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SOLID DISPERSIONS: AN OVERVIEW ON SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

PARVE BALASAHEB*, TELI BALAJI AND BIRAJDAR AVINASH

Department of QAT, NDMVPS College of Pharmacy, Nashik, India.

ABSTRACT

Improving oral bioavailability of solid dosage forms is a challenge for the formulation scientists due to their solubility problems. The dissolution rate could be the rate-limiting step in the absorption of poorly water soluble drugs Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. This strategy has proven to improve the bioavailability by dispersing the lipophilic drug as very fine particles within hydrophilic matrix that results in increased solubility with increased surface area available for dissolution. This article reviews the need for the solubility enhancement of poorly water soluble drugs, historical background, advantages, disadvantages, various categories of solid dispersions, manufacturing methods, factors influencing the drug release, characterization of solid dispersions.

KEYWORDS: bioavailability, solubility, dissolution, solid dispersion, lipophilic.

PARVE BALASAHEB
Department of QAT, NDMVPS College of Pharmacy, Nashik, India.

***Corresponding author**

INTRODUCTION

Oral bioavailability of drugs depends on it's solubility and/or dissolution rate, therefore major problems associated with these drugs are its low solubility in biological fluids, which results in to poor bioavailability after oral administration[1-5].Model List Of Essential Medicines Of The World Health Organisation (WHO) has assigned BCS (Biopharmaceutical Classification System) on the basis of data available in the public domain. Out of 130 orally administered drugs on the WHO list, 61 could be classified with certainty.

- 84% of the drugs belong to Class I (Highly soluble ,Highly permeable)
- 17% to Class II (Poorly Soluble, Highly Permeable)
- 39% to Class III (Highly Soluble, Poorly Permeable)
- 10% to Class IV (Poorly Soluble, Poorly permeability)

A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption [6]. Therefore pharmaceutical researcher's focuses on two areas for improving the oral bioavailability of drugs which include:

I. Enhancing solubility and dissolution rate of poorly water soluble drugs and
II. Enhancing permeability of poorly permeable drugs[7].

It has been estimated that 40% of New Chemical Entities currently being discovered are poorly water soluble[8,9].The rate and extent of absorption of class II and class IV compounds is highly dependent on their solubility [10,11]. Thus, a greater understanding of dissolution and absorption behaviour of drugs with low aqueous solubility is required to successfully formulate them into bioavailable product [15]. Although various method as shown in Table1, have been commonly used to increase dissolution rate of the drugs, there are few practical limitations with these techniques i.e., the desired bioavailability enhancement may not always be achieved.[12,13]Therefore formulation approaches are being explored to enhance bioavailability of poorly water soluble drugs. One such formulation approach that has been shown to significantly enhance dissolution of such drugs is to formulate solid dispersions.

Table 1
Various methods to increase the solubility of drugs [15]

PhysicalModification				
a. Particle size reduction	**b.Modification of the crystal habit**	**c. Drug dispersion in carriers**	**d. Complexation**	**e. Solubilisation by surfactants**
1 Micronization 2 Nanosuspension • Homogenization • Wet milling 3 Sonocrystallization 4 Supercritical fluid process 5 Spray drying	1.Polymorphs 2.Pseudo polymorphs	1.Eutectic mixtures •Hot plate method •Solvent evaporation method •Hot-melt extrusion •Melting-solvent method	1.Use of complexing agents • Inorganic Coordination • Chelates • Metal-olefin • Inclusion •Molecular complexes	1 Microemulsions 2. Self-micro-emulsifying drug delivery systems
Chemical Modification				
a. Soluble prodrugs	b. Salt formation			
Other Techniques				
a. Co-crystallisation	b. Cosolvency	c. Hydrotrophy	d. Solubilizing agents	e.Nanotechnology approaches

Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bioavailability as a result of reduction in particle size. However, micronization of drugs often lead to aggregation and agglomeration of particles, which results in poor wettability. Solid dispersions of poorly water soluble drugs with water soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable

method to enhance bioavailability of poorly water soluble drugs overcame the limitations of previous approaches such as salt formation, solubilisation by co-solvents and particle size reduction. Studies revealed that drugs in solid dispersions need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming solid dispersions. [14]

SOLID DISPERSION

The term solid dispersion refers to a group of solid products consisting of at least two different compounds, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[15,16] Pharmaceutical polymers are used
to create this matrix and their selection is ba sed on many factors, including physicochemi cal (e.g. drug-
polymer miscibility and stability) pharmacoki netic (e.g. rate of absorption) constraints. [17]
"A dispersion involving the formation of Eutectic mixture of drugs with water soluble carriers by melting of their physical mixtures." Based on molecular arrangement, six different types of solid dispersions can be distinguished as described in figure 1moreover; not the preparation method but the molecular arrangement governs the properties of Solid dispersions.

