

POLYMERIC DISPERSIONS: PROCESS TO MODIFY RELEASE BEHAVIOR OF DRUGS

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Abstract

Pharmaceutical excipients now come in a wide range of hydrophobic and hydrophilic carriers that are used to create solid dispersions. The composition of sustained release solid dispersions and/or quick release solid dispersions depends on the nature of the carriers. The original carriers used were crystalline, nevertheless they were changed into amorphous form dispersions with improved characteristics. The earlier carriers mostly consisted of synthetic ones. The usage of synthetic carriers has recently been supplanted by a recent trend toward the use of biological carriers. This article gives an overview of the many hydrophilic carriers—synthetic, natural, semi-synthetic, and modified natural—that are utilized to create solid dispersions.

INTRODUCTION

An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problem, controlled release and sustained release delivery systems are receiving considerable attention from pharmaceutical industries worldwide. A controlled release drug delivery system not only prolongs the duration of action, but also results in predictable and reproducible drug-release kinetics. One advantage of controlled release dosage forms is enhanced patient compliance. Drug delivery systems based on the principles of solid dispersion (1). The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. As Figure 1 indicates that salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. Much of the research that has

been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption in vivo will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) (Figure 2) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs (2). Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

Oral drug delivery is the simplest and easiest way of administering drugs (3). Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosage forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration (4, 5). In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration, which can detract from the drug's inherent efficacy (6, 7). Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window (8, 9). Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs (10). Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects. Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.

In addition to the improvement of bioavailability, most of recent researches on solid dispersion systems have been being directed toward their application to the development of extended-release dosage forms. However several factors such as complicated preparation method, low reproducibility of physicochemical properties, difficulty of formulation development and scale-up and physical instability for solid dispersion make it difficult to apply the systems to solid dispersion dosage forms. Especially in order to maintain a supersaturation level of drug for an extended time, re-crystallization of drug must be prevented during its release from dosage form (11). Dissolution retardation through the solid dispersion technique has become a field of interest in recent year. Shaikh et al prepared prolonged release solid dispersions of acetaminophen and theophylline by a simple evaporation method using ethyl cellulose as water-insoluble carrier. (12). Oral devices made to be retained in the stomach for a long time and to ensure slow delivery of drug above it's absorption site, could provide increased and more reproducible drug bioavailability (13).

During the last decade, the sustained release technique has been largely utilized to obtain the controlled release of pharmaceutical forms of both water soluble and sparingly soluble drugs using hydrophobic and hydrophilic polymers, respectively. Limitations in the development of solid dispersions were mainly due to physical instability of these systems. During this time phase separation of components can occur. Furthermore, polymeric materials are not in thermodynamic equilibrium below their glass transition temperatures (T_g), so the solid polymer approaches its more stable state (lower energy). If these macromolecular rearrangements occur during the experiments, a variation of the mechanical and permeation properties of the materials can be observed. This process is known as ‘Physical ageing’ (14).

