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Review Article

**Solid Dispersions as Strategy to Improve Oral Bioavailability of
Poor Water Soluble Drugs**

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ABSTRACT

Currently only 8% of new drug candidates have both high solubility and permeability. More than 60% of potential drug products suffer from poor water solubility. This frequently results in potentially important products not reaching the market or not achieving their full potential. Experience with solid dispersions over the last 20-30 years indicates that this is a very fruitful approach to improving the release rate and oral bioavailability of poorly water soluble drugs. So this article highlights technology various approaches for the preparation of solid dispersion, technology involved, detail description of poorly water soluble drugs & carriers.

Keywords: Solid solution, Solid dispersion, Dissolution, Carriers.

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of both, drug and carrier, and depending on their ratio, a solid solution or a solid suspension of the drug in the carrier material may be formed. The mechanisms involved in solubility and dissolution rate enhancement include transformation of stable modifications into less stable ones or even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wettability and solubility of the drug by the carrier material. However, if a solid dispersion represents a thermodynamic. Especially for substances according to the Biopharmaceutics Classification System, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. mically unstable system, it is prone to convert into amore stable state. Especially supersaturated solid solutions of the drug are subjected to recrystallization phenomena solid dispersion refers to a group of solid products consisting of at least two different components,

generally a hydrophilic matrix and a hydrophobic drug.^{1,2}

Process of solubilization

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.³
Fig No.1

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 system⁴.

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 described by⁵

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

S is the solubility of infinitely large particles

S_0 is the solubility of fine particles

V is molar volume

R is the radius of the fine particle

T absolute temp in degree kelvin

R universal gas constant

Temperature

Generally, an increase in the temperature of the solution increases the solubility of a solid solute.

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 solubility⁶.

Nature of the solute and solvent

While only 1 gram of lead 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 solubility's of these two substances is the result of differences in their natures⁷.

Molecular size

The larger the molecule or the higher its molecular weight the less soluble 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 solvent³. Table No.1

Polarity

Polarity of the solute and solvent molecules will affect the solubility. 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. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces.

Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of

both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities².

Definition of solid dispersion

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 or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Solid dispersions should preferably be designated according to their molecular arrangement.

Types of Solid Dispersion

I. Simple eutectic mixtures

II. Solid solutions

III. Glass solution and suspension

IV. Amorphous precipitations in a crystalline Carrier

I. Simple eutectic mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solidsolid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus the X-ray diffraction pattern of a eutectic constitutes an additive composite of two components.⁴ Fig No.2. Ex. Chloremphenicol-urea; Paracetamol-urea; Griseofulvin & Tolbutamide-PEG 2000.

T A – M.P. of solid A

T B – M.P. of solid B

TE – Eutectic Point

II. Solid solutions

In a solid solution the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in the solid state in all proportions. Fig No.3 and 4

III. Glass solutions and suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated

particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points, instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. Fig No.5

IV. Amorphous precipitations in a crystalline carrier

The difference between this group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter. Sulfathiazole was precipitated in the amorphous form in crystalline urea.⁷

Selection of carriers

The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature. should generally have the following characteristics:

- Readily soluble in water and in gastrointestinal fluids.
- Physiologically inert.
- Melting point not much higher than that of the drug.
- Thermal stability at melting temperature.
- Relatively low vapour pressure, and
- Should have high molecular weight to fulfill the requirement of the host.
- They should be nontoxic.

Polyethylene glycol 20000 (PEG 20,000), P.E.G 6000, P.E.G 4000, urea, Polyvinyl pyrrolidone, desoxycholic acid, citric acid, pentaerythritol, sugar etc. are some of the carrier which have been generally used. Table No.2

Common methods used for preparation of solid dispersion

- Fusion method.
- Solvent method.
- Melting solvent method.
- Solvent-deposition method.
- Melt agglomeration process.
- Solvent evaporation method

- Crystallization in aqueous solvent
- Use of adsorbent
- Kneading Method
- Supercritical Fluid Method
- Lyophilization method
- Extruding method
- Spray drying
- Electrospinning

Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method.