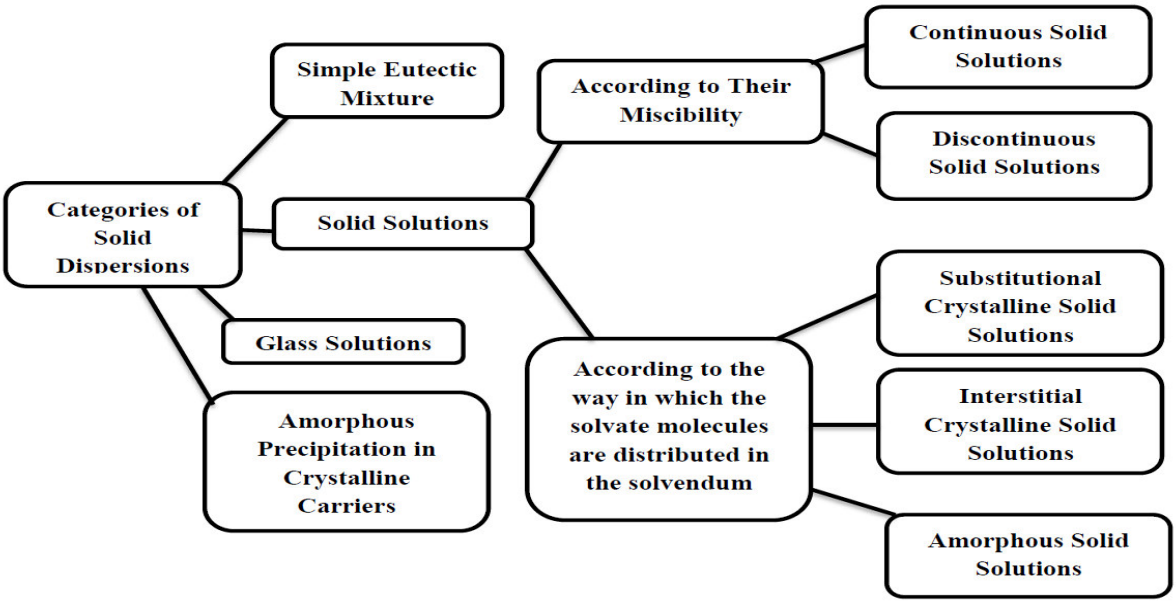

Figure 1
Different types of Solid Dispersions

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug release as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailabiity of poorly water soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. Solid dispersion techniques was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water soluble drugs such as Sulfathiazole by the formation of eutectic mixture with a water soluble and physiologocally inert carriers like Urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of the fine dispersion of the drug in solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52percent w/w of sulfathiazole and 48 percent w/w of urea. The possibility of using a solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced.[14]

ADVANTAGES OF SOLID DISPERSION:[15,16-21]

The major advantages of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition[5] and results in rapid dissolution therby improving the bioavailability of drug. Along with this, the approach may also offer other advantages which include:

1. Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (e.g.PEG) as a solid dispersion to increase it's aqueous solubility and dissolution. The superdisintegrant (e.g.cross carmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therby enabling patient for self-medication even without the aid of water. [20]

2. As a formulation vehicle

Solid dispersion can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain.

3. Particles with reduced particle size

Solid dispersion represents the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability.[16]

4. Particles with improved wettability

Enhancement of drug solubility is related to the drug wettability. 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 , significantly increases the wettability of drug. Moreover carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.[16]

5. Particles with higher porosity

Particle in solid dispersions have been found to have a higher degree of porosity. Solid dispersions containing linear polymers produces larger and more porous particles than those containing reticular polymers and, therefore, results in higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release rate.[16]

6. Drugs in amorphous state

The enhancement of drug release can be usually be achieved if the drug in it's amorphous state, because no energy is required to break up the crystal lattice during the dissoluiton process. In solid dispersions , drugs are presented as supersaturated solutions after system dissolution, and it is speculated that if drugs precipitate as it is metastable polymorphic form with higher solubility than the most stable crystal form. [16]

DISADVANTAGES OF SOLID DISPERSIONS :[15,21]

Disadvantages of solid dispersions are mainly related to their instability. Basically changes occur in several systems in crystallinity and a decrease in dissolution rate with ageing and system may be destabilised through physical treatment such as pulverization and aging. There is more deteriorating effect of moisture and temperature on solid dispersions than on physical mixtures. [21]

Usually solid dispersions are prepared with water soluble low melting point synthetic polymers such as polyvinyl pyrrolidone , mannitol or polyethyline glycol. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/polymer) ratio. An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of carrier, i.e., more than 50% to 80% w/w, is required to achieve the desired dissolution. Solid dispersion is a high energy metastable form. Phase seperation, crystal growth or conversion from the amorphous to the crystalline form during

storage decrease solubility and dissolution rate and result in variable oral bioavailability.