Figure 1. Approaches to Increase solubility/ Dissolution

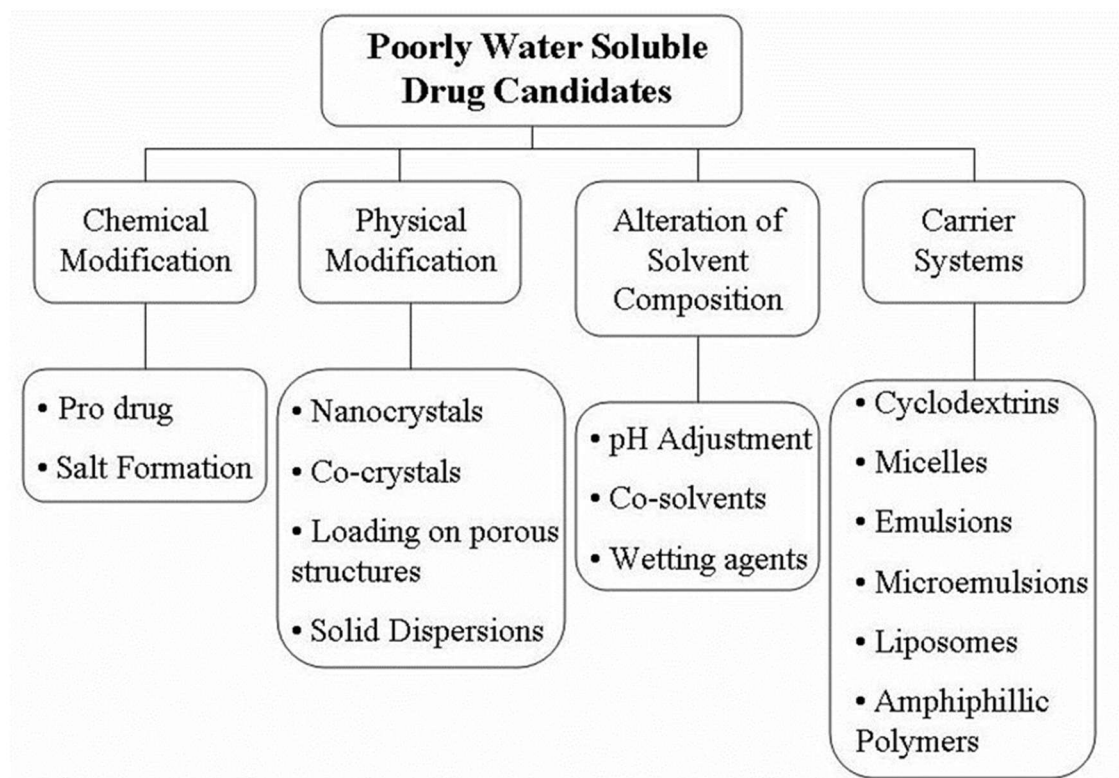
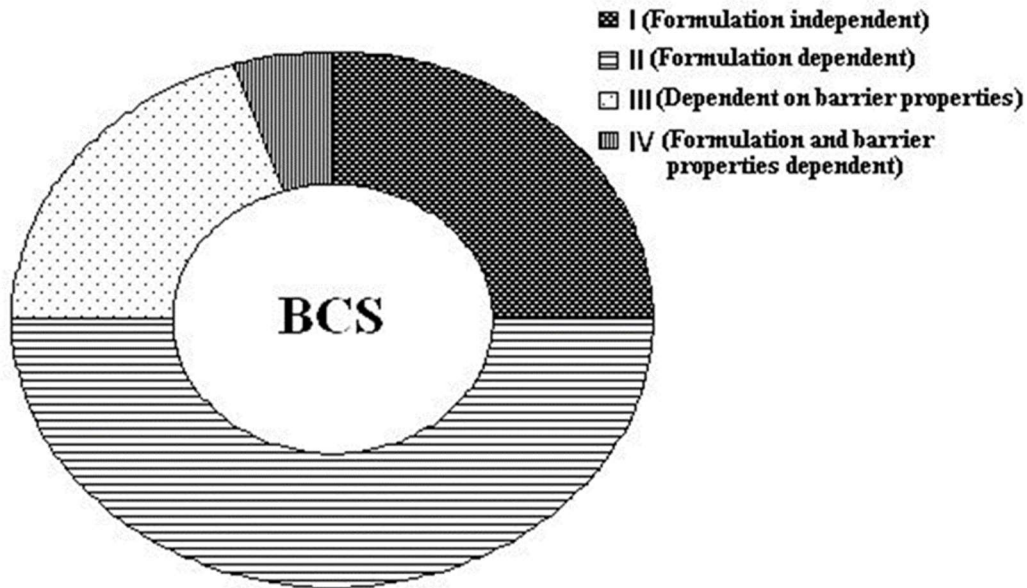


Figure 2. Biopharmaceutical Classification System break down of the pharma new chemical entity pipeline



CLASSIFICATION OF SOLID DISPERSION

Depending on the molecular arrangement, solid dispersions can be of the following types: (2)

1. Eutectic mixtures: solid eutectic mixtures are usually prepared by rapidly cooling the co-melt of the two components in order to obtain a physical mixture of very fine crystals of the two components.

2. Solid solutions

Depending on the miscibility, the two types of solid solutions are:

Continuous solid solutions: In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the components is stronger than the bonding between the individual component.

Discontinuous solid solutions: In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature.

Depending on the distribution of the solvates in the solvent, solid solutions can be of two types:

Substitutional crystalline solution: These are those solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.

Interstitial crystalline solid solution: These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice.

3. Amorphous solid solutions: In amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.

4. Glass solutions and glass suspension: A glass solution is a homogenous system in which the solute dissolves in the glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. The term glass refers to a pure chemical or a mixture of pure chemicals in the glassy state.

Classification of solid dispersion on the basis of recent advancement (3)

1. First generation solid dispersion: These solid dispersions are prepared by using crystalline carriers. Urea and sugars were the first crystalline carriers that were used in the preparation of solid dispersions. These have a disadvantage of being thermodynamically unstable and they do not release drug at a faster rate.

2. Second generation solid dispersion: These solid dispersions are prepared using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier.

The polymeric carriers are divided into two groups:

Synthetic polymer: povidone, polyethylene glycols and polymethacrylates.

Natural polymers: hydroxypropyl methylcellulose, ethyl cellulose, starch derivatives like cyclodextrin.

3. Third generation solid dispersion: These solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These achieve the highest degree of bioavailability for the drugs that are having poor solubility. The surfactants being used in the third-generation solid dispersion are such as inulin, poloxamer 407 etc.

POLYMERS USED IN SOLID DISPERSIONS (9):

Polyethylene Glycol (PEG): These are compounds are obtained from a reaction of ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides.

