SOLID DISPERSION: AN EVOLUTIONARY PLAN FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Although marvelous advancement in drug delivery, oral route remains the preferred route for the administration due to higher levels of patient compliance. It can be a complicated and unproductive means of delivery for water-insoluble drugs with high permeability or Class II drugs in FDA’s Biopharmaceutical Classification System (BCS). Such drugs in general exhibit dissolution rate limited absorption resulting in poor bioavailability when delivering via the oral route. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. The experience with solid dispersions over the last 20-30 years indicates that this is a very productive 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 remarkable potential in the area of controlled release dosage forms. This strategy has proven to improve the bioavailability by dispersing the hydrophobic drug as very fine particles within hydrophilic matrix that results in increased solubility with increased surface area available for dissolution. The expansion of solid dispersions as a practically viable method to boost bioavailability of poorly water-soluble drugs and overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction. Being versatile in their application, solid dispersions can form the basis of products applied for various routes of administration and for various dosage forms. The focus of this review article is on advantages, disadvantages. Also covers brief preface of solid dispersion highlighting various approaches for their preparation, technology involved, selection of carriers and methods of characterization.

Keywords: Dissolution, cosolvent, bioavailability.

INTRODUCTION

It has been estimated that 40–60% of drugs in development have poor bioavailability due to low aqueous solubility. This percentage is likely to increase in the future with the
increased use of combinatorial chemistry in drug discovery targeting lipophilic receptors. Poor bioavailability results in increased development times, decreased efficacy, increased inter-and intrapatient variability and side-effects, and higher dosages that reduce patient compliance and increase cost. Thus, the ability to improve drug solubility and hence bioavailability through formulation and process technology is critical to improving a drug product’s efficacy and safety and reducing its cost. Solid dispersion technology, where the API is dispersed at the molecular or nano particle level as an amorphous material within a solid matrix, is a proven and highly effective technique for improving drug solubility[1].

Many potential drug candidates are characterized by a low oral bioavailability. Often poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability. Thus aqueous solubility of any therapeutically active substance is a key property a sit governs dissolution, absorption and thus the in vivo efficacy. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi[2].

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.
Solid dispersion: Definition- Chiou and Reigelman first by defined solid dispersion in 1971 as “dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method”[^2]

**ADVANTAGES OF SOLID DISPERSION[^3]**

1. **Particles with reduced particle size**

Molecular dispersions, as solid dispersions, represent 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. A high surface area is formed, ensuing in an increased dissolution rate and, accordingly improved bioavailability.

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 it may significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

3. **Particles with higher porosity**

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. **Drugs in amorphous state**

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the
dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

DISADVANTAGES

1. Reproducibility of its physico-chemical properties.
2. Poor stability of dosage form.
4. Aggregation, agglomeration and air adsorption during formulation.
5. Decrease in dissolution rate with aging ford.
6. Difficulty in pulverization and sifting because of their tacky and soft nature
7. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures.

TYPES OF SOLID DISPERSION

(A) Eutectic Mixtures

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

(B) Solid Solutions

According to their miscibility two types of solid solution are

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.

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, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease.

According to the way in which the solvate molecules are distributed in the solvendum the two type of solid solution are –

Substitutional Crystalline Solutions

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial Crystalline Solid Solutions
In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

(C) Amorphous Solid Solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers such as urea and sugars such as sucrose, dextrose, and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose.

(D) Glass Solutions and Glass Suspensions

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature \(^{[14-15]}\).

**SELECTION OF A CARRIER**

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Freely water-soluble with intrinsic rapid dissolution properties.
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.

5. Able to preferably increase the aqueous solubility of the drug.

6. Chemically compatible with the drug and not form a strongly bonded complex with the drug.

First generation carriers
Example: Crystalline carriers: Urea, Sugars, Organic acids.

Second generation carriers:
Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins.

Third generation carriers
Example: Surface active self emulsifying carriers:
Poloxamer 408, Tween 80[12].

SELECTION OF SOLVENTS
Solvent to be included for the formulation of solid dispersion should have the following criteria:

1. Both drug and carrier must be dissolved.

2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.

