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Review on Manufacturing Methods of Solid Dispersion Technology for Enhancing the Solubility of Poorly Water-Soluble Drugs

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ABSTRACT

The article combines recent literature reviews on solid dispersion technology to improve the solubility of poorly water-soluble drugs with a particular focus on different solid dispersion manufacturing techniques. The article outlines required criteria for solvents and carriers used in solid dispersions; Types, advantages, limitations and application of solid dispersions. This overview also discusses some of the future prospects and recent advances in the field of solid dispersion technology. There are various methods for preparing solid dispersions, such as melting process, solvent evaporation process, melt evaporation process, kneading process, spray drying process, co-grinding process, freeze drying process, hot melt extrusion, melt agglomeration, supercritical fluid technology. The oral bioavailability of poorly water soluble drugs when administered as solid dosage forms remains a challenge for formulation development due to their low solubility characteristic. Solid dispersion techniques have overcome this problem by increasing the dissolution rate of highly lipophilic drugs, thereby improving their bioavailability. From this article it can be concluded that solid dispersions prepared using a variety of pharmaceutically acceptable polymers using various new technologies have become a very fruitful approach to improve the release rate and oral bioavailability of poorly water-soluble drugs; also play an important role for formulation scientists in the development of some solid dispersions-based formulations for their commercial use and clinical applications.

Keywords: *Solid dispersion, Solubility, Dissolution rate, Bioavailability, Carriers, Solid dispersion manufacturing methodologies.*

INTRODUCTION

The formulation of poorly soluble compounds, typically Biopharmaceutical Classification System (BCS) class II drugs, that exhibit low water solubility and high membrane permeability for oral administration is currently one of the most common and major challenges faced by formulation scientists in the pharmaceutical industry. Almost 40% of potential new drugs identified by the pharmaceutical industry are poorly water soluble. A number of strategies have been worked on to overcome the poor water solubility crisis, such as chemical modification, changing solvent composition, use of a carrier system and physical modification including the solid dispersion method. Among all technologies, solid dispersion technology stands out as the most promising approach that increases the solubility of poorly soluble drugs (1). Chiou and Reigelman first defined soild dispersion as a dispersion of one or more active ingredients in an inert carrier or solid-state (hydrophilic) matrix prepared by melt, solvent, or melt evaporation processes (2) (3) (4) or soild dispersion is defined as a dispersion involving the formation of eutectic mixtures of drugs with carriers that are easily soluble in water by melting their physical mixtures (5) (6). Solid dispersion consists of a hydrophobic drug dispersed in at least one hydrophilic carrier, resulting in an increased surface area, resulting in higher drug solubility and dissolution rate. Improving wettability and dispersability, reducing aggregation and agglomeration of drug particles result in improved drug bioavailability.

TYPES OF SOLID DISPERSION

On the basis of molecular arrangement, the solid dispersions can be divided into six groups as simple eutectic mixtures, glassy solutions/suspensions, solid solutions, amorphous precipitates of a drug within a crystalline carrier, compound or complex formation, and any combination of these groups (Figure 1). According to phase solid system solid dispersions can be divided into single-phase and two-phase solid systems (Figure 2).

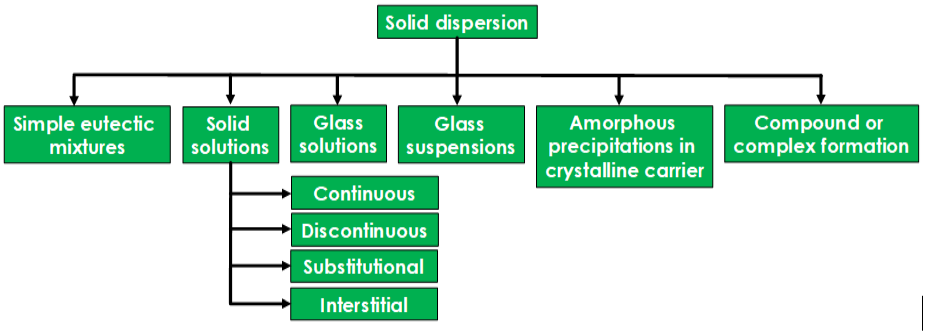

Fig 1: Types of Solid Dispersions - on molecular arrangement basis

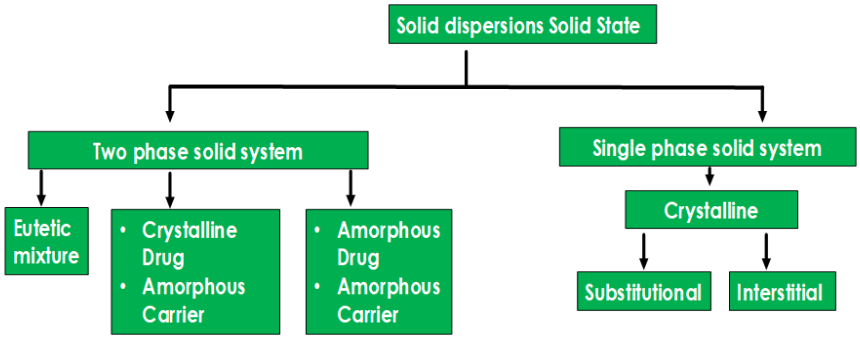

Fig. 2: Solid Dispersions classification - on phase solid system

Simple Eutectic Mixtures

A simple eutectic mixture is a mixture of two components that are completely miscible in the liquid state but negligibly in the solid state. Components A and B were co-melted at the eutectic point (E) (Figure 3), where the melting point of the mixture was lower than either component A or B alone. In 1961, Sekiguchi and Obi (7) prepared a eutectic mixture of sulfathiazole and urea, which showed the improved absorption and excretion after oral administration of sulfathiazole in the eutectic mixture compared to that of the conventional drug.