Phospholipids: The complexity of glycerides advances by modification of the terminal hydroxyl with phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters. As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures. Solubility of phospholipids is intimately linked to the conformation of the aggregate material rather than strictly a chemical function of the molecule. Monoacyl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions

Polyvinyl Pyrrolidone (PVP): PVP molecular weight ranges from 2500 to 3000000. It is having solubility in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP gets decomposed at high temperature therefore it is not suitable for preparation of solid dispersions prepared by melt method because melting takes place at a very high temperature.

Cyclodextrins: Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.

ADVANTAGES OF SOLID DISPERSION

Solid dispersion results in particles with reduced particle size and thus the surface area are improved and increased dissolution rate is attained. Hence bioavailability is increased (4).

The carrier used in the solid dispersion plays a major role in improving the wettability of the particles. Improved wettability results in increased solubility thus improving the bioavailability (5).

In solid dispersion drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting the drug in amorphous form and increases the solubility of the particles (5).

ADVANTAGES OF SOLID DISPERSIONS OVER OTHER STRATEGIES TO IMPROVE BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches (15). Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its in vivo conversion into acidic or basic forms (16). Moreover, these types of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a NCE.

Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do. Milling or micronizations for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 μm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle (17).

ADSORBENT CARRIER CHALLENGES

Difficult to process powders (pulverization, poor compressibility, poor flow, scale-up) and amorphous stability (conversion of amorphous forms back to crystalline form) are the major

problems associated with commercialization of this technology. Solid powders with low particle size have poor flowability and may stick to the tableting machines making it difficult to handle. The amorphization achieved by solid dispersion may have stability problems due to temperature or moisture stress during storage. Undoubtedly, the physical and chemical properties of the carrier will impact the bioavailability.

LIMITATIONS OF SOLID DISPERSION SYSTEMS

Limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include:

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process, and
5. Stability of the drug and vehicle.
6. its method of preparation,

Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. Some of the suggested approaches to overcome the aforementioned problems and lead to industrial scale production are discussed here under alternative strategies.

SUITABLE PROPERTIES OF A CARRIER FOR SOLID DISPERSIONS

Following criteria should be considered during selection of carriers: (a) High water solubility – improve wettability and enhance dissolution (b) High glass transition point – improve stability (c) Minimal water uptake (reduces Tg) (d) Soluble in common solvent with drug –solvent evaporation (e) Relatively low melting point –melting process (f) Capable of forming a solid solution with the drug-similar solubility parameters

FIRST GENERATION CARRIERS

Crystalline carriers: Urea, Sugars, Organic acids

Second generation carriers

Amorphous carriers: Polyethylene glycol, Povidone, Polyvinyl acetate, Polymethacrylate, cellulose derivatives Third generation carriers

Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, Gelucire 44/14.

SOLVENT SELECTION FOR SOLID DISPERSION SYSTEMS

In order to prepare solid dispersion, solvents should be selected on the basis of following criteria: (a) Dissolve both drug and carrier (b) Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane (c) Ethanol is a less toxic alternative (d) Water based systems preferable (e) Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point.

Class I Solvents (Solvents to be avoided)

Solvents in Class I should not be employed in the manufacture of drug substances, excipients and drug products because of their deleterious environmental effect Table 1.

Class II Solvents (Solvents to be limited)

Solvents in Table 2 should be limited in pharmaceutical products because of their inherent toxicity.

Class III Solvents (Solvents with low toxic potential) Solvents in class III (shown in table 3) may be regarded as less toxic and of lower risk to human health. Class III includes no solvents known as a human health hazard at level normally accepted in pharmaceuticals.

Class IV Solvents (Solvents for which no adequate toxicological data was found)

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products for example Petroleum ether, isopropyl ether. However, no adequate toxicological data on which to base a PDE was found.

SOLID DISPERSIONS DISADVANTAGES

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization and dissolution rate decrease with ageing. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization (18). Moreover, most of the polymers use in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during in vivo performance (19).

Table 1. List of some Class I Solvents

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazards
1,2-dichloroethane	5	Toxic
1,1-dichloroethene	8	Toxic
1,1,1-trichloroethane	1500	Environmental hazards

Table 2. Class II solvents in pharmaceutical products

Solvent	PDE (mg/day)	Concentration limit (ppm)
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-dichloroethene	18.7	1870
Ethylene glycol	6.2	620
Methanol	30.0	3000
Pyridine	2.0	200
Toluene	8.9	890

Table 3. Class III solvents which should be limited by GMP or other quality based requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
1-Butanol	Isopropyl acetate
2-Butanol	Methyl acetate
Butyl acetate	3-Methyl-1-Butanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethylacetate	1-Propanol
Ethyl ether	2-Propanol
Formic acid	Propyl acetate