3. Ethanol can be used as alternative as it is less toxic.

4. Water based systems are preferred.

5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration[8].
MECHANISM OF INCREASED DISSOLUTION RATE

The main reasons postulated for the observed improvements in dissolution of these systems are as follows:

a) Reduction of particle size
In case of glass, solid solution and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area solubilization.

b) Solubilization effect
The carrier material, as it dissolves may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea as well as for numerous other drugs.

c) Wettability and dispersibility
The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retarding agglomeration or aggregation of the particles, which can slow the dissolution process.

d) Metastable Forms
Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide was 17 K Cal per mol, whereas that for 1:2 furosemide: PVP co-precipitate was only 7.3 K Cal per mol.

METHODOLOGIES

The core steps involved in the formation of solid dispersion between a drug and polymer are

1. Transforming drug and polymer from their solid state to fluid or fluid-like state through
2. Processes such as melting, dissolving in solvent or co-solvent, or subliming.
3. Mixing the components in their fluid state.
4. Transforming the fluid mixture into solid phase through processes such as congealing, solvent removal, and condensation of sublimed mixture. Basically, there are two methods of preparing solid dispersions, fusion and solvent processes. In case of thermo labile drugs or those with high melting points, a modified method is employed known as melting solvent method. The latter method is limited to drugs with low therapeutic doses, i.e. below 50 mg. However, for the preparation of solid dispersions, several methods have been reported in literature, which are described as under.

**Fusion method**

In this method, the carrier is heated to a temperature just above its melting point and drug is incorporated in to the matrix. If the drug has high solubility in the carrier, the drug could remain "dissolved" in the solid state, yielding a solid solution. The melt is solidified in an ice bath under rigorous stirring, pulverized and then sieved. Rapid congealing is desirable, because it results in supersaturation of drug as a consequence of entrapment of soluble molecule in the solvent matrix by instantaneous solidification.

The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix\(^9\) which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling\(^9-11\).

**Advantages**

1. It is more convenient and economical method for drugs stable at temperature below 1000\(^\circ\)C.
2. Technically it is an easier method if the drug and carrier are miscible in the molten state.
3. It precludes the use an organic solvent thereby circumventing the enigmas of its removal from the dispersion.

4. Dissolution for dispersions obtained by melting technique are much faster than those prepared using solvent techniques.

Drawbacks
1. High melting carrier cannot be used.
2. Thermal degradation or instability may result at the melting point.
3. Decomposition may take place, often dependent upon composition, fusion time and rate of cooling.
4. Evaporation or sublimation and polymeric transformation of the dispersion component may take place.
5. Solidified melt may be tacky and unhandlable.
6. Immiscibility between drug and carrier results in irregular crystallization that causes obvious problems during formulation\[12\].

Solvent evaporation technique

Tachibana and Nakamura first reported this method in 1965. This technique involves dissolving the drug and the carrier in a suitable organic solvent or a combination of solvents to get a clear solution. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent is then evaporated directly on a water bath or hot plate or using a rotavapour. The resulting solid dispersion is stored in the desiccator under vaccum and pulverized to obtain the desired size fraction. The important prerequisite for the manufacturing of solid dispersion using the solvent method is that both drug and the carriers are sufficiently soluble in the solvent\[22\]. Solid dispersion prepared by solvents removal process termed by Bates as co-precipitates\[5\]. A basic process of preparing solid dispersion of this type consists of dissolving the drugs and the polymeric carrier in
a common solvent, such as ethanol, chloroform, or a mixture of ethanol and dichloromethane\textsuperscript{[6]}. 

Advantages

1. High melting carries can also be utilized.
2. Thermal decomposition of drug and carriers associated with the fusion method can be avoided.

Drawbacks

1. Larger volumes or organic solvent have to be used which makes the process slightly expensive.
2. Removal of the solvent is difficult.
3. Residual solvent can have possible adverse effect.
4. Difficulty of reproducing crystal forms.
5. Supersaturation of the solute cannot be attained unless the system goes through a highly viscous phase.
6. Selection of common solvent is difficult.
7. Drug particle size is affected by temperature and rate of evaporation\textsuperscript{[7]}.

Types of solvent technique

The choice of solvent and its removal rate are critical to the quality of the dispersion. Depending upon the method of evaporation, there are various types of techniques.

