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Solid Dispersion: Approaches, Technology involved, Unmet need & Challenges

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ABSTRACT

More than 60% of potential drug products suffer from poor water solubility. This frequently results in potentially important products not reaching the market or not achieving their full potential. Most of the chemical entities are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery system. Experience with solid dispersions over the last 20-30 years indicates that this is a very fruitful approach to improving the release rate and oral bioavailability of poorly water soluble drugs and the availability of a wide variety of polymers that are themselves poorly soluble or which swell under aqueous conditions suggests that solid dispersions have tremendous potential in the area of controlled release dosage forms.

Keywords: Solid solution, Solid dispersion, Dissolution, Glass solutions, Eutectic mixtures

INTRODUCTION

The oral route of drug administration is the most important method of drug administering for systemic effects and it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route. [1,22] Among them tablets and capsules are most frequently given by these route. These solid dosage forms are always prepared with some excipients/ carriers, which effects the physicochemical properties of a drug. Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, nifedipine, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now a days presents one of the most frequent and greatest challenges to formulation scientists. [2,20]

It is estimated that 40% or more of new chemical entities (NCEs) being identified through combinatorial screening programs are poorly soluble in water, which is a critical determinant of oral bioavailability and solubility of many newly developed high-potential drugs is an obstacle in formulation development, in addition Biopharmaceutical Classification System (BCS) highlights dissolution as the rate-limiting step for oral absorption of class II and IV drugs. Conventional dosage forms of these drugs, therefore, often have erratic and variable performance in preclinical and clinical evaluation leading to sub-optimal therapeutic concentration. [3] A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it take to be absorbed in the gastrointestinal tract and the ability to deliver poorly soluble drugs will grow in significance in the coming

years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Similarly, generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry. [4]

Relative to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher inter-patient variability. Poorly soluble compounds also present many in vitro formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the in vivo absorption. [3]

Thus a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Solubility and dissolution

The physicochemical properties of the drug substance play a prime role in controlling its dissolution from the dosage form in which the aqueous solubility of the drug is the major factor which determines its dissolution rate.

Dissolution is the process by which a solid of only fair solubility characteristics enters into solution. In 1897, Noyes and Whitney suggested that the rate of dissolution of solid substances is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. They developed the mathematical relationship that correlates the dissolution rate to the solubility gradient of the solid. Their equation is still the basic formula upon which most of the modern mathematical treatments of the dissolution phenomenon revolve, which is

$$dc/dt=k(C_s-C_t) \quad (1)$$

where, dc/dt is the dissolution rate of the drug, k is the proportionality constant,

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C_s is the saturation concentration (maximum solubility), C_t is the concentration at time t and $(C_s - C_t)$ is the concentration gradient. The proportionality constant, k also is called the dissolution constant and equation has been shown to obey first order kinetic. [5]

Drug dissolution is a prerequisite for absorption from the gastro-intestinal tract. However, after oral administration dissolution of drugs poorly soluble in aqueous solutions (lipophilic drugs) is often slow and irreproducible due to the aqueous environment of the gastro-intestinal lumen. As a result, the oral bioavailability of class II drugs (highly permeable over the intestinal membrane and poorly soluble) can be improved by increasing the dissolution rate of the drug.

Nernst and Brunner introduced the diffusion layer model. They assumed that dissolution at the solid-liquid interface is rapid and transport of the solute to the bulk is completely determined by diffusion through a stagnant boundary layer surrounding the dissolving interface. The dissolution rate of a solid is then given by:

$$dm/dt = A.D\delta(C_s - C_{bulk}) \quad (\text{eq.2})$$

in which dm/dt is the dissolution rate (kg-s⁻¹), A represents the area available for dissolution, D the diffusivity of the dissolving compound in the solvent, δ the thickness of stagnant boundary layer, C_s is the equilibrium solubility and C_{bulk} is the concentration in the bulk.

