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Review Article

TO ENHANCE THE SOLUBILITY OF POORLY WATER SOLUBLE DRUGS BY USING SOLID DISPERSION: A REVIEW

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Abstract: Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. The solubility behaviour of drug is one of the most challenging aspects in formulation development. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. Thus a greater understanding of dissolution and absorption behaviour of drug with low aqueous solubility is required to successfully formulate them into more soluble and hence bioavailable drug product. Solid dispersion is generally prepared with drug which is having poor aqueous solubility and hydrophilic carrier. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. The 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 .The present article reviews the basic concept about solid dispersion, various types of solid dispersion, criteria of solvent selection, the methods of preparation, characterization, their advantages, limitations, applications.

Key**words:** Solubility ,Solid Dispersion, Bioavailability

INTRODUCTION

Solubility is an important parameter which affecting the absorption of drugs and their therapeutic effectiveness. Poor aqueous solubility leads to formulation development failure[1.] Poorly water soluble drugs, not well-absorbed after oral administration which can reduce from the drug's inherent efficacy[2]. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs[3]. Pharmaceutical companies have been primarily employing two strategies: rational drug design and high throughput screening for drug discovery. In both, lead compounds are identified according to screening in an environment in relation to biological system.[3,4]

The poorly soluble drug having dissolution rate too slow therefore uptake cannot be completed within the time at absorption site .Aqueous solubility and poor dissolution of insoluble drugs always remains a problem to the pharmaceutical industry. Lipophillic molecules especially those belonging to the Biopharmaceutics Classification System (BCS) Class II and IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability etc [4].Numerous efforts have been used to improve drug dissolution rate, these include, (a) reducing particle size to increase surface area,(b) solubilization in surfactant systems, (c) formation of water-soluble complexes, (d) use of pro-drug and drug derivation such as electrolyte salt forms that usually have higher dissolution rate, and (e) manipulation of solid state of drug substance to improve drug dissolution5. Therefore, there is need of a new approach for enhancing solubility of drug.[6] and the solid dispersion is the most commonly used technique for improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients as it is simple, economic and advantageous.[4] The term solid dispersion technology is the science of dispersing the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method. Solid dispersions is an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs. 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 The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption.[1,2] Solid dispersions of poorly water-soluble drugs with water-soluble carrier have been reduced the incidence of these problems and enhanced dissolution. 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.[5,6]

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 solid so 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. Fig No.1

T A– M.P. of solid A
T B – M.P. of solid B
TE – Eutectic Point[7,8]

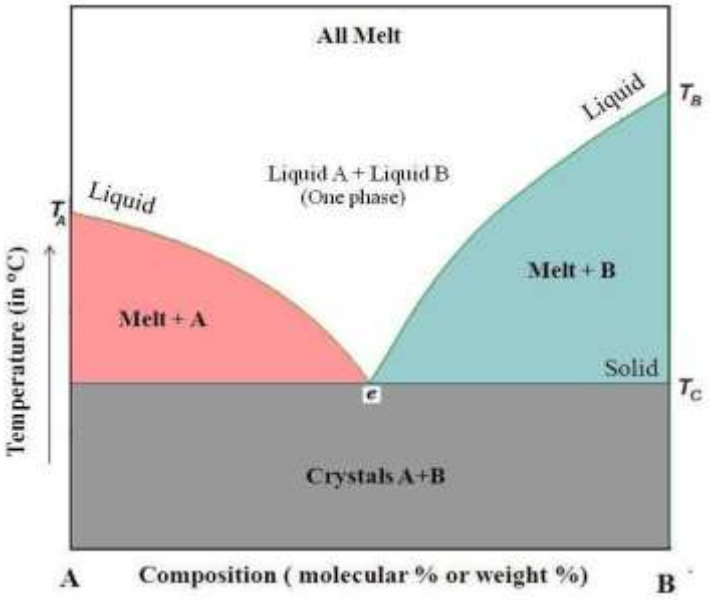

Figure 1: Phase diagram of a eutectic mixture

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 component are miscible in the solid state in all proportions.

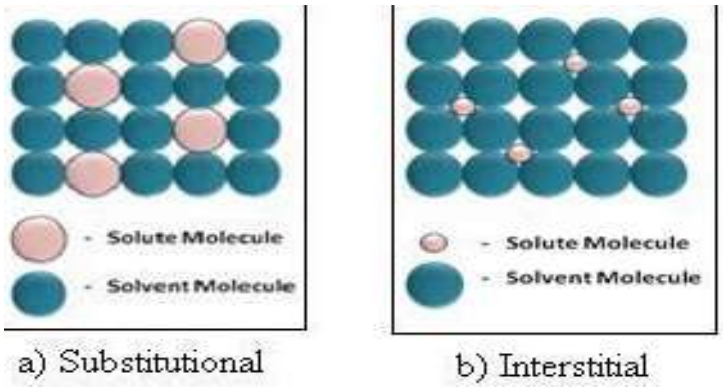

Figure 2: Schematic representation of substitutional and interstitial solid solutions[9]

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.[8,9 10]

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.[7,8]

SELECTION OF CARRIER(S)

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier ought to meet the following prerequisites for being suitable for increasing the dissolution rate of a drug [6,7,8].

