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Techniques used to Enhance Bioavailability of BCS Class II Drugs: A Review

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Abstract:
Traditionally, nearly 40% of the new chemical entities (NCEs) identified by pharmaceutical industry screening programs have failed to be developed because of poor water-solubility, which makes their formulation difficult or even impossible. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The various traditional and novel techniques that that can be used for solubility enhancement of BCS Class II drugs are briefly discussed in this article. The Traditional techniques that has been discussed in this article includes use of co-solvents, Hydrotropy, Micronization, change in dielectric constant of solvent, amorphous forms, chemical modification of drug, use of surfactants, inclusion complex, alteration of pH of solvent, use of hydrates or solvates, use of soluble prodrugs, application of ultrasonic waves, functional polymer technology, controlled precipitation technology, evaporative precipitation in aqueous solution, use of precipitation inhibitors, solvent deposition, precipitation, selective adsorption on insoluble carriers. Novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are size reduction technologies, lipid based delivery system, micellar technologies, porous micro particle technology. Solid Dispersion Technique and various types of solid dispersion systems have also been explained briefly.

Keywords: NCE, Amorphous state, characterization, dissolution enhancement.

Introduction

Although the oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption due to poor solubility of drugs resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. 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[1]. The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature[2]. In the other words the solubility can also define as the ability of one substance to form a solution with another substance[3]. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs[1,2,3]. Definition for different solubility terms are given in Table 1.

Table 1: Definition of Solubility (I.P.1996)

Definition	Parts of solvents required for one part of solute (in ml)
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

Although the oral route of drug administration is the most common and preferred method of

delivery due to convenience and ease of ingestion, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption due to poor solubility of drugs resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route [4].

FACTORS AFFECTING SOLUBILITY

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system[5].

Particle size:

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be explained as per the following equation[6]. Where, **S** is the solubility of infinitely large particles, **S** is the solubility of fine particles, **V** is molar volume, **G** is the surface tension of the solid, **R** is the radius of the fine particle.

Temperature:

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature[7]. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases[8].

Pressure:

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility[8].

Nature of the solute and solvent:

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their nature[8].

Molecular size:

The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent[9].

Polarity:

Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction[9].

Polymorphs:

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric

arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell.The capacity for a substance to crystallize in more than one crystalline form is polymorphism[10].

Bioavailability: [FDA CDER 2004]

"Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action"[5].

The bioavailability of a drug is controlled by three principal factors[6]. These variants are namely,

- Rate and extent of release of the drug from the dosage form
- Subsequent absorption from the solution state
- Biotransformation during the process of absorption

According to BCS[7], a drug on the basis of these solubility and permeability characteristics can be classified in one of the four possible categories as indicated in Table 2.

Table 2: Classification of drugs using Biopharmaceutical

BCS Class	Solubility / permeability	Problems
Class I	High solubility High permeability	Enzymatic degradation, gut wall efflux
Class II	Low solubility High permeability	Solubilization and bioavailability
Class III	High solubility Low permeability	Enzymatic degradation, gut wall efflux, Bioavailability
Class IV	Low solubility Low permeability	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

A Class II drug will typically exhibit dissolution rate limited absorption and a Class IV drug will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research focus on improving the oral bioavailability of an API [(4)].

These are:

- Enhancing solubility and dissolution rate of poorly water-soluble drugs
- Enhancing permeability of poorly permeable drugs

In this article, the various techniques that that can be used for solubility enhancement of

BCS Class II drugs are discussed in this article with emphasis on the solid dispersion technique and its application. Formulation of solid dispersion in water-soluble carriers has been widely researched over the past four decades for solubility and related bioavailability enhancement. Despite 40 years of active research, there has not been much products in market based on this technique. The main reason for this being stability and scale up problems associated with this method, as reported by several authors.

Solubility Enhancement of BCS Class II Drugs:

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized in three basic approaches:

1. Traditional Techniques
2. Newer and Novel Techniques
3. Solid Dispersion Technique

1. TRADITIONAL TECHNIQUES:

Traditional techniques includes

- Use of co-solvents
- Hydrotropy
- Micronization
- Change in dielectric constant of solvent
- Amorphous forms
- Chemical modification of drug
- Use of surfactants
- Inclusion complex or clathrates

- Alteration of pH of solvent
- Use of hydrates or solvates, use of soluble prodrugs
- Application of ultrasonic waves
- Functional polymer technology
- Controlled precipitation technology
- Evaporative precipitation in aqueous solution
- Use of precipitation inhibitors
- Solvent deposition, precipitation
- Selective adsorption on insoluble carriers.