Spray drying

Manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. This method consists of dissolving or suspending the drug and carrier, then spraying it in to a stream of heated air flow to remove the solvent \textsuperscript{[6]}. Spray drying usually yields drug in the amorphous state, however sometimes the drug may have (partially) crystallized during processing.

Advantages

1. Ability to work with temperature sensitive APIs.
2. Tremendous formulation flexibility from the wide variety of solvents, polymers and adjuvants that can be employed.

3. Enhancement in performance that can be obtained by mixing the API and polymer at the molecular level in solution and then freezing this morphology in place through rapid solvent removal\(^{[9-11]}\).

**Drawbacks**

1. Added costs associated with the use and consumption of the organic solvents.

2. Requirement of unit operation for residual solvent removal.

**Freeze drying**

To overcome the disadvantages of the above discussed techniques and to obtain a much faster dissolution rate, freeze drying technique has been proposed. The drug and the carrier are dissolved in a common solvent, which is immersed in liquid nitrogen until it is fully frozen then; the frozen solution is further lyophilized. The instance includes that a solid dispersion of tenoxicam with skimmed milk, prepared using freeze drying showed 23-fold increase in solubility with respect to the plain drug\(^{[11]}\).

**Advantages**

1. Risk of phase separation is minimized as soon as the solution is vitrified.

2. Offers the potential to customize the size of the particle to make them suitable for further processing.

**Drawbacks**

1. The tablets are very fragile.

2. The manufacturing process is very expensive.

3. The technique is not suitable for all the products.

**Super critical fluid technology**

Super critical fluid technology (SCF) has been introduced in late 1980s and early 1990s. A SCF is a substance that exists above its critical point, which is defined by the conditions of temperature and pressure at which liquid and gaseous states of a substance...
coexist. When a liquid is heated, its density continues to decrease, while the density of vapor being formed continues to increase\cite{14,16}.

At the critical point, densities of liquid and gas are equal and there is no phase boundary, as shown in Figure 1. Above the critical point that is, in the supercritical region, the fluid possesses the penetrating power typical of a gas and the solvent power typical of a liquid

![Figure 1](image.png)

Supercritical region of a hypothetical compound (Indicated by the dotted lines).

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), 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 (RESS). However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low (<0.01 wt-%) and decreases with increasing polarity.
Schematic of the RESS apparatus is shown in Figure 2[27-29].

![Figure 2](image)

**Figure 2**
Schematic of the RESS apparatus used in supercritical fluid technology.

**Advantages**
1. Dissolving power of the SCF is controlled by pressure and/or temperature.
2. SCF is easily recoverable from the extract due to its volatility.
4. High boiling components are extracted at relatively low temperatures.
5. Thermally labile compounds can be extracted with minimal damage as low temperatures can be employed by the extraction.
6. Non-inflammable and inexpensive technique [30-32].

**Drawbacks**
1. Elevated pressure required.
2. Compression of solvent requires elaborate recycling measures to reduce energy costs.
3. High capital investment for equipment.
Co-evaporates
This technique, drug and copolymer are dissolved separately in same organic solvent and then these two solutions are mixed with further evaporation of solvent under either vacuum or using flash evaporation to give evaporates. Co-evaporates have mainly been employed for dermatological products, e.g., co-evaporates of hydrocortisone acetate-PVP and betamethasone dipropionate-PVP, both of which showed improved cutaneous penetration[23].

Co-precipitates
Co-precipitates are produced by adding a non-solvent with agitation to a drug and polymer mixture in an organic solvent. The co-precipitates are later filtered and dried.

Spin-coated films
It is a new process to prepare solid dispersion by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped on to a clean substrate highly spinned. Solvent is evaporated during spinning. This process is indicated to moisture sensitive drug since it is performed under dry condition[6].

Solvent melt technique
To overcome the problems associated with fusion technique, a blend of fusion and solvent evaporation method has also been proposed. In this technique, the drug is dissolved in an organic solvent and mixed with the melted carrier. The solvent is then evaporated and the resultant product is pulverized to the desired size.

Advantages
1. Possesses unique advantages of both the fusion and solvent evaporation methods.
2. Useful for thermolabile drugs with high melting point[34].

Drawbacks
1. Technique is limited to drugs with a low therapeutic dose (less than 50 mg).