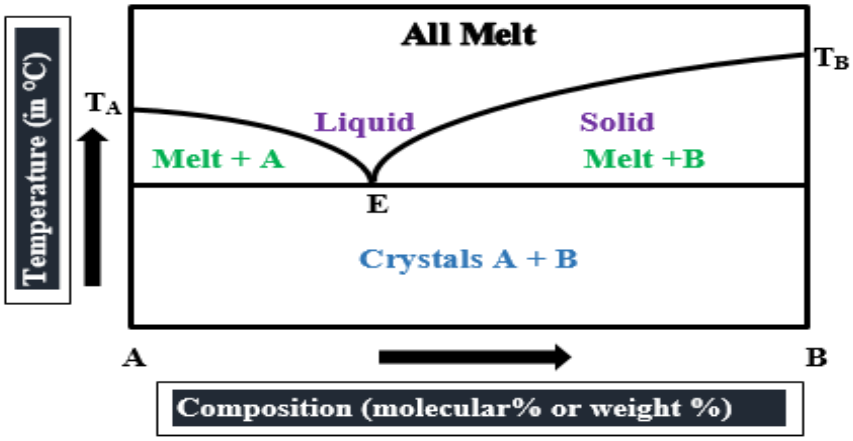

Fig. 3: Phase diagram of a eutectic mixture. A, B (drug, carrier), E (eutectic point).

Solid Solutions

This type of solid dispersion is miscible in its solid state and also miscible in its liquid state. It gives either a crystalline or an amorphous type. The main advantage of this type is a better dissolution rate compared to the eutectic mixture due to a smaller particle size of the drug. The dissolution rate of the drug depends on the dissolution of the carriers.

Firstly, the solid solution is categorized as continuous and discontinuous solid solutions based on the miscibility and molecular size of the components. Continuous concerns about the bond strength between the components, *i.e.* the bond strength of the individual component is weaker than the bond strength of the two components. Discontinuous concerns about component solubility, *i.e.* each of the components tend to have limited solubility in the solid solvents.

Secondly, based on the distribution of solvate molecules in the solvent, the solid solution is classified as substitutional and interstitial solid solutions. In substitution solid solution, one solvent molecule is replaced by another solute molecule in the crystal lattice. In interstitial solid solutions, the interstitial space in the solvent lattice is replaced by the solute molecule.

Glass Solutions

These are homogeneous glassy systems in which the solute dissolves in the glass support.

Glass Suspensions

These are mixtures in which precipitated particles are suspended in glass solvent. The lattice energy is much lower in glass solution and suspension (8).

Amorphous Precipitations in a Crystalline Carrier

In this case, a drug can precipitate in the crystalline carrier in an amorphous form, which distinguishes it from a eutectic mixture (9) in which both the drug and the carrier crystallize out at the same time. The amorphous form of a drug has a higher dissolution rate than the crystalline form. According to Taylor and Zografi, drug release enhancement can usually be achieved by using the drug in its amorphous state, since energy is not required to break the crystal lattice during the dissolution process (10). For example, the amorphous form of novobiocin has been found to have higher solubility and dissolution rate than its crystalline form (11).

Compound or Complex Formations

In this type of system, drug and matrix interact strongly with each other in an aqueous environment to form complexes. During the dissolution of a drug from a complex or compound in the body, the availability of a drug depends on its solubility, its dissociation constant, and the intrinsic rate of absorption of the complex. Compared to pure insoluble drugs, the rate of dissolution and GI absorption can be enhanced through the formation of a soluble complex with a low association constant (11).

Based on the composition and manufacture of solid dispersions, it can be classified into four generations as shown in Figure 4.