CATEGORIES OF SOLID DISPERSIONS

1) Simple eutectic mixtures

When a mixture of A and B with composition E is cooled, A and B crystallize out simelteneiusly 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 comelt 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. [1,6] The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

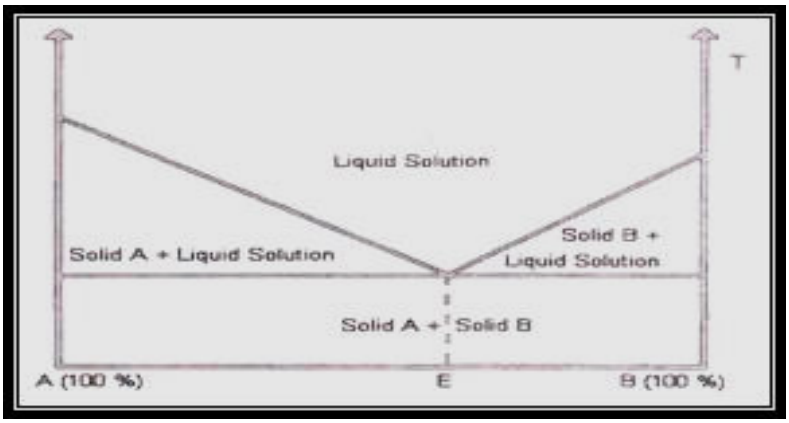

Figure 2
phase diagram for a Eutectic System

2) Continuous solid solutions

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. Solid solutions of this type have not been reported in the pharmaceutical literature to date.[8]

3) Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram shown in figure 3. Shows the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component . Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg [8]that the term solid solution should only be applied when the mutual solubilities of the two components exceeds 5%. Whether or not the 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 dose of the drug components the upper limit for tablet or capsule is about 1 g.

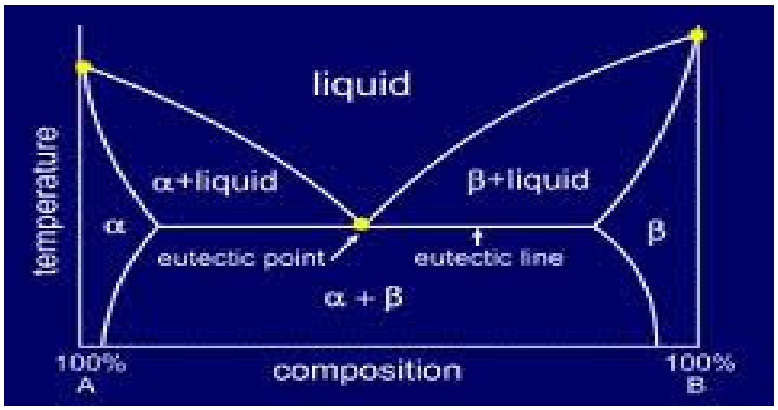

Figure 3
Phase diagram for discontinuous solid solutions

4) Substitutional crystalline solid solutions

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. A substitutional crystalline solid dispersion is depicted in figure 4. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. [22]

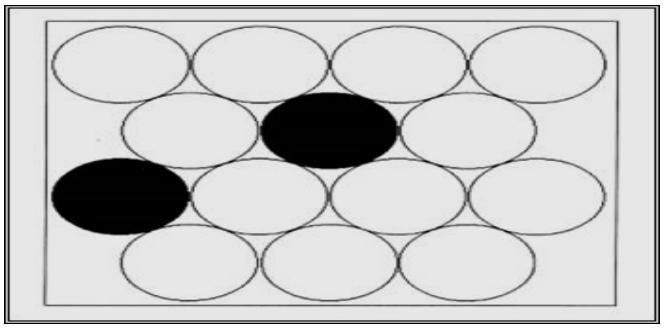

Figure 4
Substitutional crystalline solid solution

5) Interstitial Crystalline solid solutions

In interstitial solid solution, the dissolved molecules occupy the interstitial space between the solvent molecules in crystal lattice (Figure 5). As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In case of the interstitial crystalline solid solutions, the solute molecule's should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter.[23] Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