It should be

- Freely water soluble with rapid dissolution properties
- Nontoxic and pharmacologically inert
- Heat stable with a low melting point for the melt method
- Soluble in a variety of solvents
- Preferably enhancing the aqueous solubility of the drug
- Chemically compatible with the drugs
- Forming only weakly bounded complex with the drug
- The various carries for solid dispersion are enlisted in following table[9,10]

Table 1: Carriers used in the preparation of solid dispersion

Chemical Class	Examples
Acid	Citric acid,Tartaric acid,Succni
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymer	Polyvinyl pyrolidone, PEG4000 , Carboxy methylcellulose, Guar gum, Xanthan gum, Methyl cellulose
Surfactants	Polyoxyethylene stearate Polaxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamin E TPGS NF

To increase the dissolution rate from equation the following approaches are available:-

- To increases the surface area available for dissolution Decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- To decrease the boundary layer thickness.
- Ensure sink condition for dissolution.
- Improve apparent solubility of drug under physiologically relevant conditions.
- Drug administered in fed state is a way to improve the dissolution rate.[10,11,12,13]

ADVANTAGES OF SOLID DISPERSIONS:-

1. **Particles with reduced particle size :** Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium . A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug. [12,13]

2. **Particles with improved wettability**: A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions . It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects .[14,15]

3. **Particles with higher porosity**: Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with SDs that prepared with reticular polymers. More porous nature of the particle results higher dissolution rate.[15,16]

4. **Drugs in amorphous state**: Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.[8,9]

DISADVANTAGES OF SOLID DISPERSIONS

1. The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir,Abboft) from the market.

2. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness [9,10,11]

PREPRATION OF SOLID DISPERSION

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the

challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control .[17,18]

METHOD OF PREPRATION OF SOLID DISPERSION

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1. Melting method
2. Solvent evaporation method
3. Spray drying
4. Lyophilization[19]

1. **Melting method:-** The melting or fusion method will be used to prepare physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and then sieved.[9]

2. **Solvent Evaporation Method**: In solvent evaporation method drug and carrier will be dissolve in a common solvent it will evaporated to form the solid mass. Basically, this solvent evaporation method involves two steps and these are:

(i) preparation of a solution that will containing both matrix material or carrier and drug.

(ii) The removal of the solvent resulting in the formation of the solid mass.[10]

3. **Spray Drying :** Spray drying method will be consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then dryed it into a stream of heated air flow to remove the solvent.[11]

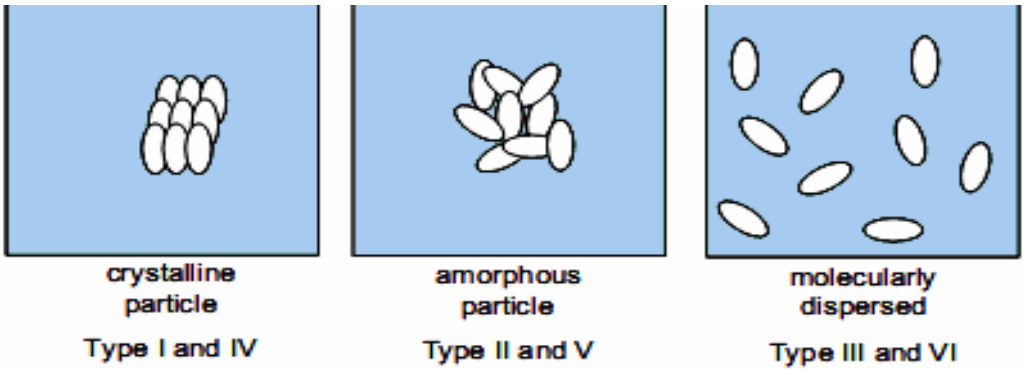

Fig. 3: **Schematic representation of three modes of incorporation of the drug in a solid dispersion**

4. **Lyophilization (freeze drying) :** An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the SDs. Lyophillization has been thought of a molecular mixing technique The drug and carrier are codissolved in acommonsolvent,Frozen and sublimed to obtain a lyophilized molecular dispersion.[11,12]

EVALUATION OF SOLID DISPERSION

A number of techniques can be employed to identify the physical nature of the solid dispersions. These are as follow -1.

1. **Powder X-ray diffraction**:- It can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.Recently developed X-ray equipment is semiquantitative[14].
2.
3. **Infrared spectroscopy (IR) :-**It can be used to detect the variation in the energy distribution of interactions between drug and matrix . Sharp vibrational bands indicate crystallinity . Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material . However in solid dispersions only qualitative detection was possible .[15,16]

4. **Dissolution Calorimetry :-**Measures the energy of dissolution, which is dependent on the crystalline of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.[19,20]

5. **Macroscopic techniques:-** hat measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity.However, also these techniques require knowledge about the additivity othese properties in intimately mixed binary solid.[20,21]

APPLICATIONS OF SOLID DISPERSIONS

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:[21]

1. To obtain a homogeneous distribution of a small amount of drug in solid state.
2. To dispense liquid or gaseous compounds in a solid dosage.\
3. To formulate a fast release primary dose in a sustained released dosage form.
4. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate absorption and bioavailabilty[9,10]
5. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.
6. To reduce side effect of certain drugs.
7. Masking of unpleasant taste and smell of drugs.
8. Improvement of drug release from ointment creams and gels.
9. To avoid undesirable incompatibilities.[11,12]
10. To obtain a homogeneous distribution of a small amount of drug in solid state.
11. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
12. To formulate a fast release primary dose in a sustained released dosage form.
13. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
14. To reduce pre systemic inactivation of drugs like morphine and progesterone[15,16,17]

CONCLUSION

There are many drugs having poor aqueous solubility and as dissolution of drug is the rate determining step for oral absorption of such drugs,which can subsequently affect the in vivo absorption of drug. So to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those techniques. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, Solid dispersion has set itself as a proven technology for the purpose with unique set of advantages and limitations. The review provides various methodologies of using solid dispersions ,and discusses as to why, when, and how to develop them. Proper selection of formulation method and carriers greatly append in solubility enhancement of poorly water soluble drugs. Solid dispersions technique will be widely applied to develop oral dosage form of poorly water-soluble drugs.

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