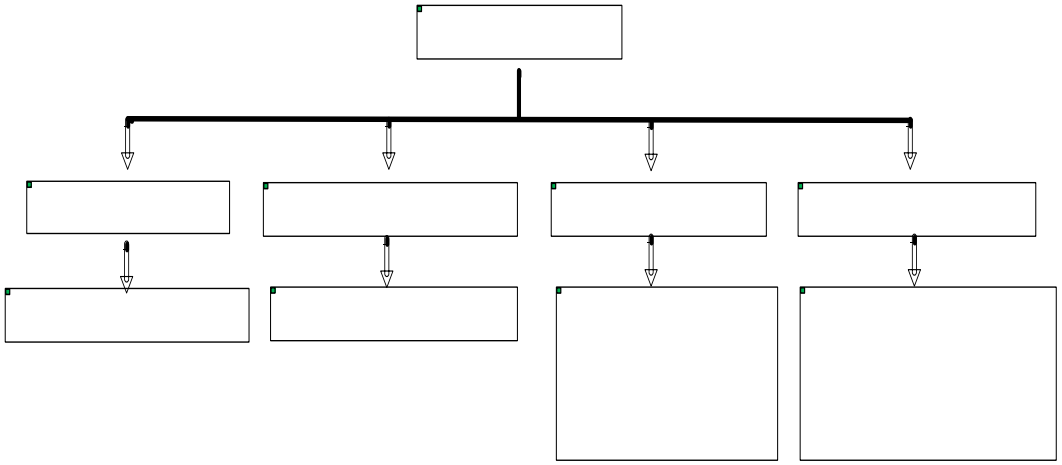

Fig. 4: Generational breakdown of Solid Dispersion

First Generation Solid Dispersions

Solid dispersions were first described by Sekiguchi and Obi, where a eutectic mixture was formed that improved the dissolution rate and also the oral bioavailability of water-insoluble drugs. These solid dispersions were termed first generation solid dispersions, which were prepared using crystalline carriers such as urea, sugars and organic acids. These first generation solid dispersions were associated with the formation of crystalline solid dispersions that were thermodynamically stable but unable to accelerate drug release like that of an amorphous dispersion (7)(8)(12)(13).

Second Generation Solid Dispersions

In the second-generation solid dispersions, crystalline supports have been replaced by amorphous supports. Here the drug is molecularly dispersed in an amorphous polymeric carrier. These supports have been used extensively for solid dispersions as they are capable of forming amorphous solid dispersions and are further divided into synthetic and natural product-based polymers. Synthetic polymers include polyethylene glycols, povidone, and polymethacrylates. Natural polymers mainly consist of several cellulose derivatives (hydroxypropyl methyl cellulose, ethyl cellulose or hydroxypropyl cellulose) or starch derivatives (cyclodextrins) (14)(15)(16).

Third Generation Solid Dispersions

Third generation solid dispersions have involved the use of a carrier that has self-emulsifying properties, or have involved the use of a mixture of amorphous

polymers and surfactants as carriers that can more effectively enhance dissolution. These should achieve the enormous bioavailability and stabilize the solid dispersion by preventing recrystallization of the active ingredient. It involves the use of excipients such as Poloxamer 408, Tween 80, Gelucire 44/14, Soluplus, Sodium Lauryl Sulfate and Compritol, Inulin (17) (18) (19).

Fourth Generation Solid Dispersions

Fourth generation solid dispersions are also known as controlled release solid dispersion (CRSD), where we use poorly water-soluble drugs with short biological half-life. It encompasses two main goals, namely solubility improvement and prolonged controlled release. In this generation, the molecular dispersion of the drug in a carrier will improve solubility, whereas the use of water-swellable polymers can delay drug release. This allows a sufficient amount of the drug to be administered over a longer period of time, which in turn offers many advantages such as reduced dosing frequency leading to patient compliance, decreased side effects, prolonged therapeutic effect for poorly water-soluble and short biological half-life drugs. The polymers used include ethyl cellulose, hydroxypropyl cellulose, Eudragit RS, RL, poly (ethylene oxide) and carboxyvinyl polymer (20).

Required Criteria for Solvents and Carriers Used in Solid Dispersion

The solvent to be included for the formulation of solid dispersion should meet the following criteria:

1) Both drug and carrier must be dissolved.
2) Toxic solvents to be avoided as residues may occur after manufacture, *e.g.* Chloroform and dichloromethane.
3) Ethanol can be used as alternative as it is less toxic.
4) Water based systems are preferred.
5) Surfactants are used to make drug carrier solutions but as they can reduce glass transition temperature care must be taken (21).

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug (22) (23) (24).

1) Freely water soluble with intrinsic rapid dissolution properties.
2) Non-toxic and pharmacologically inert.
3) Heat stable with a low melting point for the fusion process.
4) Soluble in a wide range of solvents and, in the solvent method, convert to a glassy state upon evaporation of the solvent.
5) Can preferably increase the water solubility of the drug.

6) Chemically compatible with the drug and do not form a tightly bound complex with the drug.

METHODS OF PREPARATION OF SOLID DISPERSION

Different methods for the production of solid dispersions are shown in Figure 5.

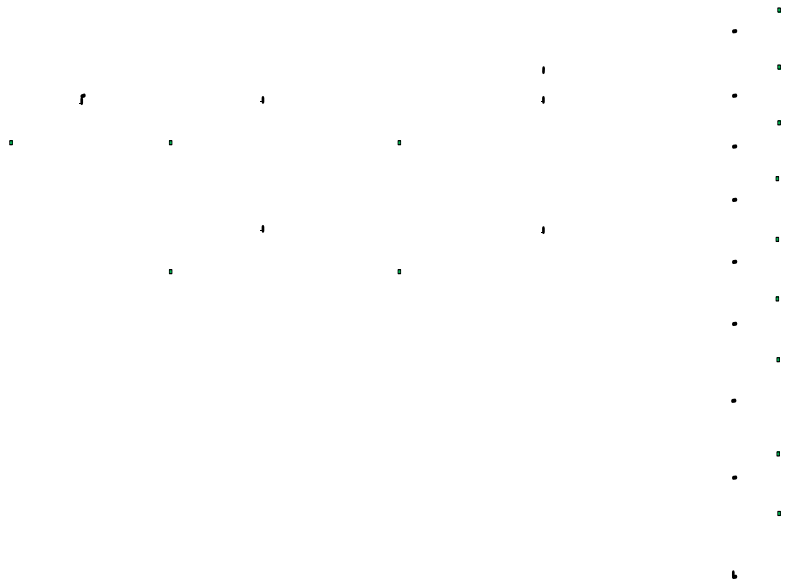

Fig. 5: Methods of preparation of solid dispersion

1) **Kneading Method:** In this process, water is added to the mixture of precisely weighed drug and carrier to form a thick paste, which is kneaded in a glass mortar for a specified time. The kneaded mixture is dried and sieved to obtain a uniform size solid dispersion (25). Ex. Furosemide and Crospovidone solid dispersion was prepared by this method.