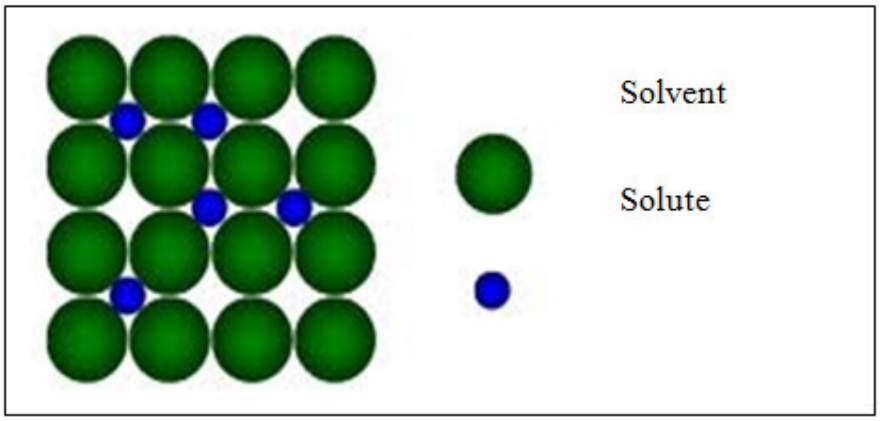

Figure 5
Interstitial crystalline solid solutions

6) Amorphous solid solutions

In Amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (figure 6). Using Greseofulvin in citric acid, Chiou and Riegelman [11] were the first 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 polyvinyl pyrrolidone (PVP), Polyethylene glycol (PEG), and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in it's glass transition temperature (T_g). [24]

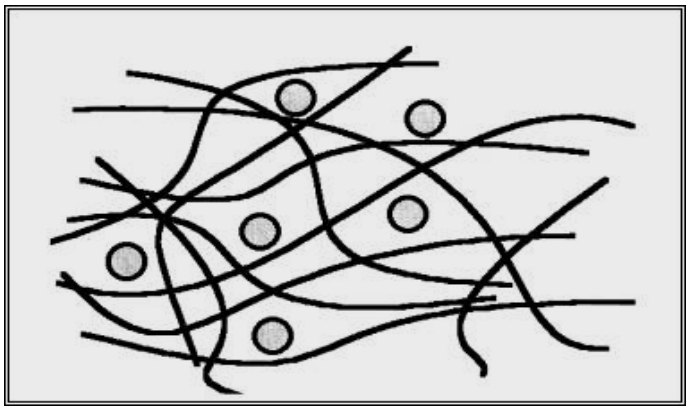

Figure 6
Glass solution And Glass suspension

MECHANISM OF BIOAVAILABILITY ENHANCEMENT:[25-27]

The enhancement in dissolution rate because of solid dispersion formation , relative to pure drug varies from as high as 400 fold to less than two fold. [5] The increase in dissolution rate can be attributed to myriad factors and it is very difficult to show experimentally that any one particular factor is more important than other. Solid dispersions increases the dissolution rate of poorly water soluble drugs by one of the following mechanism.[26]

- Reduction in particle size
- Improvement in wettability and dispersibility
- Changing the crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles

SELECTION OF CARRIER(S)

Properties of carriers have 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.[4]It should be

i. Freely water soluble with rapid dissolution properties.
ii. Nontoxic and pharmacologically inert, chemically compatible with the drug.
iii. Heat stable with a low melting point for the melt method.
iv. Soluble in a variety of solvents, preferably enhancing the aqueous solubility of the drug.
v. Forming only weakly bounded complex with the drug.

CURRENT TRENDS IN SOLID DISPERSION TECHNIQUES

New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. It is intended to discuss the recent advances related on the area of solid dispersions. The classification of Solid dispersions according to implementation and recent development. [14]