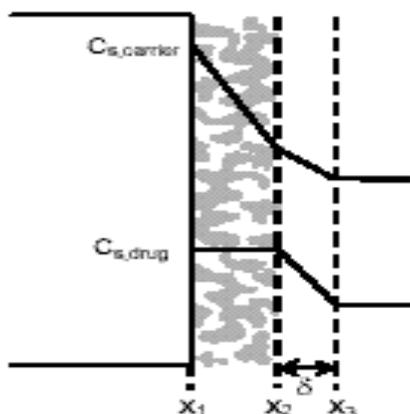


Figure 1: Concentration profiles of drug and carrier during dissolution of a binary mixture

However, the dissolution rate of a two component system can be more complex. Higuchi et al. investigated a uniform, intimate, non-disintegrating mixture of two dissolving compounds both in crystalline state. One of the compounds (e.g. the carrier: C) generally dissolves faster, resulting in a porous layer consisting of the other compound (e.g. the lipophilic drug: D) (see figure 1). Author investigated the effect of this layer and the composition of the mixture on the dissolution rate of the fast dissolving component C . In fact the deceleration of the dissolution of C was discussed while dissolution of D was assumed to remain unchanged. They considered only the steady state release portion of the problem and assumed that in the porous layer the concentration of D is equal to its solubility ($C_{Drug} = C_s, Drug$). This implies that no supersaturation of D occurs in the liquid compartment of the porous layer. It also implies a constant flux of D to the bulk,

since the thickness of the stagnant boundary layer δ will be constant. [6]

Various approaches of solubility enhancement -Enhancement of bioavailability of poorly water soluble drug remains one of the most challenging aspects of drug development. Various approaches have been suggested to en-

hance the solubility which include

- a) pH Control
- b) Cosolvency
- c) Solubilization
- d) Complexation
- e) Chemical modification of the drug
- f) Particle size reduction
- g) Salt formation
- h) Hydrotropy

Solid dispersion

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. More specifically Chiou and Riegelman defined these systems as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method'. Solid dispersion was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. It was defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by melting (fusion), solvent or melting-solvent method. More than 500 papers have been published on the subject and various materials are employed as drug carriers. [7]

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, solubilization by cosolvents, and particle size reduction. It has been reported that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. 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 addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size.

Because of the simplicity of manufacturing and scale up processes, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared by using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. Single or combination of carriers are essential for development of solid dispersion. [4]

Mechanisms responsible for solubility enhancement from solid dispersion A number of theories have been proposed by which the dissolution rate is improved. These are-

Particle size reduction and reduced agglomeration

These may be usefully considered together as both are related to increase in the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties, hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area. [8]

Increased solubility or dissolution rate of the drug

Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in vitro experiments the carriers often elicit

minimal solubility increases. This does, however, work on the assumption that the concentration of the carrier after complete dissolution in the water bath (e.g. 0.5 g/l) may be used as a model of the behaviour at the dissolving surface. Similarly, the carrier and drug may form a soluble complex, although the evidence for this occurring with other carriers is weaker. Finally, changes to the physical properties of the drug such as degree of crystallinity and polymorphic form may also be considered under this category.

Overall, therefore, there appear to be two sets of observations with regard to the mechanism of drug release from solid dispersions. In the first instance, some systems appear to show carrier-controlled release whereby, at least at low drug loadings, the rate of release is controlled by that of the carrier and is independent of drug properties. Secondly some systems show release behaviour that is dependent on the properties of the drug rather the polymer, even at low drug loadings. The following questions therefore arise; what is happening to the drug during either of these processes, which factors determine whether the dissolution is carrier- or drug- controlled and what are the implications of understanding the mechanism for dosage form design? [7]

Possible mechanism of dissolution from solid dispersions and implications for manufacture

The release mechanism will depend on whether the drug dissolves in the polymer diffusion layer rapidly or not which will in turn be dependent largely on the solubility of the drug in this layer. However, other considerations must also be borne in mind. For example, the hydrodynamics of the dissolution process may also play a role in determining the mechanism in that more rapid stirring speeds may favour drug-controlled dissolution by enhancing the rate of polymer dissolution into the bulk in relation to drug dissolution into the diffusion layer. Similarly by changing the physical form of the drug (e.g. size reduction), one could conceivably change the mechanism by altering the dissolution kinetics into the diffusion layer. Furthermore, while the process has been described above as one of two extremes it is possible that in many cases elements of both are present, e.g. the particles may partially dissolve in the diffusion layer before being released intact, thereby providing two simultaneous mechanisms of dissolution. However, the model does serve to provide an explanation for the differences in behaviour of various drugs and also suggests that the measurement of drug solubility in carrier solutions may, with refinement, provide a means of predicting the dissolution mechanism. [7]