Advantages

- The main advantage of direct melting method is its simplicity and economy.
- In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

Disadvantages

- Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature.
- When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion.
- This can be prevented by using surfactants
- Secondly, a problem can arise during cooling when the drug-matrix miscibility changes.
- In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions.
- Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug^{6&8}

Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces

two challenges. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution and solid dispersions are obtained.

Advantages

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Disadvantages

The disadvantages include the higher cost of preparation, the difficulty in completely removing liquid solvent and possible adverse effect of the supposed negligible amount of the solvent on the chemical stability of drug are some of the disadvantages of this method⁸.

Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide, which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO₂ is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO₂ is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution.

Advantages

- The supercritical anti-solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.
- The general term for this process is precipitation with compressed anti-oven. More specific examples of PCA are Supercritical Anti Solvent when supercritical CO₂ is used, or Aerosol Solvent Extraction System, and Solution Enhanced Dispersion by Supercritical fluids.
- However, as with the other solvent techniques, the critical step in these precipitation techniques might be the dissolution of drug and matrix in one solution. The use of water is limited,

because the water solubility in compressed CO₂ is limited.

Disadvantages

- Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix which are more in cost^{4,5}.

Melting solvent method

In this method drug is first dissolved in a suitable liquid solvent. Solution is then incorporated directly into the melt of polyethylene glycol obtainable below 70°C, without removing the liquid solvent. It has been shown that 5-10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

Advantages

- In this method that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Disadvantages

- As the practical point of view, the melting - solvent method is limited to drugs with a low therapeutic dose, e.g., below 50mg.
- Moreover, it is possible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol.
- The feasibility of the method has been demonstrated on spironolactone polyethylene glycol 6000 system⁶.

Lyophilization Techniques

Lyophilization has been thought of a molecular mixing technique. The drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Melt agglomeration method

This technique has been used to prepare where in the binder acts as a carrier. In addition, are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer³⁵. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. In addition the melt in procedure also results in homogenous

distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion. The mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles⁴

Electrospinning

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through millimeter scale nozzles. This process involves the application of a strong electrostatic field over a conductive capillary attached to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical value, a charged polymer jet is ejected from the apex of the cone. The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried.

Advantages

- This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine
- Process is simplest, the cheapest.
- This technique can be utilized for the preparation of solid dispersions in future.

Disadvantages

- Less economical for all the drugs and carriers^{3,7}.

Characterization of solid dispersion system

Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture.

- Thermal analysis.
- Spectroscopic method.
- X-ray diffraction method.
- Dissolution rate method.
- Microscopic method.
- Thermodynamic method.
- Modulated temperature differential scanning calorimetry
- Environmental scanning electron microscopy
- Dissolution testing

Thermal Analysis Techniques

Thermal analysis comprises a group of techniques in which a physical property of a substance is measured as a function of temperature, while the substance is subjected to a controlled temperature programme. In differential thermal analysis, the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat treatments. The related technique of differential scanning calorimetry relies on difference in energy required to maintain the sample and reference at an identical temperature. Length or volume changes that occur on subjecting materials to heat treatment are detected in dilatometry; X-ray or neutron diffraction can also be used to measure dimensional changes. Both thermogravimetry and evolved gas analysis are techniques which rely on samples which decompose at elevated temperatures. The former monitors changes in the mass of the specimen on heating, whereas the latter is based on the gases evolved on heating the sample. Electrical conductivity measurements can be related to changes in the defect density of materials or to study phase transitions.