Hot melt extrusion
Hot melt extrusion approach represent the advantageous mean of preparation of solid dispersions by using the twin screw hot melt extruder where only thermostable components are shown in Figure 3. The physical mixture is introduced in to the hopper that is forwarded by relevant. The extruder consists of a hopper, barrel, a die, a kneading screw and heaters as feed screw and finally is extruded from the die. The effect of screw revolution speed and water content on preparation of solid dispersions should be investigated, since these parameters have profound impact on the quality of solid dispersions. To reduce the melt viscosity in the extrudate and to be able to decrease temperature settings, a plasticizer can be added to the formulation. Typically, conventional plasticizer such as triacetin or polyethylene glycol is used in concentration range of 5-30 % weight of the extrudate that lower the processing temperature. Carbon dioxide can act as temporary plasticizer. During extrusion, carbon dioxide is transformed on gaseous phase. As a consequent carbon dioxide escapes from extrudate and does not appear in final product. The role of methyl parabene and sorbitol has also been investigated as plasticizer in preparation of sold dispersions in extrusion method [25-28].

Figure 3
Schematic showing components of a single screw melt extruder.
Advantages

1. Possibility of continuous production makes it be suitable for large scale production.
2. The product is easier to handle because at the outlet of the extruder, the shape can be adapted to the next processing step without grinding.

Drawbacks

1. High energy inputs require shear forces and temperature.
2. Design of screw assemblies and extruder dies, have significant impact on degradation of drugs and excipients\(^{[29]}\).

Melt agglomeration process

This technique has been used to prepare solid dispersion where the binder acts as a carrier. In addition, solid dispersions are prepared either by heating binder, drug and excipients to a temperature above the melting point of the binder (melt in procedure) or by spraying a dispersion of drug in molten binder on the heated excipients (spray on procedure) by using a high shear mixer. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersions by melt agglomeration. It has been investigated that the spray on procedure with PEG-3000, Poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition, the melt in procedure also results in homogeneous distribution of drugs in agglomerate\(^{[23]}\).

Effervescent method

Effervescent solid dispersions incorporate sodium bicarbonate and organic acids (citric, tartaric or succinic), which react with each other to yield an effervescent mixture. By combining poorly soluble drugs with organic acids, one should obtain an effervescent solid dispersion, which may increase the dissolution and absorption rates of poorly soluble drugs. Citric acid/sodium bicarbonate was found to be the most effective carrier for releasing prednisone and primidone and sodium bicarbonate/succinic acid was
observed to be the best carrier for griseofulvin. Such dispersion can be made by fusion technique as explained above\textsuperscript{[30]}.

**Adsorption on insoluble carriers**

These dispersions are also referred to as surface solid dispersions. In this method, the support material is suspended in a solution of the drug followed by evaporation of the solvent. The resulting material contains the drug in a “molecularly micronized” state on the surface of the carrier. Here, adsorbents maintain them concentration gradient (Cs-Ct), to its maximum, thus increasing the dissolution rate. A special technique under these methods is the fluidized bed system. It involves first preparation of spraying solution by dissolving both drug and carrier and then sugar spheres are charged to fluidized bed granulator and coated.

These spheres are fluidized by spraying solution and the coated pellets are dried. Solid dispersion of poorly water-soluble drug nifedipine was prepared in hydroxypropylmethylcellulose (HPMC) on sugar spheres using this technique\textsuperscript{[14]}.

**Co-Grinding**

In this method, accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill for grinding. Strong grinding force gives to solid increases in the activation energy on the surface and in the distortion of the crystal lattice together with comminution. Boldyrev et al have termed this process as mechanical activation. Some drugs like griseofulvin lose their crystallinity when ground with microcrystalline cellulose in a vibrational ball mill with subsequent increase in dissolution rate and bioavailability\textsuperscript{[24]}.

**PLAUSIBLE FACTORS INFLUENCING DRUG RELEASE**

1. **Nature of carriers**

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 matrix. However, incorporation of poorly water soluble drug into water-soluble carrier(s) leads to acceleration of drug release\textsuperscript{[14,17]}.