2) **Melting Method:** The melting or fusion method was first used by Sekiguchi and Obi in 1961(7). The basic principle of the fusion process is that a physical mixture of a drug and a hydrophilic carrier is directly heated until they melt at a temperature slightly above their eutectic point. The melt is then cooled in an ice bath with vigorous stirring and quickly solidified. The final solid mass is crushed and sieved. The advantages of this method are simplicity and economy. However, this method has several disadvantages as it is not relevant for thermolabile drugs and high melting point polymers such as polyvinyl pyrrolidone (13). Some of the means of overcoming these problems could be to heat the physical mixture in a sealed container or to melt it under vacuum or in the presence of an inert gas such as nitrogen to prevent oxidative degradation of the drug or carrier.

Several drug solid dispersions have been prepared using this method, such as sulfathiazole (7), fenofibrate (26), furosemide (27), albendazole (28) and paclitaxel (29).

3) **Hot Melt Extrusion:** Hot melt extrusion produces an amorphous solid dispersion with no solvents, eliminating residual solvents in the formulation. This process is carried out through a combination of the melt process and an extruder in which a homogeneous mixture of drug, polymer and plasticizer is melted and then extruded through the equipment. The concentration of active ingredient in the dispersions is always 40% (w/w) and a plasticizer in the concentration between 5-30% weights of the extrudate can be added to decrease the viscosity of melt in the extrudate (30). For example, the melt extrusion process has been used to increase the dissolution and oral bioavailability of oleanolic acid by preparing its solid dispersion using polyvinyl pyrrolidone VA 64 as a carrier (31). The advantage of the process is to put various shapes and designs of the heated drug-matrix mixture into ophthalmic inserts, implants or oral dosage forms. An important advantage of the hot melt extrusion process is that the drug/carrier mixture is exposed to elevated temperature for only about 1 minute, allowing processing of somewhat thermolabile drugs.

4) **Meltrex TM:** This type of solid dispersion is patented and based on the principle of hot melt extrusion. There are two independent hoppers connected with a special screw extruder to continuously feed the extruded mass to the extrusion channel. It acts very quickly and requires less residence time (about 2 min) for the material and also avoids the thermal stress of carrier and drug (32). The temperature during formulation can be easily regulated from the low temperature of 30 °C to the high temperature of 250 °C (33). The main advantage of this technique is that it protects the drug candidate from oxidation and hydrolysis by completely removing oxygen and moisture.

5) **Melt Agglomeration:** This technique was used to prepare a solid dispersion in which the binder acts as a carrier. It is prepared by heating a mixture of drug, carrier, and excipients to a temperature within or above the melting range of the carriers (melt-down method), or by spraying a dispersion of drug in molten binder onto the heated excipient (spray-on method) using a high-shear mixer(34). A rotary processor is used as an alternative equipment for melt agglomeration due to better control of temperature and high feasibility of binder content to be incorporated into

the agglomerates(24). The influence of binder type, manufacturing process and particle size are critical parameters when preparing a solid dispersion by melt agglomeration. In addition, the melting process also leads to a homogeneous distribution of the drug in the agglomerate. Larger particles lead to densification of agglomerates, while fine particles cause complete adhesion to the mass on the bowl shortly after melting, which is due to the distribution and coalescence of the fine particles. For example, a tadalafil solid dispersion was prepared by a melt agglomeration technique using Pluronic as a carrier (35).

6) **Solvent Evaporation Method:** In this method, the physical mixture of drug and carrier is dissolved in a common volatile solvent such as ethanol, chloroform, a mixture of ethanol and dichloromethane, which is evaporated until a clear, solvent-free film is left. The film is further dried to constant weight. Usually, the resulting films are pulverized and ground. For example, a solid dispersion of ofloxacin with polyethylene glycol was prepared by a solvent evaporation process(36). The main advantage of the solvent method is that the thermal decomposition of drugs or carriers can be prevented because the evaporation of the organic solvent occurs at a low temperature. However, there are some disadvantages associated with this method, such as:
   - The higher manufacturing costs.
   - The difficulty of completely removing liquid solvent.
   - The potential adverse effect of trace solvent on the chemical stability.
   - The selection of a common volatile solvent.
   - The difficulty of reproducing crystal form.
   - In addition, super saturation of the solute in the solid system cannot be achieved except in a system showing highly viscous properties.

7) **Modified Solvent Evaporation Method:** Here the drug is dissolved in an organic solvent at its saturation solubility with continued stirring for some time. The polymer is suspended in sufficient amount of water. The drug solution is immediately poured into the polymer suspension. All solvent is evaporated. The mass obtained is dried and ground(37).