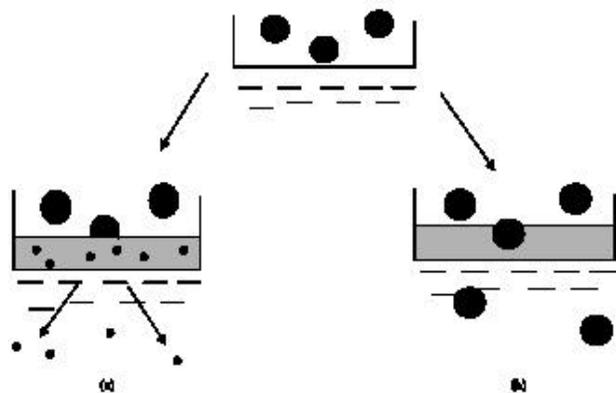


Fig. 2 Schematic diagram showing the fate of drug particles during the dissolution process.

- (a) Carrier-controlled dissolution, whereby the drug dissolves into the concentrated carrier layer prior to release and
- (b) Drug-controlled dissolution whereby the drug is released effectively intact into the dissolution medium. Large spheres represent undissolved drug particles, small spheres partially dissolved drug particles, shaded regions correspond to hydrated material.

Author proposed a model, outlined in Fig.8 that attempts to explain how the drug particles may be behaving during the dissolution process. The model works on the premise of there being a highly concentrated polymer layer at the dissolving surface (at least at low drug loadings) through which the drug must pass prior to release into the bulk phase. Fig. No. 3 presents a representation of the salient features of the solid dispersion structure relevant to the proposed model shown in Fig No.2.

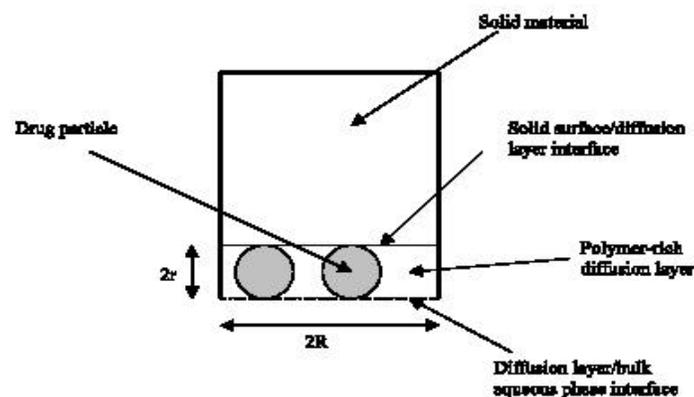


Fig.no.3 Representation of the salient features of the solid dispersion Structure(Craig D.Q.M.2001)

Types of solid dispersions

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. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 1.

Table No.1- Different types of solid dispersion [9]

Solid Dispersion Type	Matrix**	Drug**	Remarks	No.Phases
Eutectics	C	C	The first type of solid dispersions prepared	2
Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
Solid solutions				
Continuous solid solutions	C	M	Miscible at all compositions, never prepared	1
Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2
Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous; 2 phases even though drug is molecularly dispersed	1 or 2
Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: drug in helical interstitial spaces of PEG.	2
Glass suspension	A	C	Particle size of dispersed phase depend on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix.	2
Glass suspension	A	A	Particle size of dispersed phase depend on cooling/evaporation rate. Many solid dispersions of this type	2
Glass solutions	A	M	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP	1

* A: matrix in the amorphous state

C: matrix in the crystalline state

** A: drug dispersed as amorphous clusters in matrix

C: drug dispersed as crystalline particles in the matrix

M: drug molecularly dispersed throughout the matrix

I. Simple eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state (Fig. 4). 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 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. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

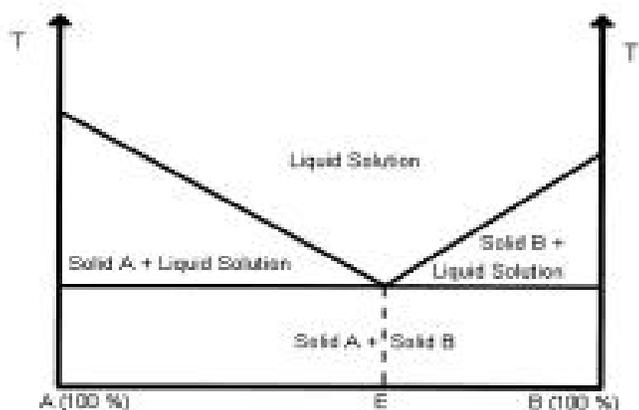


Fig.4 Phase Diagram for Eutectic mixture

I. Amorphous solid solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig. 5). 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 that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