2. Drug carrier ratio

The dissolution rate of a drug increases with increase in the proportion of drug carrier. However, this is true only 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 out carrier could form a concentrated layer of solution around the drug particle, resulting in lowering of release rate. Accordingly, for the solid dispersion to be effective in enhancing the solubility, an appropriate drug-carrier proportion is desired. It would certainly be more advantageous if carrier is used in minimal amounts. Co-precipitates of flurbiprofen, phospholipids, for instance, when used in the ratio of 20:1, yields 9-fold greater dissolution rate of flurbiprofen. Albeit the proportion of carrier is far less as compared to that of drug, yet it is quite effective in dissolution enhancement. This is because phospholipids spontaneously form liposome bilayer structures in an aqueous media that entrap solutes either in an aqueous phase or bilayer, thereby hastening the dissolution process. Similarly, in case of glipizide the rate of dissolution was increased when the ratio of polymer is increase, about 5-fold greater dissolution rate of glipizide with poloxamer 188 in the ratio of 1:10\textsuperscript{[24,25]}.

Method of preparation

Solid dispersions prepared by melting generally showed faster dissolution rates than those prepared by solvent method. Solid dispersions 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 diazepam particles\[15\].

**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 aluminum 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\[26\].

**Synergistic effect of two carriers used**

This has been exemplified in ibuprofen solid dispersions using PEG, talc and PEG-talc as dispersions carriers. It was reported that in 9.1% drug loading, ibuprofen dissolved at the end of 120 min was about 66% 73% and 93% from Ibuprofen talc, ibuprofen-PEG and PEG-talc dispersions respectively. Workers attributed this synergism to the partial replacement of PEG with talc. This would cause improved wettability of ibuprofen and hence enhanced solubility of drug by overlapping the diffusion layers between PEG and ibuprofen\[17\].

**Influence of carrier chain length/molecular weight**

The carrier chain length or its molecular weight may play a significant role in drug release from solid dispersions. Chain length of PEGs or Molecular weight (MW) 4000-6000 are the most frequently used for the manufacture of solid dispersion, because in this MW range the water solubility is still very high, but hygroscopic is not a problem and the
melting points are already over 50°C. Usually PEGs with MW weights of 1500-20000 are used. If PEG with too low MW is used, this can lead to product with a sticky consistency that is difficult to formulate in to pharmaceutically acceptable product. Similarly, the chain length of PVP has very significant influence on dissolution rate of the dispersion as the aqueous solubility of the PVPs become poorer with increasing chain length and a further disadvantage of high MW PVPs is their much higher viscosity at a given concentration\cite{22}.

**CHARACTERIZATION**

A number of techniques can be employed to identify the physical nature of the solid dispersions. No single method however, can furnish the complete information and hence a rational combination of the methods is preferred.

**Thermal Analysis**

**Thermo-microscopic Methods**

This is a visual method of analysis using a polarized microscope with a hot stage to determine the thaw and melting points of solids. The method is advantageous as small amount of sample is required and direct observation of the changes taking place in the sample through the thaw and melt stages. The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems\cite{28}.

**Differential thermal analysis (DTA)**

This is an effective thermal method for studying the phase equilibria of pure substance or solid mixture. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transition, evaporation, sublimation, desolvation and other types of changes such as decomposition of the sample can be detected. The method has been used routinely to identify different types of solid dispersion\cite{28}. The greatest advantage of using this technique is in constructing phase
diagram of high reproducibility; a higher temperature range is permitted, greater resolution realest. A sample size of less than 1 mg can be used [5].

**Differential Scanning Colorimetry (DSC)**

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 behavior of crystallization and melting and deriving phase diagrams of solid dispersions.[23,20].

**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[29,30].

1. Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances.
2. 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, \( \theta \), and the distance between each set of atomic planes of crystal lattice, \( d \), is given by equation: \( M \lambda = 2d \sin \theta \), where \( M \) represent the order of diffraction [19,31].

**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 matrix [29,33].

**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. 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.

**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.

**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.

**CONCLUSION**

Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bio availability 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.

The increasing number of poorly water soluble compounds entering pharmaceutical development pipeline in the recent years has prompts the use of several different formulation approaches to enhance oral bioavailability of such compounds.
REFERENCES


19. Muhrer GU, Meier F, Fusaro S, Mazzotti M. Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of


29. V. Kamalakkannan et al. Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review Journal of Pharmacy Research 2010, 3(9), 2314-2321


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