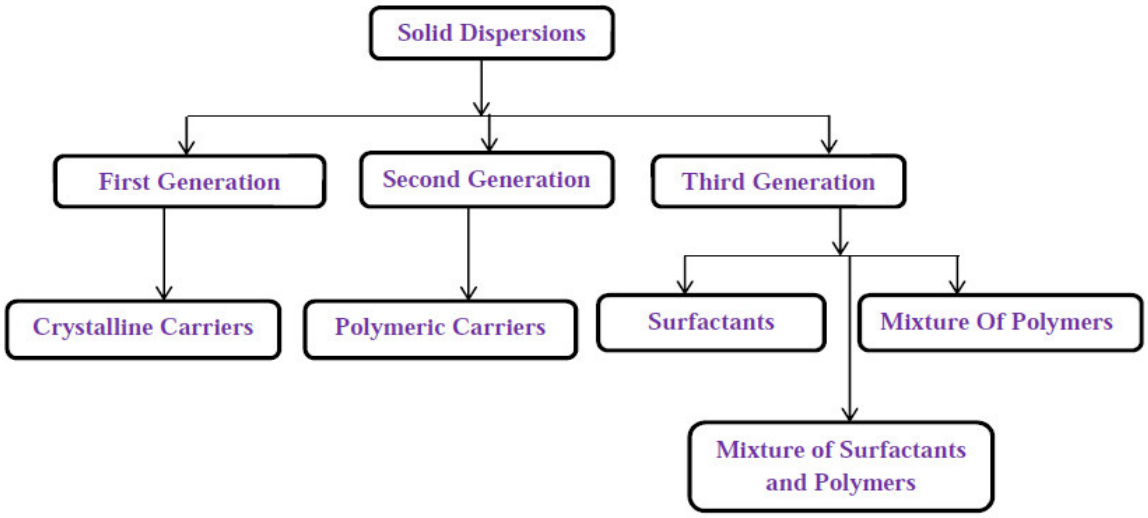

Figure 7
Classification of Solid dispersions according to implementation and recent developments

1 First generation Solid Dispersions

The first description of Solid Dispersion was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures the rate of drug release and consequently, the bioavailability of poorly water soluble drugs. In the same decade, several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole [1] and Chloramphenicol [29] using urea as a water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drugs were the main reason for the observed improvements in bioavailability. Later Levy and kaning[30] developed solid dispersion systems, containing mannitol as carrier, by preparing solid solution through molecular dispersions instead of using eutectic mixtures. These solid dispersions, which could be designed as a first generation solid dispersions were prepared by using crystalline carriers (e.g.urea[1,29] and sugars[31]). They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and don't release the drug as quickly as amorphous as ones.

2 Second generation solid dispersion

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as

effective as the amorphous, because the former were more thermodynamically stable.[2,31-32] Therefore second generation solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter the drugs are molecularly dispersed in an irregular form within the amorphous polymeric carrier.[33]These carriers are divided into fully synthetic polymers and natural product based polymers as follows

Table 2

Examples of carriers used in the preparation of second generation solid dispersion.[34-41]

Synthetic Polymers	Natural Product Based Polymer	
	Cellulose Derivatives	Starch Derivatives
Povidone (PVP) Polyethylene glycol (PEG), Polymethacrylates	Hydroxypropylmethyl cellulose (HPMC) Ethyl cellulose, hydroxylpropyl cellulose.	Cyclodextrins

Amorphous solid dispersions can be classified according to molecular interaction of drug and carriers in solid solutions, solid suspensions or mixture of both.[35] Amorphous solid solutions: drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them.[47]In these systems the drug and carrier energy is extremely high, resulting in a true solution. The use of polymers in the preparation of a true solution creates an amorphous product in which crystalline drug is dissolved.[42]This type of solid dispersion is homogeneous on molecular level. Therefore, only one phase is present. Amorphous solid suspensions: occur when the drug has limited carrier solubility or extremely high melting point.[2]Molecularly obtained dispersions do not have a homogeneous structure, but is composed of two phases. When drug is both dissolved and suspended in the carrier, a heterogeneous structure is obtained with mixed properties of amorphous solid solution and amorphous solid suspension.[20, 47] In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilisation in carrier.[41]These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers.[43, 44]

3 Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier or a mixture of surfactants and amorphous polymer as carriers. These solid dispersions are intended to achieve highest degree of bioavailability of poorly water soluble drugs and to stabilize the solid dispersions, avoiding drug recrystallization. The use of surfactants such as inulin,[47] inutec,[42]compritol888ATO, [45]gelucire 44/14 and poloxamer 407 [46]as carrier was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability. The dissolution rate of LAB68, a poorly water soluble drug, was improved after being dispersed in a mixture of PEG and Polysorbate 80. The bioavailability of this dispersion was 10 fold higher compared to the dry blend of micronized drug. In addition the solid dispersion system was physically and chemically stable for at least 16 months.[48]The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles. HPMC was also associated with poloxamer and polyethylene hydrogenated castor oil to prepare an amorphous felodipin solid dispersion.[40]

MANUFACTURING METHODS

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a carrier and a drug, preferably on a molecular level. While carrier 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 and therefore unwanted. It was already recognized in one of the first studies on solid dispersion that the extent of phase separation can be minimized by a rapid cooling procedure (Chiou and Riegelman 1971, Sekiguchi and Obi, 1961). Generally the phase separation can be prevented by maintaining a low molecular mobility of carrier and drug during preparation. On the other hand , phase separation is prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible. Various methods used for the preparation of Solid dispersion are explained as follows.

