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Review Article

# Solid Dispersions: A Review

*Sumant saini[1], Yashwant[2]

[1]*College of Pharmacy, Chitkara University, INDIA*
[2]*Division of Research and Development, Lovely Professional University, INDIA*

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**ABSTRACT**
Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. This article reviews the various preparation techniques for solid dispersion and compiles some of the recent technology transfers. The different types of solid dispersions based on the molecular arrangement have been highlighted. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier, solvent and methods of physicochemical characterization, along with an insight into the molecular arrangement of drugs in solid dispersions are also discussed. In this review, it is intended to discuss the recent advances related on the area of solid dispersions.

**Key Words:** Solid dispersion, carrier, solubility, bioavailability.

## INTRODUCTION

Oral drug delivery is the most popular, simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms1. More than 90% of drugs have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble2. After administering a drug orally, it firstly dissolves in gastric and or intestinal fluids before it, and then permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.

Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs3. 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) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS

Class II drugs Modified Noyes-Whitney equation gives some idea how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$\frac{dc}{dt} = (AD(C_s - C))/h$$

Where, dC/dt is the rate of dissolution,
A is the surface area available for dissolution,
D is the diffusion coefficient of the compound,
Cs is the solubility of the compound in the dissolution medium,
C is the concentration of drug in the medium at time t, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Surface area directly proportional to rate of dissolution, it is increased by decreasing the particle size of drug or by optimizing wetting characteristics. Particle size reduction, salt formation, complexation and solubilization of drug in solvent(s) also useful to increase dissolution, however, there are limitations for this techniques. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media7. Solid dispersion offers

a various preparation method and carrier option that allow the flexibility when formulating oral delivery system for poorly water soluble drugs.

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the

*Author for correspondence: E-mail: sumantarya15@gmail.com

solid state in order to achieve increased dissolution rate, sustained release of the drugs, altered solid state properties,

| **Table 1.** Biopharmaceutical Classification System (BCS)[1]. | |
|---|---|
| Class I | High Solubility, High permeability |
| Class II | High solubility, low permeability |
| Class III | Low solubility, High permeability |
| Class IV | Low solubility, Low permeability |

and enhanced release of the drugs from dosage form. This is performed for:

- Enhancing the dissolution rate
- Obtaining the sustained release dosage form
- Enhance the release of the drugs from the dosage form
- Improve the solubility and stability of the active pharmaceutical ingredients

Ideal Candidates For Solid Dispersion: Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly watersoluble 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 (Dhirendra *et al*[2]. 2009). In the Biopharmaceutical Classification System (BCS) Class II drugs are those with low aqueous solubility and high membrane permeability (Amidon *et al*., 1995) and therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances are classified in four groups as shown in Table 1 (FDA 2000). Table 2 represents some BCS Class II drugs on the WHO model list of Essential Medicines. The table is adopted from Lindenberg *et al*., 2004, only for the BCS Class II drugs.

**Table 2.** Some BCS class II drugs on the WHO model list of Essential Medicines. Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs with reliable solubility and permeability.

| **Drug** | **Functional category** |
|---|---|
| Carbamazepine | Antiepileptic |
| Dapsone | Antirheumatic/leprosy |
| Griseofulvin | Antifungal |
| Ibuprofen | Pain relief |
| Nifedipine | Ca-channel blocker |
| Nitrofurantoin | Antibacterial |
| Phenytoin | Antiepileptic |
| Sulfamethoxazole | Antibiotic |
| Trimethoprim | Antibiotic |
| Valproic acid | Antiepileptic |

Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs for which complete solubility and/or permeability data are lacking

Solid Dispersion: Classification: Chiou and Riegelman (1971) in their review article classified solid dispersions into six categories on the basis of their major fast-release mechanisms. This classification was adopted by Journal of Applied Pharmaceutical Science 01 (07); 2011: 13-20 Dhirendra *et al*. (2009)[2] based on the molecular arrangement and they tabulated six different types of solid dispersions as shown in the following table.

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. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution.[3]

Amorphous precipitation in crystalline matrix: This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form.

Solid solution: Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions[3] and the dissolution rate is determined by the dissolution rate of the carrier. 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).