Figure 3. Solid State Solid Dispersions

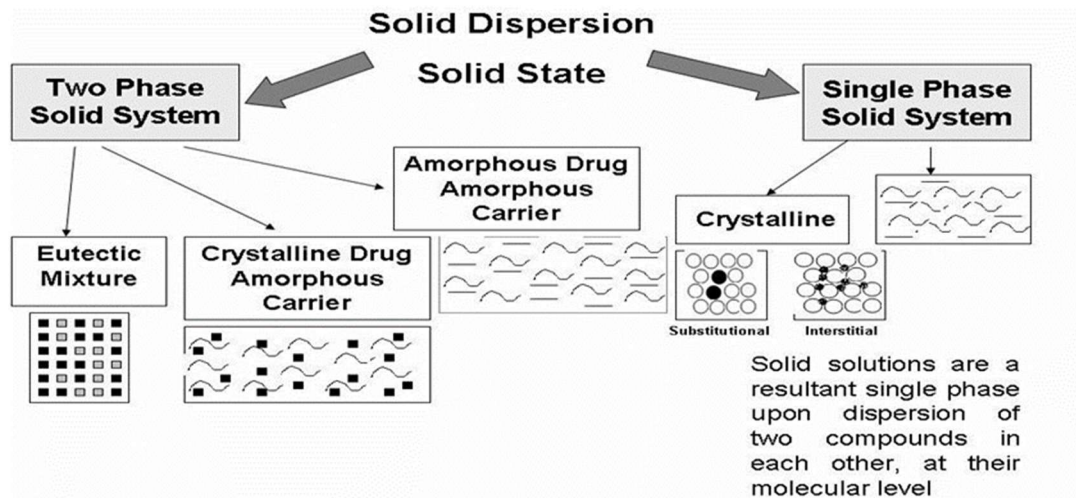
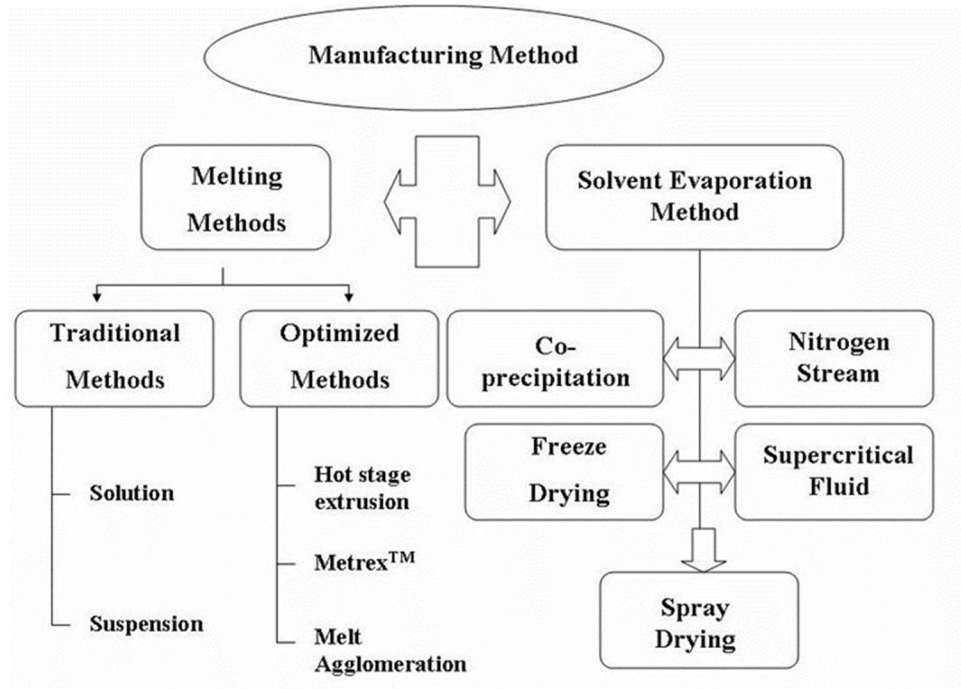


Figure 4. Methods of preparation of Solid Dispersion



METHOD OF PREPARATION

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level (Figure 3), while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure (20). Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible. Techniques for preparation of solid dispersions (Figure 4) are as follows:

a) Fusion method

Sekiguchi and Obi prepared solid dispersions of sulfathiazole in such carriers as ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, and urea by melting various drug-carrier mixtures. To minimize melting temperatures, eutectic mixtures of the drug with carriers were used. Yet, in all cases, except acetamide, the melting temperatures were $>110\text{ }^{\circ}\text{C}$, which could chemically decompose drugs and carriers. High temperatures ($>100\text{ }^{\circ}\text{C}$) were also utilized by Goldberg et al. in preparing acetaminophen- urea, griseofulvin- succinic acid, and chloramphenicol- urea⁸ solid dispersions. After melting, the next difficult step in the preparation of solid dispersions was the hardening of melts so that they could be pulverized for subsequent formulation into powder-filled capsules or compressed tablets. Sekiguchi and Obi cooled the sulfathiazole- urea melt rapidly in an ice bath with vigorous stirring until it solidified (21). Chiou and Riegelman facilitated hardening of the griseofulvin-PEG 6000 solid dispersion by blowing cold air after spreading it on a stainless steel plate and then storing the material in a desiccator for several days (18-19). In preparing primidone-citric acid solid dispersions, Summers and Enever spread the melt on Petri dishes, cooled it by storing the Petri dishes in a desiccator, and finally placed the desiccator at $60\text{ }^{\circ}\text{C}$ for several days. Allen et al. prepared solid dispersions of corticosteroids in galactose, dextrose, and sucrose at 169, 185, and $200\text{ }^{\circ}\text{C}$, respectively, and then placed them on aluminum boats over dry ice. Timko and Lordi also used blocks of dry ice to cool and solidify phenobarbital-citric acid mixtures that had previously been melted on a frying pan at $170\text{ }^{\circ}\text{C}$. The fusion method of preparing solid dispersion remained essentially similar over the period of time. More recently, Lin and Cham prepared nifedipine-PEG 6000 solid dispersions by blending physical mixtures of the drug and the carrier in a V-shaped blender and then heating the mixtures on a hot plate at $80\text{-}85\text{ }^{\circ}\text{C}$ until they were completely melted. The melts were rapidly cooled by immersion in a freezing mixture of ice and sodium chloride, and the solids were stored for 24 h in a desiccator over silica gel before pulverization and sieving. Mura et al. solidified naproxen-PEG melts in an ice bath and the solids were then stored under reduced pressure in a desiccator for 48 h before they were ground into powders with a mortar and pestle. In another

study, Owusu-Ababio et al. prepared a mefenamic acid-PEG solid dispersion by heating the drug-carrier mixture on a hot plate to a temperature above the melting point of mefenamic acid (253 °C) and then cooling the melt to room temperature under a controlled environment (22).

b) Solvent method

Another commonly used method of preparing a solid dispersion is the dissolution of drug and carrier in a common organic solvent, followed by the removal of solvent by evaporation (23). Because the drug used for solid dispersion is usually hydrophobic and the carrier is hydrophilic, it is often difficult to identify a common solvent to dissolve both components. Large volumes of solvents as well as heating may be necessary to enable complete dissolution of both components. Chiou and Riegelman used 500 ml of ethanol to dissolve 0.5 g of griseofulvin and 4.5 g of PEG 6000. Although in most other reported studies the volumes of solvents necessary to prepare solid dispersions were not specified, it is possible that they were similarly large (18, 19). To minimize the volume of organic solvent necessary, Usui et al. dissolved a basic drug in a hydroalcoholic mixture of 1 N HCl and methanol, with drug-to cosolvent ratios ranging from 1:48 to 1:20, because as a protonated species, the drug was more soluble in the acidic cosolvent system than in methanol alone. Some other investigators dissolved only the drug in the organic solvent, and the solutions were then added to the melted carriers. Vera et al. dissolved 1 g of oxodipine per 150 mL of ethanol before mixing the solution with melted PEG 6000. In the preparation of piroxicam-PEG 4000 solid dispersion, Fernandez et al. dissolved the drug in chloroform and then mixed the solution with the melt of PEG 4000 at 70°C. Many different methods were used for the removal of organic solvents from solid dispersions (23, 24). Simonelli et al. evaporated ethanolic solvent on a steam bath and the residual solvent was then removed by applying reduced pressure. Chiou and Riegelman dried an ethanolic solution of griseofulvin and PEG 6000 in an oil bath at 115 °C until there was no evolution of ethanol bubbles. The viscous mass was then allowed to solidify by cooling in a stream of cold air. Other investigators used such techniques as vacuum-drying, spray-drying, spraying on sugar beads using a fluidized bed-coating system, lyophilization, etc., for the removal of organic solvents from solid dispersions. None of the reports, however, addressed how much residual solvents were present in solid dispersions when different solvents, carriers, or drying techniques were used.

c) Supercritical Fluid Method

Under the influence of pressure and temperature, pure substances can assume a gas, liquid and solid state of matter except where the equilibrium saturation curve converges such that all three phases co-exist at the triple point. Extension of the liquid-gas phase line ends at the critical point and represents the maximum temperature and pressure in which the liquid and vapor phases co-exist in equilibrium, after which gas and liquid have the same density and appear as a single phase. A fluid is said to be supercritical when its temperature and pressure are in a state above its critical temperature (T_c) and critical pressure (P_c), permitting both gaseous and liquid phases to co-exist. The most important property of supercritical fluid is the liquid-like density, large compressibility and viscosity intermediate between the gas and liquid extremes. Large density confers solvent power whereas high compressibility affords a strategy for continuously adjusting this solvent