8) **Rotary Evaporation:** In this process, the volume of solvent is reduced by spreading it as a thin film over the interior of a vessel at elevated temperature and reduced pressure. The risk of phase separation is minimized here. This avoids the degradation of active ingredient and

carrier at high temperature. After evaporation of the solvent, the final solid dispersion is stored in a vacuum desiccator to completely remove residual solvent(32).

9) **Freeze Drying/Lyophilization:**Freeze drying involves the transfer of heat and mass to and from the product to be prepared. Lyophilization is a molecular mixing technique in which a lyophilized molecular dispersion is prepared by dissolving the drug and carrier in a suitable solvent and then freezing the solution in liquid nitrogen (38). This method is typically used for thermolabile products that are unstable in aqueous solutions but stable in the dry state over long periods of storage. First, the drug and carrier solution are kept in liquid nitrogen until completely frozen, and then the frozen sample is lyophilized (39). An important advantage of freeze-drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important benefit of freeze drying is that once the solution is vitrified, the risk of phase separation is minimized. The solid dispersion of nifedipine and sulfamethoxazole was prepared by a freeze drying method using Soluplus and PEG 6000 as carrier(40).

10) **Spray Drying:** In this method, the drug is dissolved in a suitable solvent and the carrier is dissolved in water to make the feed solution. Then the two solutions are mixed by sonication or other suitable method until the solution is clear. The feed solutions were first sprayed into fine droplets in a drying chamber using a high-pressure nozzle. The droplets formed consist of drying liquid (hot gas) and form nano- or micro-sized particles(41). Clinically, the spray drying method has been widely used to prepare a solid dispersion to improve the solubility and bioavailability of poorly water-soluble drugs such as nilotinib, spironolactone, valsartan, rebamipid, and artemether. For example, in a study by Herbrink *et al.* (42)prepared a solid nilotinib dispersion by spray drying to improve solubility. Soluplus was selected as the best carrier based on in vitro dissolution studies. At a drug: Soluplus (1:7) ratio, the solubility of nilotinib was improved 630-fold compared to neat drug.

11) **Supercritical Anti-solvent:** This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as solvent-free. Supercritical carbon dioxide is used as an anti-solvent for the solute but as a solvent with respect to the organic solvent. There are a number of favorable properties such as low

surface tension, high diffusibility and low viscosity, and the pressure can be easily adjusted. It can easily control the solubility of many drugs (33). Application of this method was performed to improve the dissolution of irbesartan by preparing solid dispersion using poloxamer as carrier(43). Process of Supercritical Anti-solvent is shown in Figure 6.

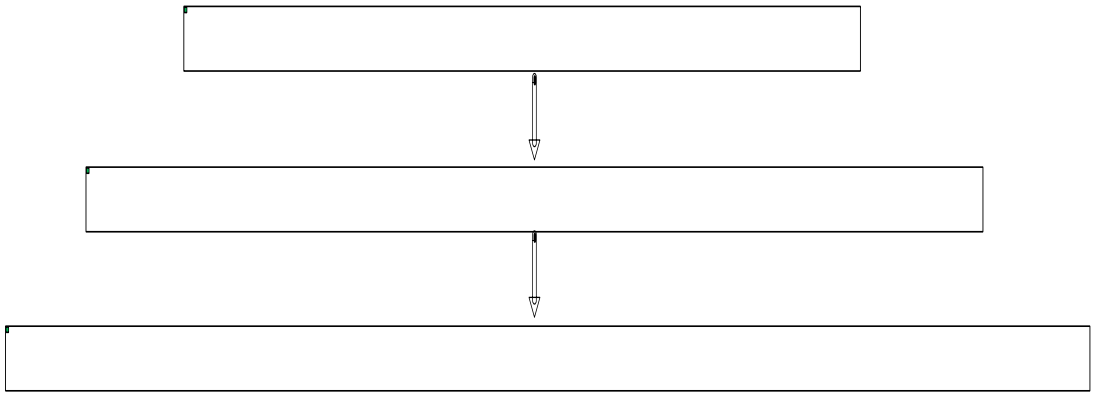

Fig. 6: Process of Supercritical Anti-solvent

12) **Co-precipitation:**In this method, the carrier is first dissolved in solvent to make a solution, and the drug is incorporated into the solution with stirring to form a homogeneous mixture. Then water is added dropwise to the homogeneous mixture to induce precipitation. Finally, the precipitate is filtered, dried and passed through sieves. In a study by Sonali *et al*.(44)a solid silymarin dispersion was prepared with hyroxypropylmethylcellulose E15LV as a carrier using various methods such as kneading, spray drying and co-precipitation. The solubility of silymarin from the solid dispersion prepared by co-precipitation improved 2.5 times compared to that of the conventional drug.

13) **Electrospinning:** This method is a combination of two techniques, nanotechnology and solid dispersion technology, which in turn is called electrostatic spinning. In this process, solid fibers are produced from a polymeric fluid stream or melt fed through a millimeter-scale die(45). As the solvent evaporates, the solid fibers are formed which can be collected on a spinning mandrel. This process involves the electrostatic forces that result in fiber formation as the solution overcomes the surface tension at the air interface. For example, itraconazole/HPMC was made using this technique(46). The process is simple, economical, and has remarkable potential for nanofiber production and drug release control (47). The main advantage of this technology is the rapid evaporation of the solvent due to the obtained amorphous particles, which have the highest dissolution.