**Table 3.** WHO model list of Essential medicines

| **Drug** | **Functional catagory** |
|---|---|
| Iopanoic acid | Contrast medium |
| Nalidixic acid | Antibacterial agent |
| Nevirapine | Antiviral |
| Praziquantel | Antihelmentic |
| Rifampicin | Antituberculotic |

Continuous solid solutions: In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical world till date.

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

Substitutional solid solutions: Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. Classical solid solutions have 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.

Interstitial solid solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter.

Glass solution and suspensions: Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent.

Lattice energy is much lower in glass solution and suspension.

**Table 4**. Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: drugs with inconclusive data

| **Drugs** | **Pharmacological catagory** |
|---|---|
| Albendazole | Antiparasitic |
| Amitriptyline | Antidepressive |
| Artemether + Lumefantrine | Antimalarial agents |
| Chlorpromazine | Antidepressive |
| Ciprofloxacin | Antibiotic |
| Clofazimine | Antibacterial agent |

Vasconcelo *et al*.[5] (2007) in their review article classified solid dispersions in three generations; i) first generation, ii) second generation and iii) third generation solid dispersions.

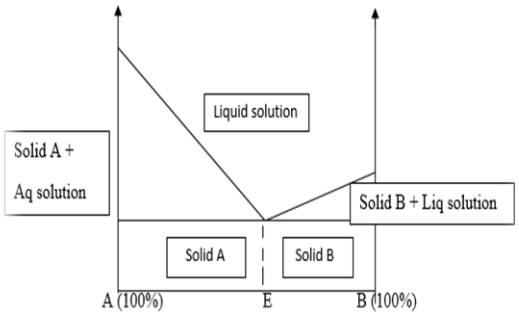


Figure 1: Indicative illustration

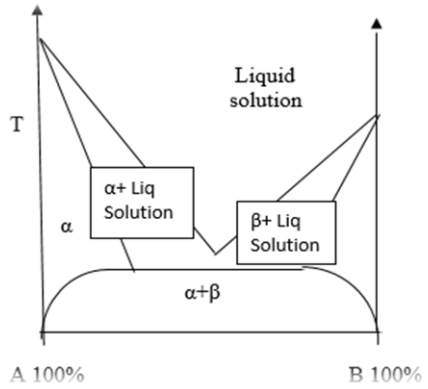


**Figure 2:** Phase diagram for a discontinuous solid solution.

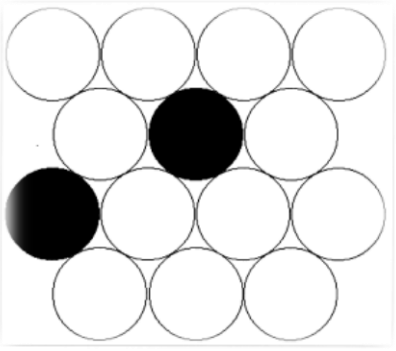

**Figure 3:** Substitutional crystalline solid solution.

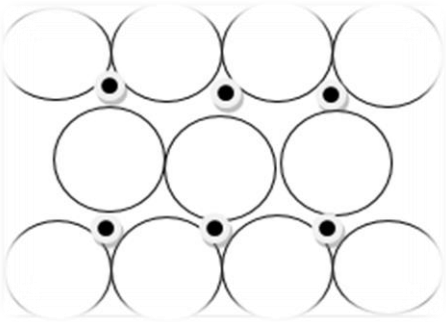

**Figure 4:** Interstitial crystalline solid solution

The first generation solid dispersions includes eutectic mixtures of sulphathiazole (Sekiguchi and Obi, 1961)[3], fused conglomerates of Chloramphenicol and urea (Sekiguchi and Obi, 1964), as prepared by Levy [6](1963) and Kanig (1964) using mannitol as carrier and using chloramphenicol-urea system (Goldberg *et al*[7]., 1965). All these solid dispersions were prepared using crystalline carriers like urea and sugars. But they have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones (Vasconcelos *et al*[8]., 2007).

Second generation of solid dispersion appeared as it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically strong (Vippagunta [9]*et al*., 2007; Simonelli[10] 1969; Urbanetz[11], 2006). In second generation solid dispersions drugs are molecularly dispersed in an irregular form within an amorphous carrier which is usually polymers (Vilhelmsen *et al*., [12]2005). The most common solid dispersions do not use crystalline carriers but amorphous one.