power between gas and liquid like extremes with small changes of pressure 25. Because density is the true measure of a supercritical fluid's solvent power, small changes in temperature and pressure can result in large changes in solubility. Supercritical fluids are typically hundreds of times denser than gases at ambient conditions but are arbitrarily more compressible. Compressibility is the fundamental degree of freedom, absent with conventional solvents but present with supercritical fluids, and gives rise to their key feature as a pharmaceutical solvent: small changes in pressure cause large changes in density (26, 27). Thus, by manipulating only pressure and temperature, the formulator may control solubility in a coacervation process. Supercritical carbon dioxide (critical pressure and temperature of about 1070 psi and 310C, respectively) has induced dipole and quadruple interactions that dissolve non-polar to moderately polar compounds⁶. Recent reports describe the use of carbon dioxide near its critical temperature and pressure to partially solvate polymers and infuse small drug molecules into their swollen networks for controlled release applications. The mechanism by which supercritical carbon dioxide mixtures achieve this effect originates, in part, from its ability to dissolve drug molecules but also their ability to function as theta solvent thereby swelling polymer matrices to permit drug loading. This approach provides advantages over conventional, unit operations (eg. Freeze drying or spray drying), which are typically heat and time intensive. Supercritical fluid processing (SFP) is rapid, characterized by high purity product and high yield due to ease of solvent removal.

Because aqueous solvents are not employed in SFP, the Stability of pharmaceuticals susceptible to hydrolytic degradation may be enhanced. Compared with other non-aqueous alternatives, carbon dioxide is generally regarded as safe as a pharmaceutical excipient, inexpensive and residual free at room temperature and atmospheric pressure, yet supercritical under benign temperatures and tractable pressures. SFP has been used as an alternative to milling to generate drug particles of narrow size distribution, to produce polymer-drug composites or to coat surfaces. SFP normally employs carbon dioxide either as a solvent or anti-solvent, in which case the process is referred to as the rapid expansion of supercritical fluid solutions or supercritical anti-solvent, respectively. Rapid expansion of supercritical fluid solutions (RESS) produces pure drug particles several nanometers in diameter when supercritical solutions expand through a very small nozzle under controlled temperature and pressure. This technique is extremely attractive because small particles enhance dissolution rate and bioavailability due to their increased surface area. However, the advantages of RESS processing of drug-in-polymer composites are offset by problems with clogged nozzle heads, low drug/polymer solubilities in SF, and congealing due to insufficiently dried product. These problems are, to various degrees, avoided by the supercritical anti-solvent (SAS) process that produces dried composites suitable for subsequent milling. However, this process invariably requires the use of co-solvent(s) to modify the non-polar supercritical milieu to more polar environment compatible with drug substance, essentially offsetting the intrinsic advantages of SF (28).

COMBINATION OF SOLID DISPERSION WITH SUSTAINED RELEASE TECHNIQUES

A combination of solid dispersion and sustained release techniques is one of the attractive approaches since super saturation of the drugs can be achieved by applying solid dispersion. However, it has been known that the super saturation level is decreased by contacting solid dispersion to water for a longer period because of re-crystallization of drugs. That is why only few reports on the application of solid dispersion to sustained release system have been presented. One approach is direct modification of character of solid dispersion by using water-insoluble or slower dissolving carriers instead of conventional hydrophilic polymers. In this technique, a selection of suitable carrier for each drug would be a critical factor. Another approach is a membrane-controlled sustained release tablet containing solid dispersion. Since the release of drug from such a diffusion-controlled system is driven by the gradient of the drug concentration resulting from penetration of water, it may have the risk for the re-crystallization of the drug because of contacting solid dispersion to water penetrated into the system for longer period. Therefore, a specific formula of solid dispersion and/or a manufacturing method may be required for each drug depending on the character of the drug in order to maintain the supersaturation.

RECRYSTALLIZATION: STRATEGIES TO AVOID IT

Recrystallization is the major disadvantage of solid dispersions. As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization. Molecular mobility is a key factor governing the stability of amorphous phases, because even at very high viscosity, below the glass transition temperature (T_g), there is enough mobility for an amorphous system to crystallize over pharmaceutically relevant time scales. Furthermore, it was postulated that crystallization above T_g would be governed by the configurational entropy, because this was a measure of the probability of molecules being in the appropriate conformation, and by the mobility, because this was related to the number of collisions per unit time. Several experiments have been conducted to understand the stabilization of solid dispersions. Recent studies observed very small reorientation motions in solid dispersions showing a detailed heterogeneity of solid dispersions and detecting the sub-glass transition beta-relaxation as well as alpha-relaxation, which may lead to nucleation and crystal growth. Molecular mobility of the amorphous system depends; not only on its composition, but also on the manufacturing process as stated by Bhugra et al. Solid dispersions exhibiting high conformational entropy and lower molecular mobility are more physically stable (29). Polymers improve the physical stability of amorphous drugs in solid dispersions by increasing the T_g of the miscible mixture, thereby reducing the molecular mobility at regular storage temperatures, or by interacting specifically with functional groups of the drugs. For a polymer to be effective in preventing crystallization, it has to be molecularly miscible with the drug. For complete miscibility, interactions between the two components are required. It is recognized that the majority of drugs contain hydrogen-bonding sites, consequently, several studies have shown the formation of ion-dipole interactions and intermolecular hydrogen bonding between drugs and polymers, and the disruption of the hydrogen bonding pattern characteristic to the drug crystalline structure. These lead to a higher miscibility and physical stability of the solid dispersions (30, 31). Specific drug polymer interactions were