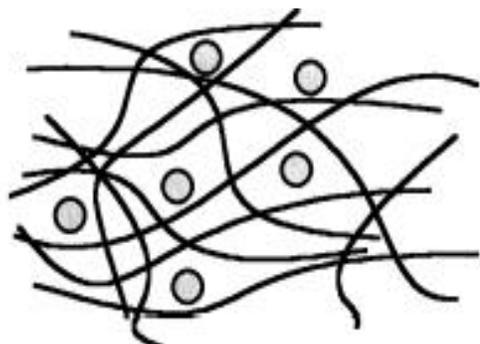


Fig.5 Amorphous solid solutions

I. Solid solutions

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

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.

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 is shown in Fig. 6. a and b show 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 et al. that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

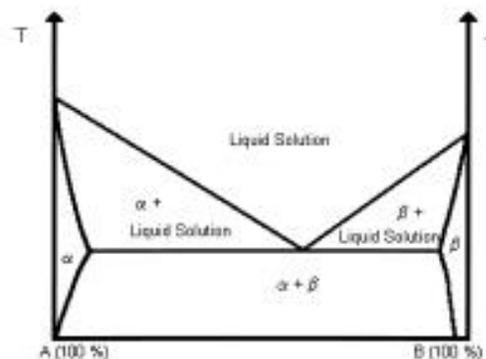


Fig. 6. Phase diagram for a discontinuous solid solution

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 fit into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig. 7. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecule.

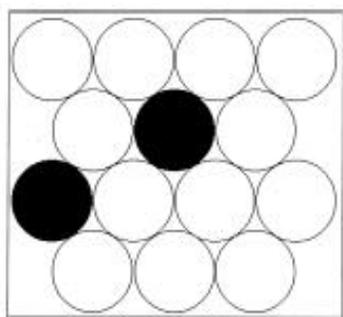


Fig. 7. Substitutional crystalline solid solution

Interstitial crystalline solid solutions-

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Figs. 8 and 9). 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.^[2]

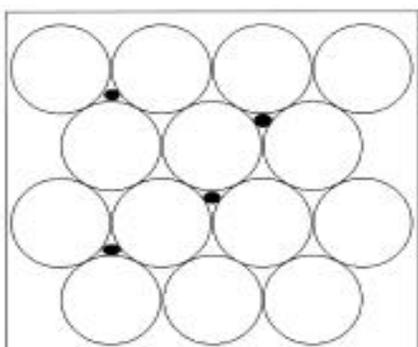


Fig. 8. Interstitial crystalline solid solution

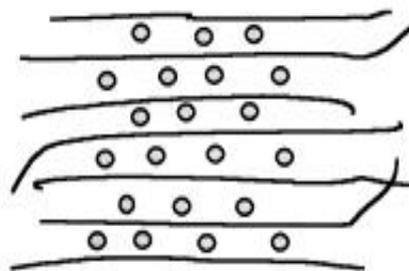


Fig.9 Interstitial solid solution of small molecules in the crystalline phase of the polymer

IV Glass solutions & suspension-

A glassy solution is a homogeneous glassy system in which a solute dissolves in a glassy carrier. 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 barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. Examples of carriers that form glass solutions and suspensions, include citric acid, sugars such as dextrose, sucrose, and galactose, PVP, urea and PEG.^[10,17]