According to molecular interaction of drug and carriers amorphous solid dispersions can be of three types; solid solutions (van Drooge[13] *et al*., 2006; Leuner and Dressman[14] 2000; Van den Mooter *et al*., 2006), solid suspensions (van Drooge *et al*., 2006; Chiou and Riegelman, 1971; Goldberg *et al*., 1966) or a mixture of both (van Drooge *et al*., 2006; van Drooge *et al*., 2006).

Second generation solid dispersions use fully synthetic polymers and natural product based polymers as carriers. Different kinds of polymers used in second generation solid dispersions are shown in Table 4.

Third generation solid dispersions are those which are prepared by using carriers having surface activity or self-emulsifying properties. These solid dispersions contain a surfactant carrier, mixtures of amorphous polymers and surfactants as carriers. Examples of carriers in third generation solid dispersions include inulin (van Drooge *et al*., 2006a), inutec SP1 (Van den Mooter *et al*., 2006), compritol 888 ATO (Li *et al*., 2006), gelucire 44/14 (Karata *et al*., 2005; Chauhan *et al*., 2005; Yüksel *et al*., 2003), poloxamer 188 (Chokshi *et al*., 2007; Tran *et al*., 2011), poloxamer 407 (Majerik *et al*., 2007; Newa *et al*., 2008c), PEG and polysorbate 80 mixture (Dannenfelser *et al*., 2004), HPMCpoloxomer and HPMC-polyoxyethylene hydrogenated castor oil (Won *et al*., 2005) polyethylene glycol-HPMC (Mesnukul *et al*., 2008; Janssens *et al*., 2008). Third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization (Vasconcelos *et al*., 2007). Leuner and Dressman (2000) reviewed some carriers (polyethylene glycol, polyvinylpyrrolidone,

| **Solid dispersion type** | **Matrix* Drug**** | **Remarks No. of phases** |
|---|---|---|
| Eutectics[4] | The first type of solid dispersion prepared | 2 |
| Amorphous precipitations In crystalline matrix | Rarely encountered | 2 |
| Solid solutions | Continuous solid solutions | Miscible at all composition, never prepared |
| Discontinuous solid solutions | Partially miscible, 2 phases even though drug is molecularly dispersed | 2 |
| Substitutional solid solutions | Molecular diameter of drug (solute) differs less than 15% from the 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 | Drug in helical interstitial spaces of PEG. |
| Glass Suspension | A C Particle size of dispersed phase dependent on cooling/evaporation rate. | 2 |
| ** A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix According to the classification of Chiou and Riegelman[4] (1971) and Dhirendra *et al*.[2] (2009) solid solutions like continuous solid solutions are classified under the term solid dispersion. But as mentioned earlier if the drug is converted to amorphous form and forms one phase system with polymer (as in continuous solid solutions) , it can be classified as a solid solution not as solid dispersion. | | |

Polyvinylalcohol, crospovidone, polvinylpyrrolidone-polyvinylacetate copolymer, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylethylcellulose, hydroxypropylmethylcellulose phthalate, polyacrylates and polymethacrylates, urea, sugar, polyols and their polymers like mannitol, sorbitol, chitosan,Emulsifers including sodium lauryl sulphate, Tween 80, alkali dodecylsulphate surfactants, bile salts and their derivatives, cholesterol and various cholesterol esters, organic acids and their derivatives , a hydrolysis product of collagen, Gelita Collagel, pentaerythritol and phospholipids) used in the preparation of solid dispersions. Advantages of Solid Dispersions: Vasconcelos *et al*. (2007) identified four advantageous features of producing solid dispersions. The features are summarized below:

- Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.
- Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles.
- Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.
- In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.

Disadvantages of Solid Dispersions: Serajuddin (1999) identified some problems limiting the commercial application of solid dispersion which involved

- Its method of preparation,
- Reproducibility of its physicochemical properties,
- Its formulation into dosage forms,
- The scale up of manufacturing processes, and
- The physical and chemical stability of drug and vehicle. Solid dispersions are not broadly used in commercial products due to mainly the problem of crystallization of the components from amorphous state during processing (mechanical stress) or storage (temperature and humidity stress) (Pokharkar *et al*., 2006; Chauhan *et al*., 2005; Vasanthavada *et al*., 2004; Vasconcelos *et al*., 2007). Moisture may increase drug mobility and promote drug crystallization and thus may hamper storage stability of amorphous pharmaceuticals (Johari *et al*., 2005; Vasanthavada *et al*., 2004). Phase separation, crystal growth or conversion of a product to more stable structure from metastable crystalline form during storage are also considered to be major hurdles to commercialize solid dispersions as they result in decreased solubility and thus dissolution rate (Wang *et al*., 2005; Vasconcelos *et al*., 2007).