X-ray crystallography

X-ray crystallography is a method of determining the arrangement of atoms within a crystal, in which a beam of X-rays strikes a crystal and diffracts into many specific directions. From the angles and intensities of these diffracted beams, a crystallographer can produce a three-dimensional picture of the density of electrons within the crystal. From this electron density, the mean positions of the atoms in the crystal can be determined, as well as their chemical bonds, their disorder and various other information. Since many materials can form well as various inorganic, organic and biological molecules X-ray crystallography has been fundamental in the development of many scientific fields. In its first decades of use, this method determined the size of atoms, the lengths and types of chemical bonds, and the atomic-scale differences among various materials, especially minerals and alloys².

Spectroscopy

Spectroscopy was originally the study of the interaction between radiation and matter as a function of wavelength (λ). In fact, historically, spectroscopy referred to the use of visible light dispersed according to its wavelength, e.g. by a prism. Later the concept was expanded greatly to comprise any measurement of a quantity as a function of either wavelength or frequency. Thus it also can refer to a response to an alternating field or varying frequency (ν). A further extension of the scope of the definition added energy

(E) as a variable, once the very close relationship for photons was realized (h is the Planck constant)⁹.

Modulated temperature differential scanning calorimetry (MDSC)

All spray-dried samples and starting materials were analyzed in triplicate. MDSC measurements performed using DSC equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50 ml/min was used to purge the DSC cell. Open aluminum pans were used for all measurements. The mass of the empty sample pan and the reference pan was taken into account for the calculation of the heat flow. The sample mass varied from 1 to 6 mg. The enthalpic response was calibrated with an Indium standard and the temperature scale was calibrated with Octadecane, Indium and Tin. The heat capacity signal was calibrated by comparing the response of a sapphire disk with the equivalent literature value at 80 °C.

Environmental scanning electron microscopy

The morphology of the spray-dried ternary solid dispersions can be characterized with a Philips XL30 ESEM FEG environmental scanning electron microscope operating at 25 kV accelerating voltage and a vacuum. The samples were sprayed on double-sided carbon tape that was mounted on conventional SEM stubs.

Dissolution testing

Dissolution experiments can be performed in triplicate on the binary and ternary dispersions. The tests were performed according to the USP 24 method 2 in a Hanson SR8plus dissolution apparatus.

To simulate the dissolution of a weak basic compound in the stomach, 500 mL of simulated gastric fluid without pepsin was used as dissolution medium at a temperature of 37 °C and a paddle speed of 100 rpm. An amount of the spray-dried powders, corresponding to drug dose of 100 mg, was added to the dissolution medium. Five-milliliter samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, and 120 min. These samples were filtered with 0.45 µm Teflon filters. The first 2 ml were discarded. The remainder was diluted with methanol (1/2) to avoid precipitation, and analyzed with HPLC.

Applications of solid dispersion

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used:

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds

Table 1: Definition Parts of solvent required for one part of solute³

Definition	Parts of solvent required for one part of solute
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

Table 2: Classification of carriers³

Category	Examples of Carriers
Sugars	Dextrose, sucrose, lactose, sorbitol, maltose, mannitol, galactose
Acids	Citric acids, Succinic Acids
Polymeric Material	Povidone, Polyethylene glycol, hydroxyl propyl methyl cellulose, Methyl cellulose, hydroxyl ethyl cellulose, pectine, galactomannan
Insoluble or enteric polymers	Hydroxypropylmethyl cellulose, phthalate, Eudragit RS
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texofor AIP, Deoxycholic acid, Tweens, Spans Miscellaneous Urea, Hydroxyalkylxanthins, Urethans

