oxygen and moisture from the mixture.

4) Melt agglomeration

Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excipients, by adding the molten carrier to a heated mixture of drug and excipients, or by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor.

4.4 Solvent method

In this method both the guest molecule and the carrier are dissolved in common organic solvent followed by total removal of solvent to constant weight. Solid dispersions and solutions that are manufactured by the solvent evaporation method are described as the Coevaporates. An important prerequisite for the manufacture of solid dispersion using solvent method is that both the drug and the carrier should be sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods such as vacuum rotary dryer, freeze drying, spray drying etc. Temperature for solvent evaporation is usually in range of 23-65ºC. It must be remembered that when an organic solvent is to be removed, small variations in the conditions used can lead to quite large changes in product performance. Another point to consider is the importance of thoroughly removing all of the solvent, since most of the organic solvents used have toxicity issues.

Advantage:

1) The method is suitable for thermolabile materials.
2) Many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities.

Limitations:

1) High cost of processing.
2) Large quantity of organic solvent is required.
3) Difficulty in complete removal of the solvents.

4) Possible adverse effect of remaining solvent on stability of drug.
5) Selection of volatile common solvent.
6) Finding a suitable solvent that will dissolve both the drug and carrier is very difficult and sometimes impossible. This is because most of the carriers are hydrophilic whereas most of the drugs are hydrophobic organic substances. This may be further complicated by the fact that different polymorphic forms of the same drug may be obtained if different solvents are used.
7) Plasticization of some polymers such as PVP has occurred with the use of some solvents.
8) The ecological and subsequent economic problems associated with the use of organic polymers make solvent-based methods more and more problematic.

Differences in solvent evaporation processes are related to the solvent evaporation procedure, which usually include vacuum drying, heating of the mixture on a hot plate, slow evaporation of the solvent at low temperature, the use of a rotary evaporator, spray-drying, freeze-drying and the use of supercritical fluids (SCF), co-precipitation method, and Spin-coated films technique (Teo filo Vasconcelos, 2007).

1) Vacuum drying: Solvent is evaporated in vacuum at reduced pressure to avoid higher heating temperature. Also it is possible to remove the solvent traces more completely.

2) Heating on a hot plate: This is the simple method of solvent evaporation in which volatile solvent is removed by heating the mixture of drug and carrier dissolved in the solvent at constant temperature.

3) Use of a rotary evaporator: Rotary evaporator can be used to maintain constant temperature and a high level of vacuum during evaporation of the solvent. Also it is possible the recovery of the solvent from the condenser and the solvent vapors are not released in the environment.

4) Spray drying: Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Van Drooge et al. (2006) prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

5) Freeze-drying: The basic freeze-drying process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized.

6) Use of Supercritical Fluids (SCF): The use of SCF, substances existing as a single fluid phase above their critical temperature and critical pressure, is an efficient method in obtaining solid dispersions. It ensures a very fine dispersion of the hydrophobic drug in the hydrophilic carrier. Carbon dioxide (CO_2) is the most commonly used SCF because is chemically inert, non-toxic and nonflammable. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. The use of processes using SCF reduces particle size, residual solvent content, without any degradation, and often results in high yield.

7) Co-precipitation: Another common process is the co-precipitation method, in which a non-solvent is added dropwise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form microparticles. At the end, the resulted microparticle suspension is filtered and dried.

8) Spin-coated films technique: Spin-coated films is a new process to prepare solid dispersions by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped onto a clean substrate highly spinned. Solvent is evaporated during spinning. This process is indicated to moisture sensitive drugs since it is performed under dry conditions

4.5 Fusion-solvent method

In this method, a carrier(s) is/are melted and the drug(s) is/are incorporated in the form of solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need of solvent removal is eliminated. This method is particularly useful for drugs that have high melting points or that are thermolabile.

4.6Carriers used in Solid Dispersion:

Carriers used in Solid Dispersion includes Polyethylene glycol (PEG); Polyvinylpyrrolidone (PVP); Polyvinyl alcohol (PVA); crosspovidone

(PVP-CL); polvinylpyrrolidone-polyvinylacetate copolymer (PVPPVA); Cellulose derivatives such as Hydroxypropyl methylcellulose (HMPC), Hydroxypropyl cellulose (HPC), Carboxymethyl-ethyl cellulose (CMEC), Hydroxypropyl-methyl cellulose phthalate (HPMCP); Polyacrylates and polymethacrylates, Urea; Sugar such as mannitol, Sorbitol, Chitosan, etc.; polyols and their polymers; Emulsifiers e.g. Tween80, SLS, Bile salts and their derivatives, etc.; Organic acids and their derivatives e.g. Citric acid, succinic acid, nicotonamide, etc.; and Other carriers such as pentaerythritol, phospholipids, Collagel, etc. (Leuner and Dressman, 2000).

4.7 Characterization of solid dispersions:

Methods for the characterization of solid dispersions are as follows:

1) Dissolution testing
2) Thermoanalytical methods: differential thermoanalysis and hot stage microscopy
3) Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change
4) X-Ray diffraction
5) Spectroscopic methods, e.g. IR spectroscopy
6) Microscopic methods including polarization microscopy and scanning electron microscopy

Among these, the most important methods are Thermoanalytical, X-ray diffraction, Infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the solid dispersion, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. Due to the complex composition of these preparations, it is often difficult to delineate precisely between molecularly dispersed and not molecularly dispersed systems and different analytical methods may yield disparate results. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions. Thermoanalytical methods include all that examine a characteristic of the system as a function of temperature. Of these, differential scanning calorimetry (DSC) is the most highly regarded method (Leuner and Dressman, 2000).

Differential scanning calorimetry (DSC):

DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of fewer than 2% cannot generally be detected with DSC.

X-ray diffraction (XRD):

The principle behind X-ray diffraction is that when an X-ray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5±10% cannot generally be detected with XRD.

Fourier Transform Infrared Spectroscopy (FT-IR):

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not.

5. MULTICOMPONENT SOLID DISPERSION:

Ternary agents have been added to solid dispersion of two components either to enhance drug dissolution rate or to overcome manufacturing or stability issues. Surfactants have been added to solid dispersions to improve the dissolution rate of poorly water-soluble drugs (Aungst BJ, 1977**)**. They have also been used to improve miscibility between drug and polymer or

simply to inhibit drug crystallization during storage (Urbanetz NA, 2006). In one study, the miscibility of griseofulvin was increased from 3%w/w to 40%w/w in PEG6000 by adding 5%w/w of sodium dodecyl sulfate (SDS) (Wulff M, 1996). Plueronic F68 was used to increase the solid solubility and dissolution rate of nifedipine from its PEG-based solid dispersion (Mehta KA et al., 2002). Ternary agents in the form of plasticizers have been used in manufacturing of solid dispersions using hot-melt extrusion (HME) technique. These agents act by lowering the processing temperature needed to extrude drug–polymer mixture, thereby minimizing potential degradation. Phuong Ha LT et al. (2008) studied the microenvironmental pH (pH_M) and crystallinity of an ionizable drug, Telmisartan, in order to enhance its dissolution using alkalizers in PEG6000 based solid dispersions.

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