Table No.2 Different carriers used for the prepration of solid dispersion

S.NO.	CARRIER	DRUG	SCIENTIST
1.	Sorbitol	Rofecoxib	Naveen Ahuja, et al.2006.
2.	Polyethylene glycol 4000&6000	Temazepam	G. Van den Mooter,et al.1997
3.	Polyethylene glycol 4000&6000	Felodipine	Evangelos et al.2006
4.	Polyethylene glycol 4000&6000	Etoricoxib	Bhanubhai N.S. et al.,2006
5.	Polyethylene glycol 4000&6000	Rofecoxib	Naveen Ahuja, et al.2006.
6.	Mannitol	Rofecoxib	Naveen Ahuja, et al.2006.
7.	Citric acid	Felodipine	Summer M.P. et al.1976
8.	Citric acid	Rofecoxib	Naveen Ahuja, et al.2006.
9.	Polysorbate80	Nifedipine	Hemant N. Joshi, et al.2003
10.	Polyvinylpyrrolidone(PVP)	Troglitazone	S. hasegawa et al.2005
11.	Polyvinylpyrrolidone(PVP)	Rofecoxib	Naveen Ahuja, et al.2006.
12.	Poloxamer188	Felodipine	Choksi Rina et al. 2007
13.	Poloxamer188	Rofecoxib	Naveen Ahuja, et al.2006.
14.	Urea	Rofecoxib	Naveen Ahuja, et al.2006.
15.	Gelucire	Flubiprofen	Solliman M.S.et al.2002
16.	Nicotinamide	Nifedipine	Suzuki H. et al.2007
17.	Ethyl urea	Nifedipine	Suzuki H. et al.2007
18.	Phosphatidylcholine and lactose	Phenacetine	Ozeki H. et al.2007
19.	Hydroxypropyl-β-cyclodextrin	Nifedipine	S. Chutimaworapan et al.2007
20.	Poloxamer 188	Ibuprofen	Passerini et al.2002
21.	Poloxamer 188	ABT-963	Chen et al.2002
22.	Poloxamer 407	Nifedipine	Chutinawarapan et al.2005
23.	Poloxamer 188, Gelucire 50/13	Nifedipine	Vippagunta et al.2005
24.	Gelucire 44/14	REV 5901	Sheen et al.2005
25.	Gelucire 44/14	LAB-687	Serajuddin et al.2003
26.	Mixture Gelucire 44/14-lecithin	Ubidecarenone	Pozi et al.2001
27.	Gelucire 44/14 and PEG 6000	Glibenclamide	Tashtoush,2003
28.	Gelucire 44/14, Vitamin E TPGS	Carbamazepine	Squillanate et al.2005
29.	Gelucire,Capmul,CapmulMCMC10	Ceftriaxone	Seong-Wan CHO et al.2005
30.	Mixture of Gelucire 50/13, Polysorbate 80, castor oil	Ritonavir	Aungst et al.2002
31.	PEG 3350- Labrasol- Polysorbate 80	RP 69698	Sheen et al.2003
32.	PEG, Myrj 2, Eudragit E 100	Indomethacin	Hadi et al.2003

Different methods of prepration of solid dispersion

Several approaches have been attempted for the preparation of solid dispersion, to improve the solubility and dissolution characteristics of poorly water-soluble drugs which include-

- a) Spray drying
- b) Fusion method
- c) Solvent evaporation
- d) Hot-melt extrusion
- e) Particle size reduction
- f) Supercritical fluid (SCF) processes.
- g) Kneading
- h) Inclusion Complexes
- i) Direct Capsule filling
- j) Electrostatic Spinning Method
- k) Surface-active Carriers

(a) Spray drying - The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule.^[18]

In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is evaporated at 40°C under reduced pressure by using vacuum evaporator, obtained mass is dried in a dessicator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent. The product is crushed, pulverized & sieved through

a suitable mesh number sieve.

This technique was successfully employed for the preparation of solid dispersions of Etoricoxib (Chauhan B. et al.2005), Carbamazepine (Koster et al.2006) and Glibenclamide (Chauhan B. et al.2005)

Limitations- Preparation of solid dispersions by conventional spray drying has been found problematic. The sticky and tacky mass is obtained by a conventional spray drying technique.^[12]

Limitations- Problem related with organic solvent limit this technology.

(b) Fusion method- The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath.^[11]

Solid dispersions containing 1-32% (w/w) primidone were prepared by fusing the drug with citric acid and rapidly cooling the melt by Summer MP Andenever RP 1976 .

Limitations- In the case of meltig method problems such as incomplete miscibility between drug and carrier may occur due to the high viscosity of a polymeric carrier in the molten state and thermally unstable drugs can be degradable due to the requirement of relatively high temperature.

Thermal instability and immiscibility have resulted in development of the fusion- solvent method which is particularly useful for drugs with high melting points or which are thermolabile.^[12]

(c) Solvent Removal Process- Solid dispersion prepared by solvent removal process were termed by Bates as "coprecipitates". In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, obtained mass is dried in a dessicator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve.

Reddy S.J. in 2005 successfully prepared a solid dispersion of Gliclazide with PEG 4000 & 6000 by this method.