observed by Teberekidis et al., showing that interaction energies, electron density, and vibrational data revealed a stronger hydrogen bond of felodipine with PVP than with PEG, which was in agreement with the dissolution rates of the corresponding solid dispersions. Other studies have shown stabilization in systems where hydrogen-bonding interactions are not possible, because of the chemistry of the system. Vippagunta et al. concluded that fenofibrate does not exhibit specific interactions with PEG, independent of the number of hydrogen bonds donating groups presented. The same conclusion was achieved by Weuts et al. in the preparation of solid dispersions of

loperamide with PVP K30 and PVP VA64, in which, hydrogen bonds were no absolute condition to avoid crystallization. Konno et al. determined the ability of three different polymers, PVP, HPMC and hydroxypropyl methylcellulose acetate succinate to stabilize amorphous felodipine, against crystallization. The three polymers inhibited crystallization of amorphous felodipine by reducing the nucleation rate. It was speculated that these polymers affect nucleation kinetics by increasing their kinetic barrier to nucleation, proportional to the polymer concentration and independent of the polymer physiochemical properties. The strategies to stabilize the solid dispersions against recrystallization strongly depend on the drug properties and a combination of different approaches appears to be the best strategy to overcome this drawback. Third generation solid dispersions intend to connect several strategies to overcome the drug recrystallization, which has been the major barrier to the solid dispersions marketing success (32).

CHARACTERIZATION OF SOLID DISPERSIONS

Characterization of polymorphic and solvated forms involves quantitative analysis of these different physico-chemical properties. Several methods for studying solid dosage forms are listed in Table 4 along with the sample requirements for each test. Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is mostly derived from the amount of crystalline material in the sample. The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behavior could be different for solid dispersions that do not contain any crystalline drug particles.

Techniques to explore molecular interactions and behavior

Drug –carrier miscibility

- Hot stage microscopy
- DSC (Conventional modulated)
- pXRD (Conventional and variable temp)
- NMR ¹H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy

- Solid state NMR

Physical Structure

- Scanning electron microscopy
- Surface area analysis

Surface properties

- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- pXRD

Stability

- Humidity studies
- Isothermal calorimetry
- DSC (T_g, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS

The dissolution behaviour of solid dispersions must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous solid dispersions, the molecular mobility should be as low as possible. However, solid dispersions, partially or fully amorphous, are thermodynamically unstable. In solid dispersions containing crystalline particles, these particles form nuclei that can be the starting point for further crystallization. It has been shown that such solid dispersions show progressively poorer dissolution behaviour during storage [33, 34]. In solid dispersions containing amorphous drug particles, the drug can crystallize, but a nucleation step is required prior to that. In homogeneous solid dispersions, the drug is molecularly dispersed, and crystallization requires another step. Before nucleation can occur, drug molecules have to migrate through the matrix. Therefore, physical degradation is determined by both diffusion and crystallization of drug molecules in the matrix. It should be noted that in this respect it is better to have a crystalline matrix, because

diffusion in such a matrix is much slower. Physical changes are depicted in figure 5. The physical stability of amorphous solid dispersions should be related not only to crystallization of drug but to any change in molecular structure including the distribution of the drug. Moreover, the physical state of the matrix should be monitored, because changes therein are likely to alter the physical state of the drug and drug release as well.

DRUG-MATRIX MASS RATIO

Several aspects determine the effect of amorphous solid dispersion composition on physical stability. Firstly, the diffusion distance for separate drug molecules to form amorphous or crystalline particles is larger for lower drug contents. Hence, the formation of a separate drug phase is significantly retarded. Secondly, low drug contents minimize the risk of exceeding the solid solubility [35, 38]. When the solid solubility is lower than the drug load, there is a driving force for phase separation. This is only relevant for drug-matrix combinations that are partially miscible or immiscible. Thirdly, the Tg of a homogeneous solid dispersion is a function of the composition. When the drug has a lower Tg than the matrix, a high drug content depresses the Tg of the solid dispersion, increasing the risk for phase separation. And finally, if drug-matrix interaction increases stability, then also low drug contents are preferred, since in that case drug-drug contacts will be rare and drug-matrix contacts omnipresent. These arguments favour the choice of low drug content. However, a high drug content can decrease the hygroscopicity of the solid dispersion and enables the preparation of a high dosed dosage forms. The drug, being hydrophobic in nature, is generally less hygroscopic than the matrix. Molecularly incorporated drug reduces the amount of water that can plasticize the solid dispersion when exposed to a particular relative humidity, thereby decreasing molecular mobility [36, 37, 40]. Therefore, more drug can not only reduce the Tg of the dry solid dispersion but also decrease the plasticizing effect of water. Which one of the two competing effects has a larger contribution is difficult to predict. A second reason for increased stability with increasing drug loads is the inhibition of crystallization of the matrix above a certain drug load, when drug molecules sterically block the migration of matrix molecules [39]. Table 5 summarizes the effects of an increased drug load.