1. Melting Method

Sekiguchi et al. were first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drugs incorporation. [49] A common adaptation to the melting phase consist of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, reducing, therefore the process temperature. To cool and solidifying the melted mixture , several processes such as ice bath agitation[29,50]stainless steel thin layer spreading followed by a cold drought,[24] solidification on petri dishes at room temperature inside a desiccator, [45]spreading on plates placed over dry ice[51]immersion in liquid nitrogen or stored in a desiccator[52]were used. After cooling the mixture must be pulverized regarding it's handling. However, use high temperatures, and the fact that several drugs can be degraded by melting process, can be a limitation of this method. [53]The incomplete miscibility between a drug and a carrier that may occur, because of the high viscosity of apolymeric carrier in molten state, is another limitation of this process. [54] To avoid all these limitations several modifications like hot stage extrusion, Meltrex TM or melt agglomeration were introduced to the original method.

2. Hot stage Extrusion

Hot stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled.[42,48] A reduction in processing temperature can be achieved by the association of hot stage extrusion with the use of carbon dioxide as a plasticizer[55,56]which broaden the application of hot stage extrusion to thermally labile compounds.[55]Solid dispersions of para amin o salicylic acid/ethyl cellulose, Itraconazole /PVP,[57]Itraconazole/ethyl cellulose were successfully prepared by this technique. Moreover, it was observed that solid dispersions of Itraconazole/inutec SP1 prepared by hot stage extrusion presented Itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying.[42] Meltrex TM is a patented solid dispersion manufacturing process, also on the basis of melting process. The crucial elements in the Meltrex TM technology is the use of a special twin screw extruder and the presence of two independent hopes in which the temperature can vary over broad temperature range. This process permits a reduced residence time of 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.[49]

3. Melt Agglomeration

Melt Agglomeration allows the preparation of solid dispersions in in conventional high shear mixer. It is made by adding the molten carrier containing the drug to the heated excipients, [57, 58] 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 thecarrier.[56] It is also possible to produce stable solid dispersion by melt agglomeration in a rotary processor.[33]

4. Solvent evaporation method

The first step in the solvent method is the preparation of a solution containing both

carrier material and drug. The second step involves the removal of solvent(s) 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 carrier 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 carrier have to be dispersed in the solvent as fine as possible, [59]preferably drug and carrier material are in the dissolved state in one solution. Various strategies have been applied to dissolve the lipophilic drug and hydrophilic carrier material together in one solution. Low drug concentrations are used to dissolve both drug and carrier material in water,[60]but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilisers like cyclodextrins or surfactants like Tween 80 ® increase the aqueous solubility of the drug substantially. However, the amount of solubiliser or surfactants in the final product is often eminent. This results in solid dispersions that, to a significant extent, consist of soubilisers or surfactants, materials that significantly change the physical properties of the carrier (decrease T_g). Moreover only dosage forms with low drug loads are possible. In addition, they are not always tolerated well in the body or may even be toxic. Chloroform[61] or dichloromethane[62] have been used to dissolve both drug and PVP as carrier simultaneously. These solvents are used also in other preparation methods. However according to ICH guidelines, these solvents belong to Class I, comprising the most toxic solvents. Therefore, the use of these solvents is unacceptable and impractical because the amount of residual solvent present in the solid dispersion after drying has to be below the detection limit. The last strategy for the dissolution of both drug and carrier is the use of solvent mixtures. Water and ethanol, [63] or dichloromethane and ethanol[64] have been used for this purpose. The second challenge in the solvent method is to prevent phase separation e.g. crystalline of either drug or carrier, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for the molecular mobility of the drug and carrier remains high, favouring phase separation (e.g. crystallization).

To dry the solutions, vacuum drying is often used.[65]The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Afterwards the formed solid dispersion is often stored in a vacuum desiccator to remove the residual solvent. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and carrier decreases slowly. Another drying technique is Spray drying. The solution is dispersed as fine particles in hot air. Due to large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersion prepared by spray drying consist of particles of which the size may be customized by changing the droplet size to meet the requirements for further processing or application (e.g. free flowing particles for inhalation). Spray drying usually yields in amorphous state [66] however sometimes the drug may have (partially) crystallized during procedure.[67] An alternative to these techniques is freeze drying. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substance in stabilizing carriers.[68]One of the reason might be the low freezing temperature of most of the organic solvents. Obviously sublimation during freeze drying is only possible when the solvent stays frozen. In addition when the formation of a glass is envisaged the sample temperature should be kept below the Tg of the maximally freeze concentrated fraction. Therefore low sample temperature are required which slows down the process. Betagery and Makarla, 1995 used a condenser temperature of -75 ^{0}C to dry a solution with cyclohexanol as organic solvent. To obtain lyophilisation the solvent should have sufficiently high vapour pressure. A suitable solvent that meet both requirements is 2-methyl-2-propanol or tertiary butanol, (TBA), because it has a high melting temperature as well as a high vapour pressure.[69] An important advantage of freeze

drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent results in even faster vitrification, thereby decreasing the risk for phase separation to a minimum.[70-71]