Use of Co-Solvents

The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a non-polar drug. This process is known as cosolvency and the solvents used in combination to increase the solubility of the drugs are known as cosolvents. The cosolvent system works by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute. It is also commonly referred to as solvent blending. Cosolvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols can be used. Ternary diagrams are used to visualize where maximum solubility occurs when more than one solvent is used[8,9].

Hydrotropy Method

Hydrotropy is a solubilization process whereby addition of large amounts of a second solute (Hydrotropic agents) results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water results in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "Hydrotropism". The solubility of rofecoxib was enhanced by using hydrotropes such as urea and nicotinamide [10].

Micronization

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods such as fluid energy mill, jet mill, rotor stator colloid mill etc. The process is also called as "Micromilling". Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Micronization of drug is not preferred because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution. Figure 2 depicts the increase in window of absorption of a drug by micronization [11].

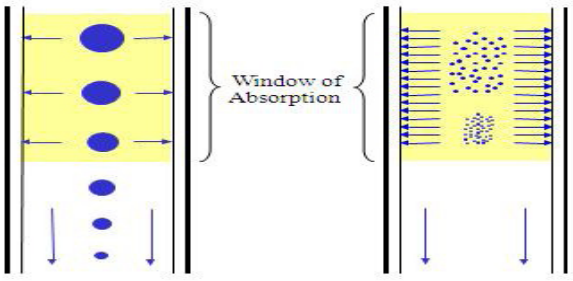

Fig. 2: Effect of Micronization on Window of Absorption

The addition of a cosolvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect a substance on the energy needed to separate two oppositely charged bodies. The

energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium[12].

Amorphous forms

In amorphous forms atoms or molecules are randomly placed and have higher thermodynamic energy than corresponding crystalline forms. Solubility as well as dissolution rates are generally greater.

Chemical modification of drug

By the addition of polar groups like carboxylic acids, ketones and amines, solubility is increased by increasing hydrogen bonding and the interaction with water[12].

Use of Surfactants

Surfactants are amphiphilic in nature having a polar end (the circular head) and non-polar end (the tail). When a surfactant such as tween-80, sodium lauryl sulphate is placed in water, it will form micelles. A non polar drug will partition into the hydrophobic core of the micelle and the polar tail will solubilize the complex. This has been illustrated by solubilization and wetting effects of bile salts on the dissolution of steroids[13].

Inclusion complex/clathrates

Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. These complexes can be prepared with ß-cyclodextrin (ß-CD) and HP-ß-CD; the required quantity of ß-CD is weighed and water added to get tough consistency. To the mass, weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for one hour and then completely dried in hot air oven at 60 0C for 2 hours. The dried mass is sieved through mesh no.120[14].

Alteration of ph of solvents

The pH of solvent when reduced causes solubility enhancement. A combined effect of pH and complexation on solubilization is also synergistic in nature. It was attempted to enhance dissolution of gliclazide using pH change approach[15].

Use of Hydrates or Solvates

A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts, commonly referred to as "Solvate", and is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as "Hydrate". A compound not containing any water within its crystal structure is termed "Anhydrous". Aqueous solubilities of anhydrous forms are higher than the hydrate forms[16].

Use of Soluble Prodrugs

The physicochemical properties of the drugs are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. The pro-drug approach has been successfully used to improve the water solubility of corticosteroids, vitamins and benzodiazepines. Enhancement of rate of dissolution of allopurinol was successfully achieved by prodrug formation[17].

Application of Ultrasonic Waves

Solubility can be increased by the use of ultrasonic vibrators. An oscillator of high frequency (100-500 KHz) is used and the device is known as "Pohlman whistle"[12].

Functional Polymer Technology

Functional polymers enhance the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which

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contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, "Resinate", can be formulated as a suspension, dry powder or tablet. The resins are insoluble and not absorbed into the body and the drug is released from resinate on exposure to the physiological fluids[12].

Controlled Precipitation Technology

In this process, the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals. The stabilizers control particle growth and enhance the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer. For e.g. nanomorph, a patented technology by Solids for controlled crystallization of drugs.