FUTURE PROSPECTS

Solid dispersion has great potential both for increasing the bioavailability of drug and developing controlled release preparations. In regard to manufacturing considerations the problem of total solvent removal in dispersions prepared by solvent method needs to be addressed [41]. The method created by Hasegawa et al that involves spray – coating of nanoparticles or any other inert core with drug carrier solution, provides a one step process of achieving a multiunit dosage form of solid dispersion. With particle – coating equipment new commercially available, this process has a promising future, as exemplified by commercial success of sporanox capsule manufactured by this technique. The problem of instability of the supersaturated state upon dissolution, which results in a stable form, has been dealt with by addition of a retarding agent. Methylcellulose used as a retarding agent in dispersions of indomethacin and flufenamic acid in PVP [42]. Controlled release formulations of acetaminophen, aminopyrine, chlorpheniramine maleate and salicylic acid that use eudragit RS as a water insoluble carrier prepared by solvent method, have been reported.

Valuable preliminary studies of the use of solid dispersions to provide sustained - release or controlled - release of drugs have been reported. A U.S. patent describes a method of preparation for a controlled release preparation of cyclosporine in biodegradable polymer such as poly-D, L-lactide, or a blend of poly-D, L-lactide and poly-D, L-lactide-co-glycolide. A novel approach that uses a less soluble derivative of drug as a carrier was used by Yang and Swarbrick to prepare sustained release solid dispersion of dapsone [43].

Some example of Solid dispersions in Market

Sporanox® (itraconazole) Intelence® (etravirine) Prograf® (tacrolimus) Crestor® (rosuvastatin) Gris-PEG® (griseofulvin) Cesamet® (nabilone)

Solufen® (ibuprofen)

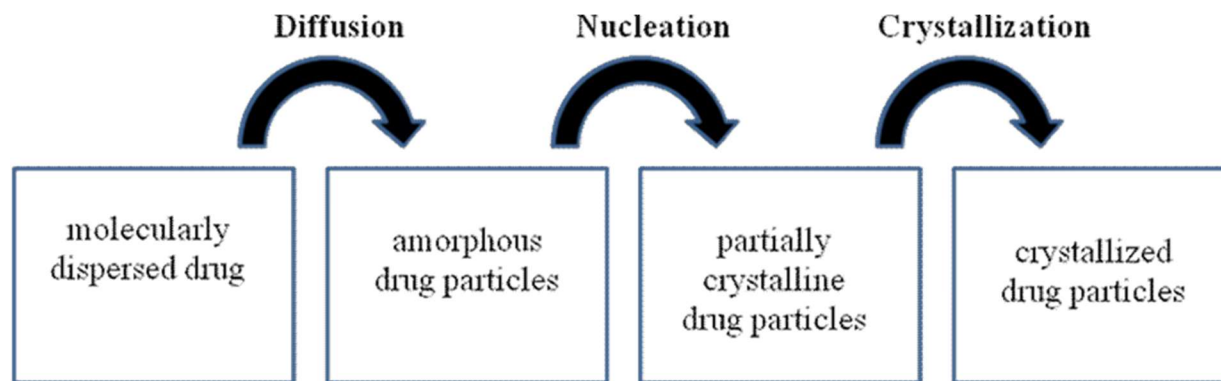
CONCLUSION

Solid dispersions can increase dissolution rate of drugs with poor water-solubility but stability of these systems needs consideration. Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. Solid dispersions can improve their stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. Moreover, new, optimized manufacturing techniques that are easily scalable are also coming out of academic and industrial research. Further studies on scale up and validation of the process will be essential.

Table 4. Analytic method for characterization of solid forms

Method	Material required per sample
Microscopy	1 mg
Fusion methods	1 mg
(Hot stage microscopy)	2-5 mg
Differential scanning calorimetry (DSC/DTA)	2-20 mg
Infrared spectroscopy	500 mg
X-Ray powder diffraction (XRD)	2 mg
Scanning Electron Microscopy	10 mg
Thermogravimetric analysis	mg to gm
Dissolution/Solubility analysis	

Figure 5. Physical changes in solid dispersions



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