Limitations-The choice of solvent and its removal rate are critical to the quality of the dispersion. Since the chosen carriers are generally hydrophilic and drugs are hydrophobic, the selection of common solvent is difficult and its complete removal, necessitated by its toxic nature, is imperative.^[12]

(d) Hot-Melt Extrusion- The extruding method, was originally designed as an extraction / casting method for polymer alloys in plastic industry, is now used to process cereals and functionalize food materials, such as tissue products from animal proteins. Hot melt extrusion approach represent the advantageous mean of preparation of SD(s) by using the twin screw hot melt extruder where only thermo stable components are relevant. The extruder consists of a hooper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die. The effect of screw revolution speed and water content on the preparation of SD(s) should be investigated, since these parameters have profound impact on the quality of SD(s). Nakamichi et al. studied that presence of kneading paddle element of screw results in super saturation on dissolution testing while slow revolution rate of screw and addition of the suitable amount of water increased rate of dissolution although no super saturation occurred. In addition, high screw speed –high feed rate processes in comparison with low screw speed–low feed rate processes caused an increase in extrudate radius and porosity and decrease in mechanical strength and drug release rate from the matrix attributed to the expansion promoted under certain extrusion conditions.^[11]

e.g. A fast-release dosage form of carbamazepine was prepared using lactose as a hydrophilic filler and PEG 4000 as a binder at a temperature below its melting point.

Melt-extruded ibuprofen dispersions were compared with the ibuprofen lysinate in healthy volunteers. Bioequivalence was demonstrated with the relevant parameters area under the curve (AUC) and maximum concentration (C_{max}). Also, the t_{max} as a measure for onset proved to be equivalent, with 0.5 hours for test and reference.

An amorphous solid dispersion of Itraconazole/HPMC (40/60 wt/wt) was formed from milled melt extrudate and resulted in a significantly increased dissolution rate compared with the physical mixture.

Limitations-The disadvantages are few and mainly relate to negative effects of shear force.^[12]

(e) Particle size reduction-

The bioavailability of low solubility drugs is often intrinsically related to drug particle size. By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction.^[12]

Limitations-However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo-sensitive or unstable active compounds., traditional comminution and micronising techniques may not be able to reduce particle size sufficiently to satisfactorily solubilise the drug, and self-emulsifying or microemulsion techniques may be applied.

Particle size reduction, whether via traditional micronisation or novel nanosizing methods, may not be applicable to all poorly soluble compounds, most notably high dose drug products and those compounds with higher melting points.^[12]

(f) Supercritical Fluid (SCF) Processes- This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursors dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups.

Since the first experiences of Hannay et al in 1879, a number of techniques have been developed and patented in the field of SCF-assisted particle design. These methods use

SCFs either as solvent: Rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance⁷⁹.

In the supercritical fluid antisolvent techniques, carbon dioxide is used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system (ASES), precipitation with a

compressed fluid anti-solvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS). The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. [11]

T. Van Nijlen et al.2003 studied improvement of the dissolution rate of artemisinin by means of supercritical fluid technology and solid dispersions 3 January 2003.

Limitations-The use of co-solvents introduces the familiar issues of achieving sufficient solvent extraction and volatile materials handling into the manufacturing process, increasing the complexity of production. The use of high pressure CO₂ may also cause significant scale-up and operation issues to arise, such as particle aggregation upon dispersion from nozzles and capillaries. [12]

(g) Kneading- In this method a mixture of drug and carrier is wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste is dried under vacuum for 24 hours. Dried powder is passed through sieve no. 60 and stored in a dessicator. solid dispersion involving PVP and valdecoxib were prepared by kneading technique.

Limitations- This method can not be applied to all poorly water soluble drugs. [13]

(h)Inclusion Complexes- The improvement in solubilisation ability within these water-soluble polymer/drug-included CD aggregates requires less cyclodextrin to solubilise the same amount of drug, reducing the volume constraints present for non-aggregated CDs and increasing the range of delivery technologies available. Drug-CD complexes are commonly formed through either supersaturating a CD solution with drug and mildly agitating the solution for an extended period of time, or adding a mass of drug to a CD and solvent slurry and 'kneading' to produce a paste which is then dried and sieved.

Although several delivery technologies have been developed to take advantage of drug-included CD formulations in both water-soluble polymer aggregated and non-aggregated forms, such as CAPSITOL® technology offered by CyDex and CAVAMAX® technology offered by Wacker-Chemie GmbH, relatively few oral CD-based drug products are currently on the market due to unfavorable regulatory positions in regard to toxicity and stability issues. [12]

Limitations-These method is not applicable to all poorly water soluble drugs.