Evaporative Precipitation in Aqueous Solution (EPAS)

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvents boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and aqueous solution to optimize particle formation and solubilization. The solubility of danazol was enhanced by this technique[18].

Use of Precipitation Inhibitors

A significant increase in free drug concentration above equilibrium solubility results in super-saturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc. which act by one or more of the following mechanisms

- Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs.
- Provide a stearic barrier to drug molecules and inhibit crystallization through specific intermolecular interaction on growing crystal surfaces.
- Adsorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals

Solvent Deposition

In this method, the poorly aqueous soluble drugs is dissolved in an organic solvent like alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose followed by evaporation of solvent[19]. Enhancement of dissolution rate of piroxicam using liquisolid compacts is an example illustrating this technology[20]. The dissolution rate of a poorly soluble drug indomethacin was enhanced using liquisolid compacts[21].

Precipitation

In this method, the poorly aqueous soluble drug is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as "Hydrosol" [22]. Hydrosols are colloidal aqueous suspensions containing drug nanoparticles of poorly water-soluble drugs for intravenous administration. They are prepared by a precipitation process as the drug solution is mixed with a relatively high volume of water (96–98% water after mixing) in the presence of stabilizing agents such as poloxamer and modified gelatins, which act as "short term

stabilizers"[23]. After precipitation, the amorphous hydrosol is stable for approximately 60 min because of the stabilizers and the high amount of non-solvent. After this time, the drug crystallizes. Because the clouding correlates with the particle size, crystallization and particle growth can be observed by a steep increase of absorbance at a wavelength where the drug substance does not absorb. Thus, for durable stabilizing the amorphous nanosized drug, the hydrosol is immediately spray-dried with excipients such as lactose or mannitol before crystallization occurs. Before use, the preparations are reconstituted with water. Hydrosols contain the drug in a particle size of approximately 200 nm and are thus suitable for parenteral application. An example is cyclosporin, which can be formed as a hydrosol (ratio drug: gelatin = 1: 20).

2. NEWER AND NOVEL TECHNIQUES:

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are

- Size reduction technologies
- Nanoparticle Technology
- Nanocrystal Technology
- Nanosuspension
- Cryogenic Technology
- Supercritical Technology
- Lipid based delivery system
- Microemulsion Technology
- Self Dispersing Lipid Formulation (SDLF)
- Micellar technologies
- Mixed Micelle
- Polymeric Micelle
- Porous Microparticle technology

Size Reduction Technologies

Nanoformulations are one of the more complex formulations. Not only must the drug particles be rendered into nanosized but they must also be stabilized and formulated rigorously to retain the nature and properties of the nanoparticles[24,25].

Lipid based delivery system

Lipid-based formulations have been shown to enhance oral absorption of lipophilic drugs[26].

Microremulsion Technology

Microemulsions are thermodynamically stable, isotropically clear dispersions of two immiscible liquids stabilized by interfacial films of surface-active molecules. The microemulsions are formed by simple agitation of oil, water, surfactant and co-surfactant. The co-surfactant together with the surfactant reduces the interfacial tension to very low and even transient negative values[27,28].

Self Dispersing Lipid Formulation (SDLF)

The SDLFs contain oil and a surfactant mixture into which the drug is incorporated.

They emulsify when mixed with aqueous environment[29].

Micellar Technologies

Mixed Micelles

In general, amphiphilic, ionic, anionic or ampholytic molecules, which are able to decrease the surface tension of a solvent, arrange in micelles above a certain critical concentration. Micelle formation can only occur above a certain solute concentration, the critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT) [30]. Mixed micelle formation Process is shown in Figure 3.

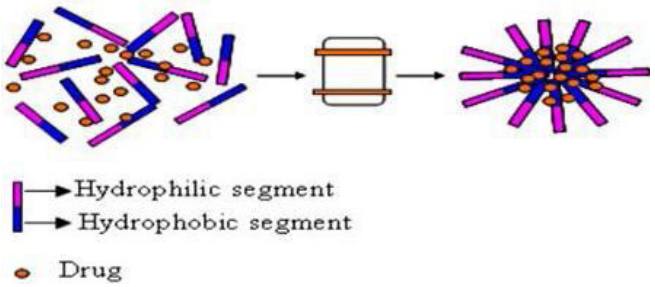

Fig. 3: Mixed Micelle Formation Process

Polymeric Micelles

Amphiphilic polymers assemble into nanoscopic supramolecular core-shell structures, termed polymeric micelles. The block copolymers used for formation of polymeric micelles are Pluronics®, poly (ethylene glycol) (PEG)-phospholipid conjugates, PEG-b-poly (ester), and PEG-bpoly (L-amino acids) The polymeric and nonpolymeric micelles are shown in Figure 4.