Manufacturing Processes For Preparation Of Solid Dispersions: Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.

Melting method: Sekiguchi *et al*. were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation21. The use of high temperatures, and the fact that several drugs can be degraded by the melting process, can be a limitation of this method.

Hot stage extrusion: Hot stage extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. The hot stage extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the molten state. Hot stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. Extrusion then collected after cooling at room temperature and milled. Moreover, it was observed that solid dispersions of itraconazole/Intec SP1 prepared by hot-stage extrusion presented itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying.

Melt agglomeration: Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excipients. It is prepare by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor.

Solvent evaporation method: The solvent evaporation method consists of the solubilisation of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature. A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled.

Spray-drying: Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Van Drooge *et al*. prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

Freeze-drying: This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.

Supercritical fluid method: Supercritical fluid methods are mostly applied with carbon dioxide ($CO_2$), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with $CO_2$. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. The use of processes using SCF reduces particle size, residual solvent content, without any degradation and often results in high yield.

Co-precipitation method: Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method nonsolvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the nonsolvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator (37°C) for 12 hrs. Finally it was passed through sieves.

Dropping method: This technique may overcome some of the difficulties inherent in the other method and developed by Ulrich *et al*.[16] to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions A solid dispersion of a melted drug carrier mixture is pipetted and then

**Table 4.** Different kinds of polymers used in second generation solid dispersions.

| **Polymer type** | **Polymer** | **Reference(s)** |
|---|---|---|
| Fully synthetic polymers | Polyvinylpyrrolidone (povidone) | van Drooge[13] *et al*., 2006a; Simonelli [10]*et al*., 1969; Karavas *et al*.,[15] 2006; van Drooge *et al*., 2006b; Pokharkar *et al*., 2006; Hasegawa *et al*., 2005; Lloyd *et al*., 1999; Yoshihashi *et al*., 2006; Chokshi *et al*., 2007; Sun *et al*., 2008; Ito *et al*., 2010; Kubo *et al*., 2011; Kaewnopparat *et al*., 2009; Bikiaris *et al*., 2005; Shinde *et al*., 2008 |
| | Polyethylene glycols | Prabhu *et al*., 2005; Urbanetz, 2006; Guyot *et al*., 1995; Yao 2005; Chiou and Riegelman 1970; Newa *et al*., 2008a; Yao *et al*., 2011; Bikiaris *et al*., 2005; Khoo *et al*., 2000; Dhumal *et al*., 2009; Newa *et al*., 2008b; Preetham and Satish, 2011; |
| Natural Product based polymers (cellulose derivatives, | Hydroxypropylmethylcel-lulose<br>Carboxymethyl cassava starch | Won *et al*., 2005; Konno and Taylor, 2006; Ohara *et al*., 2005; Engers *et al*., 2010; Dobaria *et al*., 2009; Papageorgiou *et al*., 2008 |
| | Ethylcellulose | Desai *et al*., 2006; Ohara *et al*., 2005; Verreck *et al*., 2006; Ying *et al*., 2011 |
| | Phospholipid | |
| | Hydroxypropylcellulose | Tanaka *et al*., 2005; Tanaka *et al*., 2006; Tiwari *et al*., 2008; Park *et al*., 2009 |
| **Polymer type** | **Polymer** | **Reference(s)** |
| Gums | Locust Bean gum<br>Xanthan gum | |
| Starch derivatives | Cyclodextrines | Garcia-Zubiri *et al*., 2006; Rodier *et al*., 2005; Rahman *et al*., 2010; Srinarong *et al*., 2009; Preetham and Satish, 2011 |
| | Skimmed milk | |
| | Poloxamer 188 | |
| | Primogel | |
| | Inulin 4kDa | |
| | Gelucire | |

dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. This method also avoids the pulverization, sifting and compressibility difficulties.