(i) Direct Capsule Filling- The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. It was not until much later that the potential application of the technique for solid dispersions was fully realized. Laboratory-scale semiautomatic equipment and large-scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. For example, the filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule-filling machine (Zanasi Co, Bologna, Italy). 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. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer. [12]

(j) Electrostatic Spinning Method- Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle⁷². This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the

cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried⁷³. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest⁷⁴⁻⁷⁷. This technique can be utilized for the preparation of solid dispersions in future. [14]

Itraconazole/HPMC nanofibers have been prepared using this technique. Electrospun samples dissolved completely over time, with the rate of dissolution being dependent on the type of formulation presentation and the drug:polymer ratio. Because the technique has been successfully used in other fields, the technique can be extended in the pharmaceutical industry for the preparation of solid dispersions. [12]

(k) Surface-active Carriers-

A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. The surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, adsolubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for the preparation of solid dispersions. [11]

Two of the important surface-active carriers are utilized for the preparation of solid dispersions that is Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 (Gattefosse Corp, Gennevilliers, France) has commonly been used in solid dispersion for the bioavailability enhancement of drugs.

Limitations- Solid dispersion in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drug. Dordunoo et al.2005 reported that the particle size of a drug in a solid dispersion remained unchanged if it is just mixed with the carrier instead of dissolving in it. On the other hand, if the drug is dissolved by heating in excess of its solubility in a carrier under normal storage condition, it may subsequently crystallize out from the solid dispersion. Either situation would defect the purpose of bioavailability enhancement of poorly water-soluble drugs by solid dispersion. Another possible limitation of the use of surface-active carrier reported by Aungst et al. is that the bioavailability of a drug may vary depending on the amount of carrier administered along with it. This variation is because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid. Serajuddin et al. reported a method whereby the rate and efficiency of dispersion of drug in aqueous media from different formulations can be studied. [4]

Evaluation parameters for solid dispersions-

- a) Phase-solubility studies
- b) Microscopy-
 - Scanning electron microscopy
 - Optical microscopy
- c) Drug content and moisture content
- d) Powder dissolution study
- e) X-ray powder diffraction (XRPD)
- f) Interaction studies
 - Fourier transform infra red spectroscopy
 - Differential scanning calorimetry (DSC)
- g) Stability study

(a) Phase-solubility studies

For phase-solubility analysis an excess amount of drug is added to the aqueous solutions of carrier in specific dissolution medium containing increasing concentrations of the carrier. After that the flasks is sealed and shaken at 37 °C for 48 h in a thermostatically controlled water bath and the samples are filtered through a 0.45 µm cellulose nitrate membrane filter. The

filtrate is suitably diluted and analyzed spectrophotometrically at suitable wavelength.^[15]

(b) Microscopy

Optical microscopy - the optical microscopy method using calibrated ocular and stage micrometer can be utilized for particle size analysis of powder. A number of particles are measured and mean diameter is calculated.

Scanning electron microscopy (SEM) - Electron microscopy techniques such as SEM are very useful in ascertaining the particle size and morphology of solid particles. It uses electron transmitted from the specimen surface.^[3]

(c) Drug content and moisture content

In this method definite amount of solid dispersion is taken and dissolved in a suitable solvent in which drug is freely soluble, then after appropriate dilution concentration are measured by UV spectrophotometry.

HPLC is also very useful tool for drug content measurement. Standard solution is prepared by diluting the stock solution with mobile phase to give solutions containing drug in the concentration range of 10-100µg/ml and appropriate quantity (approx 20µl) of the standard solutions is injected manually under operating chromatographic conditions and absorbance is measured at specific wavelength. Calibration graph is constructed by plotting peak areas versus concentration of drug and the regression equation is calculated.^[3]

(d) Powder dissolution study

The powder dissolution can be performed according to USP paddle (100 rpm) using powder equivalent to specific quantity of pure drug distilled water/ 0.1N HCl equilibrated at 37 ± 0.2 °C. Suitable aliquots are withdrawn at different time interval and are replenished with fresh dissolution medium maintained at the same temperature and aliquots are filtered through 0.45-µm membrane syringe filter. Amount of drug released is measured by UV spectrophotometrically at suitable wavelength.^[13]