5. Supercritical fluid method

Supercritical methods are mostly applied with the carbon dioxide (CO_2) which is used as either a solvent for drug and carrier or as anti-solvent[73, 74]when supercritical CO_2 is used as solvent, the carrier and drug are dissolved and sprayed through a nozzle, into expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in cooling. This technique does not require the use of organic solvents and since CO_2 is considered as environmentally friendly. This technique is referred to as 'solvent free'. The technique is known as 'Rapid Expansion of Supercritical Solution' (RESS). However the application of this technique is very limited because the solubility in CO_2 of most pharmaceutical compound is very low[75] and decrease with the increase in polarity. All the supercritical techniques are precipitation methods. Although generally labelled as solvent free but all these use the organic solvents to dissolve drug and the carriers and exploit the low solubility of pharmaceutical compounds in CO_2. Infact, these techniques represents alternative methods to remove solvents from a solution containing typically a drug and a polymer. Moneghni and co-workers (2001) reported their method as solvent free, but they dissolved PEG and carbamazepine in acetone. They used a technique that is called the Gas Anti-solvent Technique (GAS) or Precipitation from Gas Saturated Solution (PGSS). The solution is brought in to contact with compressed CO_2. The conditions are chosen so that CO_2 is completely miscible with the solution under supercritical conditions. Whereas the drug and carrier will precipitate upon expansion of the solution. When the volume of solution expands the solvent strength (i.e. ability to dissolve the drug) decrease. This results in precipitation of drug and carrier.

The second type of precipitation technique involves the spraying of a solution containing drug and carrier through a nozzle into a vessel that contains a liquid or supercritical anti-solvent. The supercritical anti-solvent rapidly penetrates into the droplets, in which drug and carrier become supersaturated, crystallize and form particles. The general term for this process is Precipitation Compressed Anti-solvent (PCA).[75]More specific example of PCA are Supercritical Anti-solvent when supercritical CO_2 is used, or Aerosol Solvent Extraction System (ASES) and Solution Enhanced Dispersion by Supercritical Fluids (SEDS). In another process called supercritical fluid impregnation, the drug is dissolved in a supercritical fluid and exposed to solid carrier material that swells and absorb the supercritical solution. By varying the pressure and the time of exposure, the diffusion process can be controlled. The absorption stops when the pressure is reduced.

6. Direct capsule filling

Direct filling of hard gelatine capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug.[34]This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.[35]

7. Electrospinning method

The electrospinning technology used in the polymer industry combines solid dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome

the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameters are formed. As the solvent evaporates, the formed fibres can be collected on a screen to give an on woven fabric, or they can be collected on a spinning mandrel. The fibre diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength.[76]This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest technique. This technique can be utilized for preparation of solid dispersions in future.[77]

8. Dropping solution method

The dropping method facilitate the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate.[78]It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermostable drugs can be used and the physical instability of solid dispersions is a further challenge.[79]

9. Coating on sugar beads using fluidized bed-coating system

This method involves the fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipient or sugar sphere to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. The method can be applied for both controlled and immediate release solid dispersions.[80]Itraconazole (Sporanox oral capsule, Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering onto sugar beads a solution of a drug and hydroxypropylmethyl cellulose (HPMC) in a mixture of suitable solvent system comprises a mixture of methylene chloride and preferably ethanol which may be denatured with butanone. As HPMC does not dissolve completely in methylene chloride, at least 10% alcohol has to be added. A solid solution of drug in HPMC is produced upon coating beads are done in a closed Wurster Apparatus.[81]

FACTOR AFFECTING THE DRUG RELEASE

a. Nature of carrier

Drug release from solid dispersion is dependent upon the nature of carrier, whether hydrophilic or hydrophobic. Thus incorporation of poorly water soluble drug into inert and slightly water soluble carrier leads to retardation of drug release from carrier. However, incorporation of poorly water soluble drug into water soluble carrier(s) leads to acceleration of drug release.