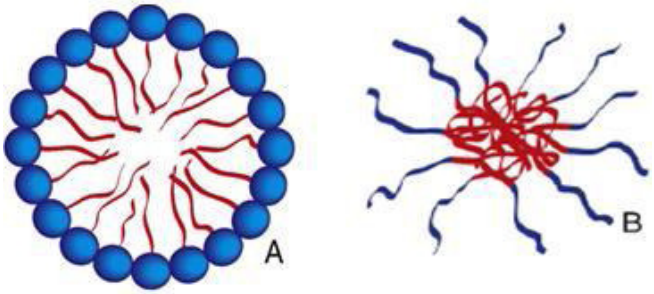

Fig. 4: (A) Micelle (non-polymeric) composed of amphiphilic surfactants and
(B) Polymeric micelle composed of amphiphilic block copolymers

Porous Microparticle Technology

The poorly water soluble drug is embedded in microparticles having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles. This is the core technology applied as HDDS™ (Hydrophobic Drug Delivery System).

3. Solid Dispersion System

Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" [31]. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

Types of Solid Dispersion System

Based on their molecular arrangement, six different types of solid dispersions can be distinguished [6, 31, 32]. They are described below in Table 3.

Table 3: Types of Solid Dispersion[4]

S. No.	Types of Solid dispersion	Matrix *	Drug **	No. of phases	Remarks	References
I	Eutectics	C	C	2	First type of solid dispersion prepared	31
II	Amorphous precipitations in crystalline carrier	C	A	2	Rarely encountered	33, 34
III (a)	Solid solution Continuous solid solutions	C	M	1	Miscible at all compositions, never prepared	35
(b)	Discontinuous solid solutions	C	M	2	Partially miscible, two phases even though drug is molecularly dispersed	32
(c)	Substitutional solid solutions	C	M	1 or 2	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter	36
(d)	Interstitial solid solutions	C	M	2	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Example: Drug in helical interstitial spaces of PEG.	31
IV	Glass suspension	A	C	2	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	31
V	Glass suspension	A	A	2	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	31
VI	Glass solution	A	M	1	Require miscibility, complex formation or upon fast cooling OR evaporation during preparation e.g. PVP	37

*A: matrix in the amorphous state, C: matrix in the crystalline state, ** A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particle in the matrix, M: drug molecularly dispersed throughout the matrix.

Simple Eutectic Mixture

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug[32,38]. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability. Figure 5 depicts the phase diagram for eutectic system.

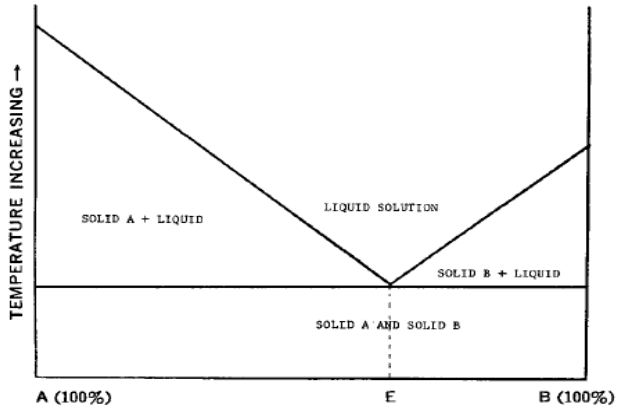

Fig. 5: Phase diagram for a eutectic system31

Solid Solution Continuous Solid Solution

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding

strength between the molecules of each of the individual components.

Discontinuous Solid Solution

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Below a certain temperature, the mutual solubilities of the two components start to decrease. It has been suggested by Goldberg that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5% (35). Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g.

Substitutional Crystalline Solid Solution

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial Crystalline Solid Solution

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. To occupy interstitial space, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent[39].

Amorphous Solid Solution

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, it was the first attempt to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose[39].

Glass Solution and Glass Suspension

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (Tg). On heating, it softens progressively and continuously without a sharp melting point[31].

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