14) **Fluid Bed Coating:** The fluid bed coating process uses drugs and carriers dissolved in a suitable solvent. Then the prepared solution is sprayed onto the surface through a nozzle (48), (49). The solvent is evaporated by supplying air and the samples are co-precipitated by deposition on the surface (50). The main advantage of this process is that the produced solid dispersion granules or pellets can be used directly for the production of tablets or encapsulation in capsules. Process of fluid bed coating is shown in Figure 7.

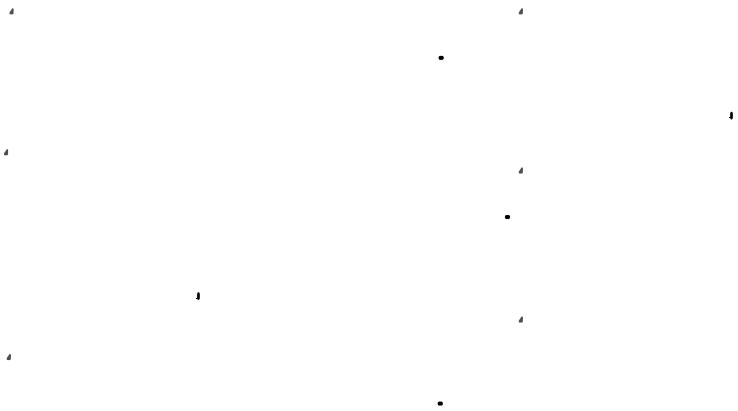

Fig. 7: Process of Fluid Bed Coating

15) **Melt Solvent Method/Melt Evaporation Method:** Melting solvent method is a combination of the solvent process and the melt process. The melting solvent method was first reported by Goldberg *et al.* (51). In their study, a solid dispersion was prepared to enhance the dissolution of griseofulvin using succinic acid as the carrier and methanol as the solvent. It involves the preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the carrier (polyethylene glycol) melt, which is then evaporated until a clear, solvent-free film is left. The film is further dried to constant weight. The 5 to 10% (w/w) liquid compounds can be incorporated into polyethylene glycol 6000 without significantly losing its solid character (52). It is possible that the selected solvent or dissolved drug will not be miscible with the melt of the polyethylene glycol. Also, the liquid solvent used can affect the polymorphic form of the drug, which precipitates as solid dispersion.

16) **Co-grinding Method:** A suitable amount of drug and carrier are mixed together using a mixer at a specified speed and ground in the chamber of a vibrating ball. The strong grinding forces increase the activation energy

and lead to the deformation of the crystal lattice. This leads to a reduction in the crystallinity of the drug when ground with a carrier in a vibratory ball mill, and consequently increases the rate of dissolution and bioavailability (53). Ex. Chlordiazepoxide and a solid dispersion of mannitol were prepared by this method (54).

17) **Dropping Method:** Ulrich *et al.*(46)facilitate the crystallization of various chemicals and produce spherical particles from melted solid dispersions. For laboratory-scale preparation, a solid dispersion of a melted excipient mixture is pipetted and then dropped onto a plate where it solidifies into spherical particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Since the viscosity is strongly dependent on the temperature, it is very important to set the temperature in such a way that the melt solidifies spherically when it is dropped onto the plate. Using carriers that solidify at room temperature can aid in the dropping process. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation. The process also avoids the pulverization, sieving, and compressibility difficulties (55)encountered with other melt processes. Disadvantages of the dropping method are that only thermostable drugs can be used and the physical instability of solid dispersions poses another challenge.

18) **Gel entrapment Technique:** Carrier, e.g. hydroxypropylmethyl cellulose, is dissolved in organic solvent (dichloromethane) to form a clear and transparent gel. Then the drug, for example carbamazepine, is dissolved in the gel by sonication for a few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are crushed and sieved using a glass mortar (56).

19) **Direct Capsule Filling:** The direct filling of hard gelatine capsules with the liquid melt of solid dispersions avoids changes in the crystallinity of the medicinal product caused by grinding (57). This molten dispersion forms a solid plug inside the capsule upon cooling to room temperature, reducing cross-contamination and operator exposure in a dust-free environment. Better fill weight and content uniformity was achieved than with the powder fill technique. However, PEG was not a suitable carrier for the direct capsule-filling process because the water-soluble carrier dissolved faster than the drug, resulting in drug-rich layers forming over the surface of dissolving plugs that prevented further dissolution of the drug.

20) **Use of Surfactant:** The utility of surfactant systems in solubilization is well known. Adsorption of surfactants onto solid surfaces can alter their hydrophobicity, surface charge, and other key properties that determine interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery, and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, which is manifested in a reduction in the melting of the pharmaceutically active ingredients, the glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of researchers for the preparation of solid dispersions. Examples: Gelucire 44/14, Polyoxyethylene Stearate, Poloxamer, Deoxycholic Acid, Tweens and Spans.