b. Drug carrier Ratio

The dissolution rate of drug increases with increase in the proportion of drug carrier. However, this is true up to a certain limit beyond which the dissolution rate decreases. As much as 38 fold increase in dissolution rate of piroxicam was reported when used as solid dispersion using drug: PVP in the ratio of 1:4. With further increase in PVP concentration the dissolution rate decreased, attributable to the leaching of carrier during dissolution. This leached outcarrier forms a concentrated layer of solution around the drug particle, resulting in lowering of release rate. The solid dispersion to be effective in enhancing the solubility, an appropriate drug carrier proportion is desired. Co-precipitate of flubiprofen: phospholipid, for instance, when used in the ratio of 20:1, yields 9 fold greater dissolution rate of flubiprofen. In case of glipizide the rate of dissolution was increased when the ratio of polymer is increased, about 5 fold greater dissolution rate of glipizide with poloxamer 188 in the ratio of 1:10.[82]

c. Method of preparation

Solid dispersions prepared by melting generally showed faster dissolution rate than those prepared by solvent method. Solid dispersion of griseofulvin PEG 6000 prepared by solvent method have been reported to yield dissolution rates much slower than the ones obtained using melting method. For example, solid dispersion of diazepam-PEG 6000, prepared by melt method with 1:10 and 1:5 w/w ratio, showed faster dissolution rates. This rapid release was attributed to very fine state of subdivision of the drug particles, and solubilizing plus wetting effect of the carrier. However, the corresponding solid dispersion prepared by co-precipitation showed slower dissolution owing probably to greater size of diazepamparticles.[83]

d. Cooling conditions

In melt technique, drug is incorporated in a molten carrier, and subsequently cooled, forming the dispersion. The method of cooling, whether slow or flash, affects the rate of dissolution. While preparing tolbutamide–PEG 6000 (1:2) dispersion, the melt has cooled by two processes. First process involved flash cooling by placing melt on aluminium and subsequently in a bath of dry ice and acetone. Second process involved slow cooling in oil bath under ambient conditions. More than 15% of drug release was observed in case of flash cooled dispersion as that of slow cooled dispersion due to the difference in particle size, as flash cooled dispersion gives smaller particle size and low crystallinity.[84]

CHARACTERIZATION OF SOLID DISPERSION

A. Differential Scanning Calorimetry

In DSC, both the sample and reference materials are subjected to linear heating, but both are maintained at the same temperature. Here change in temperature is not recorded, but the heat flow into the system is recorded which is required to maintain isothermal conditions. The method is useful to study the behaviour of crystallization and melting and deriving phase diagrams of solid dispersions.

B. X-ray diffraction (XRD)

In this analytical tool, intensity of x-ray reflection is measured which is a function of diffraction method. The diffraction method is very important and efficient tool in studying the physical nature of solid dispersion which has been used in crystal structure studies in two different ways.

- Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances.
- Power x-ray diffraction dealing with the study of crystal lattice parameter, where the x-ray diffraction intensity from a sample is measured as a function of diffraction angles. Thus, changes in diffraction pattern indicate changes in crystal structure.

The relationship between wavelength, of the x-ray, the angle of diffraction, θ, and the distance between each set of atomic planes of crystal lattice, d, is given by equation:

$n\lambda=2d \sin \theta$

Where, M represent the order of diffraction[2, 85.]

C. FT-IR Spectroscopy

FT-IR spectroscopy used to study the possibility of an interaction between drug and polymer in solid state. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and carrier.[86]

D. Dissolution rate determination

The method involves comparing the in vitro dissolution rates of the solute component from a

Constant- surface tablet made from molecular dispersion (i.e., solid or glass solution) with a

physical mixture of the same chemical composition. The technique is simple to perform.[2] It tells whether the solid dispersion has improved the dissolution rate or not. The degree of crystallinity can also be studied if it is carried out under standard conditions.

E. Scanning Electron Microscopy

It usually gives primary information of system and tells about the amorphous or crystalline nature of solid dispersions. The application of the electron microscope technique, however, usually limited to chemicals with high resolution.

F. Thermodynamic methods

In this analysis, the phase diagrams of eutectic and solid solution systems give the value of heats of fusion, entropies and partial pressures at various compositions that helps

to determine the solubility gap below the solid-liquid equilibrium temperature. [2]

G. Solubility study

Solubility studies are done for the finding out the solubility behaviour shown by the solid dispersion system in different types of solvent system and body fluids.[15]

CONCLUSION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of drugs, which can subsequently affect the in vivo absorption of drug. Because of solubility problem of many drugs the bioavailability of these gets affected and hence solubility enhancement becomes necessary. Solid dispersion is one of the most important techniques used for the solubility enhancement of poorly water soluble drugs. Hydrophilic carriers, co-solvents, surfactants are used as solubilisers that aids in solubility enhancement. Improved understanding of physical stability of solid dispersions is the main driver for increasing future relevance of solid dispersions.

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