(e) Powder X-ray diffraction studies-

Powder X-ray diffraction (PXRD) patterns can be obtained by employing X-ray diffractometer. The samples is analyzed over 2θ range of 2–40° with scan step size of 0.020° (2θ) and scan step time of 1 s.^[15]

(f) Interaction studies

▪ **Fourier transform infra red spectrophotometry**

Fourier transform infrared (FT-IR) spectroscopy can be employed to characterize the possible interactions between the drug and the carrier in the solid state on an FT-IR multiscope spectrophotometer by the conventional KBr pellet method. In this method Fourier transformed Infrared (FTIR) spectra of samples (Solid dispersion, pure drug, carrier) are obtained, using an FTIR spectrophotometer (Shimadzu). About 10 mg of the sample is mixed with dried potassium bromide of equal weight and samples are scanned. The spectra are scanned over a frequency range 4000–500 cm⁻¹ with a resolution of 4 cm⁻¹.

Differential scanning calorimetric (DSC) analyses- is another method to study the possible interaction between drug, carrier, solid dispersion formulation and its corresponding physical mixture. In this method Samples (approx. 6.5–10.9 mg) are heated under nitrogen atmosphere on an aluminum pan at a rate of 10 °C/min over the temperature range of 5 and 300 °C. Thermal data analyses of DSC thermograms are obtained.^[16]

(g) Stability study

The stability of the optimized preparations should be monitored at 40 ± 2 °C/ 75 ± 5% RH and samples are evaluated for saturation solubility, in vitro release and change in crystallinity using DSC and XRPD.^[3]

Application of solid dispersions in dosage forms

The formulation of solid dispersions into drug administration forms also presents a

great challenge. Essential steps like milling, sieving or granulation can affect the properties of the solid dispersion. Stress induced crystallization has been observed

for amorphous trehalose glasses resulting in degradation of the incorporated protein. Therefore, sugars with low crystallization tendency are preferred. Furthermore, many dissolution studies are performed with powders or grinded solid dispersions, instead of tablets. This is probably because disintegration of the tablet is problematic. Many matrices become waxy and sticky or even melt during tablet compaction. The two most used matrices, PEG and

PVP, have very good binding properties. Moreover, they fill up the pores during the compaction process thereby hindering rapid dissolution of the tablet. Sometimes capping is caused by the elastic behaviour of completely dry amorphous materials. The use of other excipients to prepare solid dispersion tablets with high tensile strength and proper dissolution and disintegration properties should be investigated. Finally, the application of fast release solid dispersions for non-oral routes needs to be investigated.

Unmet needs and challenges

In spite of almost thirty years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far. Amongst these are:

- 1.) Gris-PEG (Novartis), griseofulvin in PEG
- 2.) Cesamet (Lily), nabilone in PVP
- 3.) Sporanox (Janssen Pharmaceutica / J&J), itraconazole in HPMC and PEG 20,000 sprayed on sugar spheres

Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization. The rare occurrence of solid dispersion based pharmaceutical dosage forms in the clinic are due to problems in scale-up of preparation methods, difficulties in dosage form development and poor and irreproducible physical and chemical stability of drug and matrix.

Knowledge about the behaviour of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occur place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Unfortunately, most reports deal with a case, in which the authors used a specific matrix to accelerate the dissolution of a specific drug in-vitro or to show increased bioavailability. These studies prove the potential of solid dispersions but for successful industrialization and clinical application, the following challenges have to be faced first.

Exploring characterization tools

Any study on solid dispersions requires physical and/or chemical characterization.

During or after preparation, during stability studies and during dissolution experiments, knowledge of the physical and chemical state of matrix and drug and

changes thereof is indispensable. Currently, characterization tools of amorphous solid dispersions are poorly developed. Furthermore, a technique is needed to measure the distribution in solid dispersions, i.e. separate molecules, homogeneously distributed, amorphous clusters or crystalline particles. Such a technique should be non-invasive for the sample, maintaining the molecular structure during the measurement. Furthermore, it should be noted that due to the lack of proper characterization tools, dissolution experiments are mistakenly used for this purpose. Sometimes physical stability is proven by an unchanged dissolution rate without any elucidation of the molecular structure. Studying either physical stability or dissolution behaviour requires proper characterization methods.^[20,21]

Conclusion : Despite many advantages of solid dispersion, issue related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water soluble drugs. Successful development of solid dispersion system for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active carriers and self emulsifying carriers. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and as expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly in near future.

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