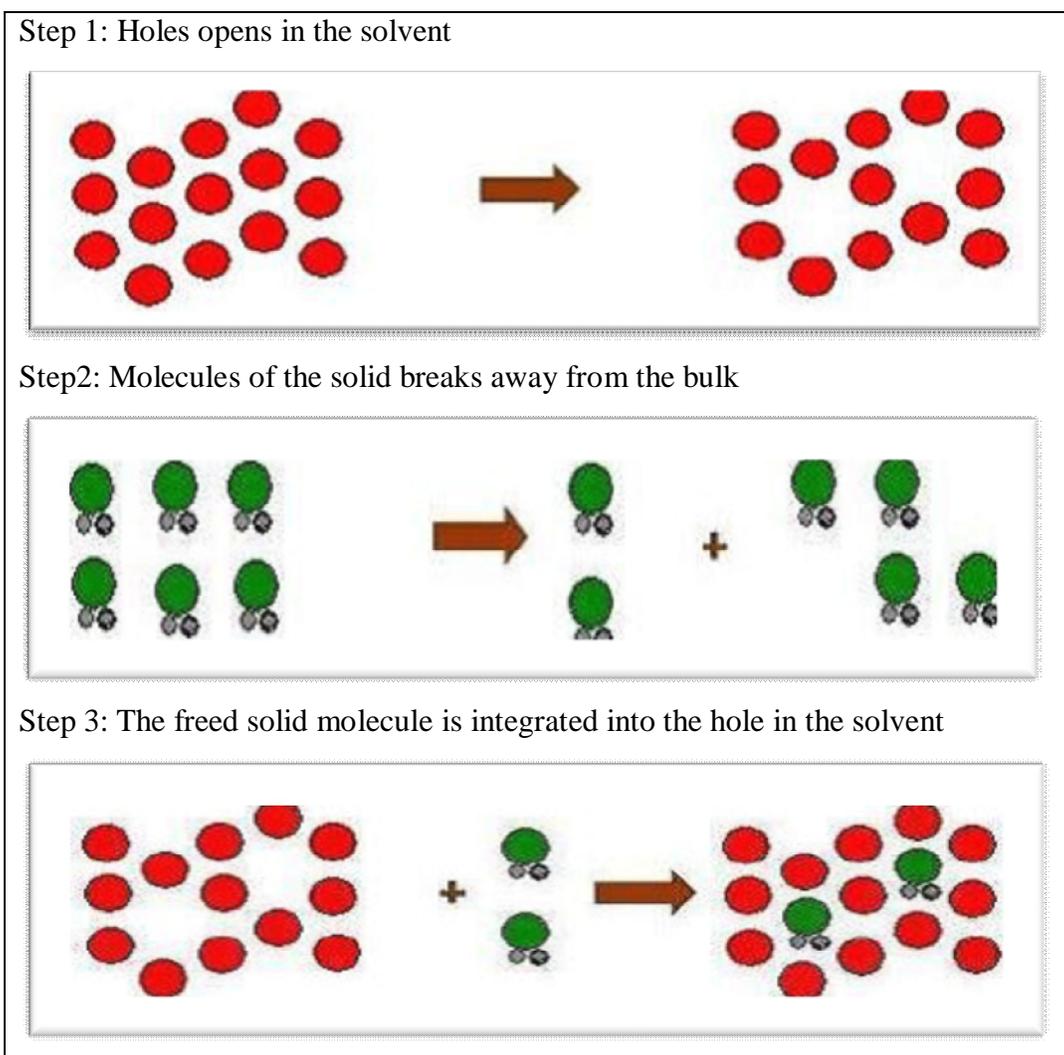


Fig. 1: Process of solubilization

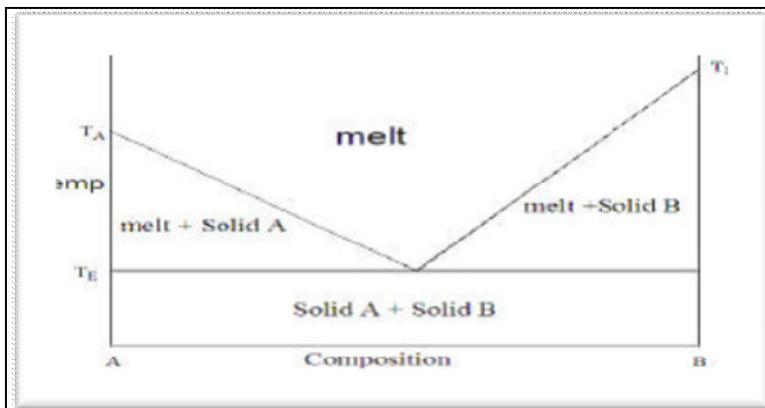


Fig. 2: Simple eutectic mixtures

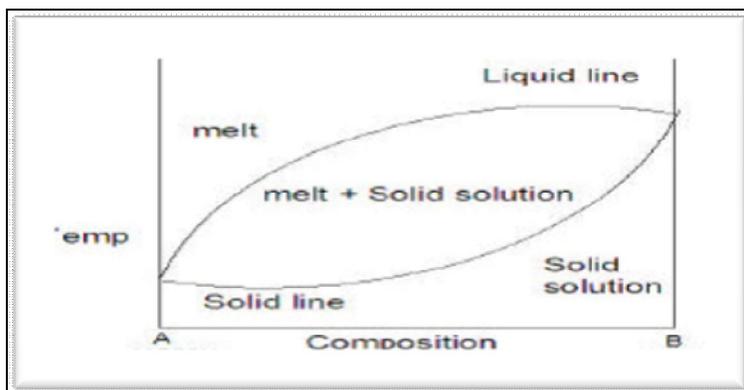


Fig. 3: Continuous Solid Solution – Two solids miscible in solid state in all proportions

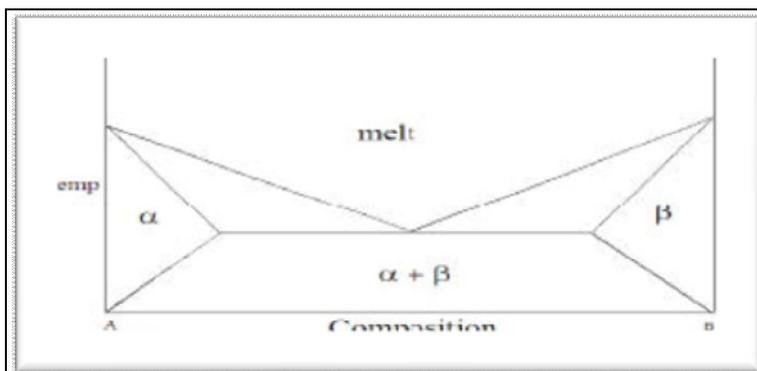
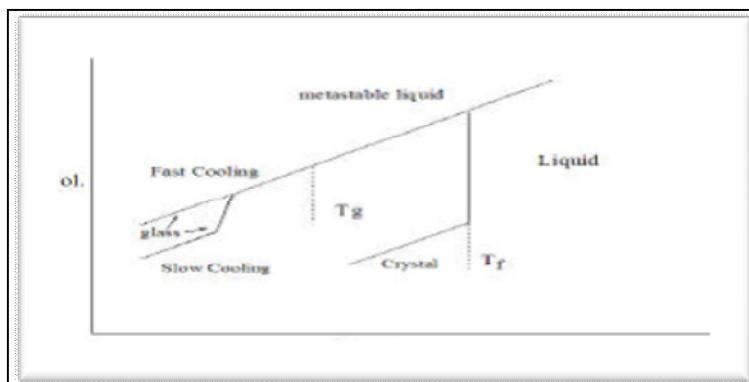


Fig. 4: Discontinuous Solid Solutions – Exist at extremes of composition



T_g – glass transition temp.

T_f – M.P. of material

Fig. 5: Glass solutions and suspensions

CONCLUSION

Experience with solid dispersions over the last 20-30 years indicates that this is a very fruitful approach to improving the release rate and oral bioavailability of poorly water soluble drugs and the availability of a wide variety of polymers that are themselves poorly soluble or which swell under aqueous conditions suggests that solid dispersions have tremendous potential in the area of controlled release dosage forms. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs. Successful development of solid dispersion system for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface active carriers and self emulsifying carriers.

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