21) **Cryogenic Processing Technique:** This method is used to prepare solid dispersions of thermolabile drugs. These methods include spray freeze drying (SFD) and ultra-rapid freezing (URF). These methods of producing solid dispersions work on the principle of increasing the rate of freezing compared to the conventional freeze-drying technique. In both of these methods, the process is carried out under sub-ambient conditions. Since there is no contact between heat or air that could promote drug degradation during the drying process, there may be less chance of drug degradation. In the SFD technique, particle size reduction occurs without the application of intense frictional or mechanical forces that lead to thermal stress degradation of drug particles (58). The drug and carrier solution are sprayed into the cold air dried container and the frozen droplets are further lyophilized using the SFD technique. There may be fewer chances of phase separation due to the direct contact of the drug particles with the coolants and the rapid vitrification. This procedure transforms the drug particles into the amorphous state due to the rapid freezing process and protects the molecular assembly into a crystalline state (59). The URF involves the application of a thermal conductivity between 10 and 20 W/(mK) with a solid cryogenic substrate (33). The cryogenic solid substrate is applied to a frozen drug polymer sample and the particles are collected from the solvent by lyophilization (60). In this process, the super coolingoccurs very rapidly and nucleation of drug crystals is reduced or completely prevented, resulting in the amorphous morphology after lyophilization (61).

22) **Microwave Irradiation:** It is a new process for industrial scale production due to its main advantage of shorter reaction time and higher product yield.

The first research report published using the microwave irradiation technique is the formulation of a solid dispersion loaded with felodipine to improve dissolution. In this technique, the solid dispersion is prepared by heating the physical mixture (drug and carrier as silicon dioxide) in a microwave oven to form inclusions (62). Recently, Alshehri *et al.*(63)prepared a luteolinloaded solid dispersion using PEG 4000 as the carrier. They used various methods such as melting, solvent evaporation, and microwave irradiation to prepare a luteolin solid dispersion. The comparative dissolution study was performed and the results showed that the solid dispersion prepared by microwave irradiation technique showed maximum drug release (i.e. 97.78 ± 4.41%) with the ratio of luteolin and PEG 4000 (1:2). The solid dispersion upon microwave irradiation showed maximum drug release due to the greater solubility of luteolin and the smaller particle size. The same samples also showed the significantly higher radical scavenging activity than pure luteolin(63).

23) **KinetiSol® dispersing (KSD) Technique:** In this process, high-energy mixing is performed to obtain amorphous solid dispersions. It uses a series of rapidly rotating blades to mix the drug and carrier using a combination of kinetic and thermal energy without the aid of external heat sources (64). Application of this procedure was used to prepare an itraconazole solid dispersion using hypromellose as the carrier. The results of the study showed that amorphous API was formed within 15 s by the KSD technique, while hot melt extrusion took over 300 s. The dissolution profile was also improved for the sample made with the KSD technique compared to the hot-melt extrusion method (64).

LAB SCALE AND INDUSTRIAL SCALE MANUFACTURING PROCESSES:

Among all manufacturing methods that produces solid dispersion, melting method and solvent evaporation method are two different processes that are widely used on laboratory and industrial scale.

On a laboratory scale, the criteria for selecting the melting process are based on melting point and thermal stability. When selecting the solvent evaporation method, the properties of the drug, the carrier, and an organic solvent are important factors to consider. For the solvent evaporation process, a rotary evaporator was mostly used to prepare solid dispersion. Recently, SCF and freeze drying have also been used. The fusion process is commonly used because of its simplicity and economy. Various types of equipment from many

manufacturers such as Brabender Technologies, Coperion GmbH, Thermo Fisher Scientific and Leistritz Advanced Technologies Corp are currently available in the laboratory, in which solid dispersion quantities from a few grams to one kilogram can be produced.

On an industrial scale, the production of solid dispersion is limited to a few manufacturing processes, since the product is large, ranging from a few to several hundred kilograms. In addition, processes must be robust, reproducible and follow good manufacturing practices (GMP). For the evaporation method, the selection criteria are based on solvent toxicity and loading capacity. These are difficult to guarantee in processes such as solvent cast evaporation or water bath melting processes. Spray drying and freeze drying are the most representative solvent evaporation methods used to produce solid dispersion. In addition, the spray drying process can be easily scaled up from laboratory scale to industrial scale. Melt agglomeration and hot melt extrusion are two types of melting processes available on an industrial scale.For instance, hot-melt extrusion is one of the most common methods used on an industrial scale to produce solid dispersion using twin-screw extruder with a large screw diameter (16–50 mm) compared with small screw diameter on a laboratory scale (11–16 mm).

ADVANTAGES OF SOLID DISPERSION

1) Solid dispersion provides bioavailable oral dosage forms for anti-cancer drugs that could replace standard injections to improve patient comfort and compliance.
2) Solid dispersion formulations have been shown to accelerate the onset of action of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS), where immediate action is critical for the relief of acute pain and inflammation.
3) Solid dispersion systems have also been found to reduce the effect of food on drug absorption, thereby increasing the convenience of drug therapy by eliminating the need to take some drugs with food.
4) Solid dispersion based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation, thereby improved the convenience of drug therapy by reducing the dosing regimen and eliminating the need for refrigerated storage.
5) Improved absorption efficiency, demonstrated for solid dispersion systems, allows for a reduction in drug content per dose, reducing the costs associated with these drug therapies.

6) It also acts as a functional carrier, providing the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption.