Physical mixture: In this technique the drug and the carrier are physically mixed so as to obtain the solid dispersion.

Microwave method: In the recent times, the microwave radiations have been used in the formulation of the solid dispersions. Microwave is an electromagnetic wave with wavelengths longer than those of terahertz waves, but shorter than radio waves. It has frequencies between 300MHz and 300 GHz. Microwave is not a form of heat, but a form of energy which manifests as heat through its interaction with materials. The transmission of microwave to an object results in vibration of molecules by induced or permanent dipoles. The intensity of vibration is dependent on the size, shape and polarizability of the molecules, as well as, the extent of intermolecular bonding of the object. Practically, the amount of energy absorbed by an object, *P*, is defined as:

$P = 2\pi f E^2 E_0 Er \tan\theta$

Where *f* = frequency of microwave, E = electric field, $E_0$ = dielectric constant of free space, *Er* = dielectric constant of object and tan θ = loss tangent.

The important aspect of microwave is that it provides rapid volumetric heating, no overheating at the surface, addressable heating energy saving and low operating cost. The microwave frequency is absorbed by the molecules and is resonance frequency of molecules. In the recent years it has emerged to be a promising tool in the synthetic chemistry. The reactions can be conducted under solvent free conditions, thus offering the possibility of reduction in

cost, wastage and residues that need to be appropriately disposed. Microwaves can bring about the phase transformations in the crystalline substances which is not possible with any conventional heating system. Microwaves have been reported to be successful in the production of β- cyclodextrins inclusion complexes.

Film freezing method: Thin film freezing (TFF) is a rapid freezing technology, which has been successfully applied to enhance the solubility of several poorly water-soluble drugs, such as itraconazole, danazol, and tacrolimus. During the TFF process, droplets of API/ excipient(s) solution are rapidly frozen onto a cryogenically-cooled substrate to form an amorphous solid dispersion. As the supercooling is extremely fast, the nucleation of API crystals is minimized or completely prevented, resulting in amorphous morphology when the formation of a vitrified solution occurs on the surface of the cryogenically-cooled substrate. The resulting product is a solid dispersion in which drug is molecularly dispersed within a polymer matrix, which is acting as a stabilizer to keep the drug in an amorphous morphology. As a result of the fast cooling rates, the TFF process has produced powders of poorly water-soluble APIs with high surface area, leading to improved dissolution rate and enhanced bioavailability in vivo

Solvent wetting method: Felodipine was dissolved in an appropriate amount of ethanol. The amount of ethanol used varied depending on the weight of drug and polymer. For PVP and HPMC, the amounts of ethanol used were 2.5 times the total weight of drug and polymer, and for the other cases, the amount of ethanol used was 1.5 times this. A mixture of ethanol and dichloromethane (1:1, v/v) or ethanol by itself was used to compare the solvent effects on the dissolution rate of drug, when HPMC was used as a carrier. After complete dissolution of felodipine, solutions were dropped onto polymeric carriers. Solvents were removed under vacuum at room temperature. The solid dispersions obtained were ground in a mortar.

Advantages of solid dispersion technology:-

- Improving drug bioavailability by changing their water solubility has been possible by solid dispersion.
- Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine.
- Increase in dissolution rate & extent of absorption and reduction in pre systemic metabolism.
- Transformation of liquid form of drug into solid form.
- Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

Drawbacks of solid dispersion technology

- Most of the polymers used 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
- Poor scale-up for the purposes of manufacturing.

Evaluation: The most important methods which are used for characterization are thermo analytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. Methods for the characterization of solid dispersions are as following

- Dissolution testing.
- Thermo analytical methods: differential thermo analysis and hot stage microscopy.
- Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change
- X-Ray diffraction
- Spectroscopic methods, e.g. IR spectroscopy, NMR spectroscopy.
- Microscopic methods including polarization microscopy and scanning electron microscopy.

Future scope: Solid dispersion systems as extremely useful tool in improving the dissolution and solubility enhancement properties of poorly water-soluble drugs. 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. Carriers with or without any surface activity, when used, can significantly increase the wettability properties of drugs. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and increases the solubility of poorly water soluble drug. Solid dispersion has also been used to produce sustained release microsphere using tedious methods. New optimized techniques are also useful in the industries

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