DISADVANTAGES OF SOLID DISPERSION:

1) The commercial application of the solid dispersion is limited to: manufacturing method (cumbersome and expensive); reproducibility of physicochemical properties; formulation into dosage forms; scale-up of manufacturing processes; physical and chemical stability of drug and vehicle.
2) Melt method processing variables affect the physicochemical properties and stability of solid dispersions.
3) Organic solvents used during preparation should be completely removed, which is a difficult process.
4) The development of the dosage form of a solid dispersion into tablet or capsule is also problematic.
5) During compression of powder into tablet, the carrier could plasticize, soften or melt, filling the pores in the tablets and thus preventing them from disintegrating.
6) Because of soft and tacky nature of solid dispersions, pulverization and sieving is very difficult. This nature of solid dispersions also creates unique stability problems that may not be encountered with other types of solid dosage forms.
7) The transformation from the amorphous state to the crystalline state on storage has resulted in physical instability that ultimately affects the dissolution profiles and also the bioavailability of the drug formulated into a solid dispersion.
8) There are many other pitfalls that also require thorough study and these include the inability to scale up the solid dosage formulation from a small scale melt quench or a solvent-evaporation technique, insufficient knowledge of the mechanism of drug dissolution from the dosage form, prevention of crystallization of some drugs taking place in the gastric fluids and the poor understanding of the in vitro-in vivo correlation between these dosage forms(65) (66).

APPLICATIONS OF SOLID DISPERSION

1) To increase the solubility of poorly soluble drugs, thereby increasing the dissolution rate, absorption and bioavailability.
2) To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo oxidation and other decomposition procedures.

3) Masking unpleasant taste and smell of drugs.
4) Improving drug release from ointment, creams and gels.
5) To avoid unwanted incompatibilities.
6) To achieve a homogeneous distribution of a small amount of drug in solid state.
7) To deliver liquid (up to 10%) or gaseous compounds in a fixed dosage.
8) To formulate a rapid-release primary dose in a sustained released dosage form.
9) To reduce pre-systemic inactivation of drugs like morphine and progesterone.

Rationale of Physical Instability and Progress to Overcome it

As discussed, the physical instability associated with solid dispersions leads to phase separation and crystallization, which limits the commercial use of solid dispersions. Proper selection of the polymer and drug loading are imperative aspects that affect the properties of the solid dispersion and its physical stability. In addition to the polymer, surfactants can be used as recrystallization inhibitors, since they have a significant impact on the physical stability of solid dispersions. Fule and Amin determined the combined effect of polymer and surfactant on the stability of lafutidin solid dispersions. The combined action of polymer and surfactant reduces molecular mobility and inhibits recrystallization during storage of solid dispersions(67).

The dosage form can be designed and manufactured using small amounts of drug substances at early stages of the drug development process, the system could have an advantage over other commonly used techniques to increase bioavailability such as micronization of drugs and encapsulation in soft gelatin.

Novel Technologies Related to Solid Dispersion

Recent research on solid dispersions focuses mainly on the use of novel polymers and scalable manufacturing techniques. Duarte*et al.* prepared nano-solid dispersions using a novel solvent-controlled precipitation process based on microfluidization. They formulated both amorphous and crystalline solid nano-dispersions that dissolve faster and have improved bioavailability compared to micron-sized amorphous powders. They concluded that particle size reduction to the nanometer range plays a more important role than amorphization of the drug in the case of solid dispersions(68). The concept of amorphization of a crystalline drug, a widely used mechanism to improve solubility, was defeated using these novel techniques.

FUTURE PROSPECTS

Of all the techniques used in industry to improve the dissolution of poorly water-soluble drugs, solid dispersion proves to be the most versatile and applicable to most compounds and their dosage requirements.

Carriers used in the manufacture of solid dispersion have been developed in recent years. Some studies used new vehicles, while other studies used more than one vehicle to produce the solid dispersion formulation. Using more than one carrier in the formulation of solid dispersion, many effective methods have been developed, recrystallization has been reduced, and stability of solid dispersion has been improved. Some recently used carriers are Inulin®, Gelucire®, Pluronic®, and Soluplus®.

In the manufacturing process, the Kinetisol Dispersing Technique (KSD)(69) (70) is a novel high-energy mixing method used to manufacture solid dispersion, in which the drug and carrier are processed using a series of rapidly rotating blades through a combination of kinetic and thermal energy without the aid of external heating sources. This brings new hope for the development of more solid dispersion products in the future.

Future research on solid dispersions should apply new techniques to study the solubility and molecular state of the drug and its interaction with the polymer to eliminate the difficulty of designing new carriers that can prevent the drug from crystallization. It is imperative that the solid dispersion technique offers tremendous potential for future research and subsequent growth, which may lead to the development of new applications for oral drugs.

CONCLUSION

The therapeutic activity of the drug mainly depends on the bioavailability of the drug and ultimately on the solubility. An increasing number of poorly water-soluble drug candidates as well as improvements in manufacturing processes for solid dispersions strongly favor the role of the solid dispersion in improving the solubility of poorly water-soluble drugs. Another advantage of solid dispersions over other approaches is that many of the applied carriers are already extensively used in the pharmaceutical industry as excipients and no toxicity studies are required. This article provides information on novel technologies used in the preparation of solid dispersions to improve the biological profile. However, commercial development of this technique requires overcoming problems such as scale-up, cost-efficiency, and instability of some of the drugs. Further research is needed for better implementation of solid dispersion

technology on an industrial scale, as it is an excellent technique for improving the solubility of poorly soluble drugs.

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