IJPSR (2013), Vol. 4, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 27 February, 2013; received in revised form, 26 April, 2013; accepted, 18 May, 2013

SOLID DISPERSIONS: A REVIEW ON DRUG DELIVERY SYSTEM AND SOLUBILITY ENHANCEMENT

Dharna Allawadi*, Neelam Singh, Sukhbir Singh and Sandeep Arora

Chitkara College of Pharmacy, Chitkara University, Chandigarh Patiala National Highway (NH-64), Tehsil-Rajpura, Distt-Patiala-140401, India

Keywords:

Solid dispersions, Bioavailability, Carrier, Crystallization, Stabilization

Correspondence to Author:

Dharna Allawadi

Research Scholar, Chitkara College of Pharmacy, Chitkara University, Chandigarh Patiala National Highway (NH-64), Tehsil-Rajpura, Distt-Patiala-140401, India
E-mail: dharna.allawadi@gmail.com

ABSTRACT: Solid dispersions, defined as the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state and an efficient technique to improve dissolution of poorly water-soluble drugs to enhance their bioavailability. Poor water solubility is one of the major problems for the various types of drugs and various approaches have been introduced for the enhancement of solubility of such drugs. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. The number of poor water soluble compounds has dramatically increased. Currently only 10-12% of new drug candidates have both high solubility and high permeability. More than 60-65% of potent drug products suffer from poor water solubility. Solid dispersions have attracted considerable interest as an efficient means for improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. Compared to conventional formulations such as tablets or capsules, solid dispersions which can be prepared by various methods have many advantages. Few of the aspects are to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization. In this review, an overview on solid dispersions in general will be given with emphasis on the various types of solid dispersions, manufacturing processes, characterization, advantages, disadvantages and the application of the solid dispersions, challenges in formulation of solid dispersion dosage forms, and various types of marketed preparations.

INTRODUCTION: The oral route of drug administration is the most common and preferred route of delivery due to convenience and ease of ingestion. From a patient's prospect, swallowing a dosage form is a comfortable means of taking medication.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(6).2094-05

Article can be accessed online on: www.ijpsr.com

As a result, patient compliance is more effective with orally administered medications as compared with other routes of administration, for example, parenteral route. Although the oral route of administration is preferred, in case of many drugs it can be a problematic and inefficient mode of delivery for a number of reasons.

Limited drug absorption resulting in poor bioavailability is amongst the potential problems that can be overcome while delivering an active agent via the oral route.

After administering a drug orally, it firstly dissolves in gastric media 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 drugs. Solubility is a predetermined and rate limiting step for absorption.

Drug has to enter in to the systemic circulation to exert its therapeutic effect. In recent technologies, innovation of combinatorial chemistry and high throughput screening (HTS) can effectively discover the new drugs which exhibit good pharmacological activities. However, 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility.

In the Biopharmaceutical Classification System (BCS) (**table 1 and figure 1**) drugs with high membrane permeability and low aqueous solubility are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly for improving the oral absorption and bioavailability of BCS Class II drugs. Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi [1].

TABLE 1: BIOPHARMACEUTICAL CLASSIFICATION SYSTEM [2]

Class	Dissolution in aqueous environment	Permeation over (intestinal) membrane
I	Fast	Fast
II	Slow	Fast
III	Fast	Slow
IV	Slow	Slow

BCS Class Boundaries:

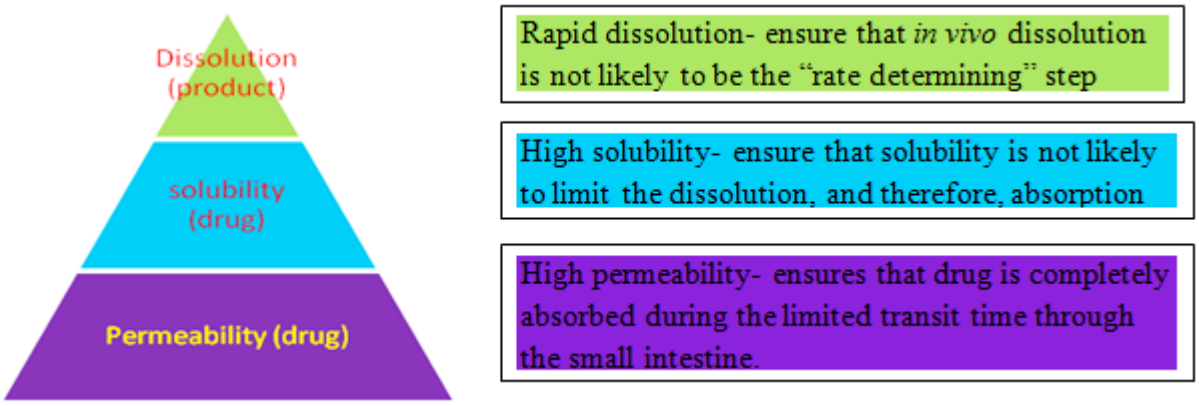

FIGURE 1: BCS CLASS BOUNDARIES

Class-I drugs dissolve rapidly in an aqueous environment and are rapidly transported over the absorbing membrane. No strategies are required to increase their absorption. When the release of the active ingredient from the formulation is slower than the gastric emptying rate, good in-vitro-in-vivo-correlation (IVIVC) can be expected.

The absorption (rate) of **class-II** drugs can be increased by accelerating the dissolution. Class-II drugs show *In- vitro – In- vivo* Correlation (IVIVC) as long as the in-vivo dissolution rate is same as in-vitro. However, because the dissolution rate is critical for class-II drugs, the *in-vivo* absorption can be affected by several physiological fluctuations, like the volume and pH of the intestinal juices, the presence of bile salts, food, enzymes, and bacteria, the motility of the gut and the viscosity in the gut lumen.

For **class-III** drugs the absorption is rate limiting and in-vitro dissolution experiments cannot be used to predict in-vivo absorption.

Also for **class-IV** drugs no IVIVC can be expected. It is up to the formulation scientist to increase the extent of absorption but also to improve the IVIVC. This will reduce the patient-to-patient variability and improve the bioavailability and the predictability of pharmacokinetic parameters [2].

It is clear that, depending on the classification of the drugs, different strategies can be applied to increase or accelerate the rate of absorption of a drug; either increasing the permeability of the absorbing membrane or increasing the amount of dissolved drug that is in contact with the absorbing membrane.

Especially supersaturated solid solutions of the drug are subjected to recrystallization phenomena. **Solid dispersion** refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug [3].

In general**, solid dispersion** is defined as the dispersion of one or more active ingredient in a carrier or matrix at solid state.

The term "**solid dispersion**" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion solvent method. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [4, 5].

Types of Solid Dispersion: (Figure 2)

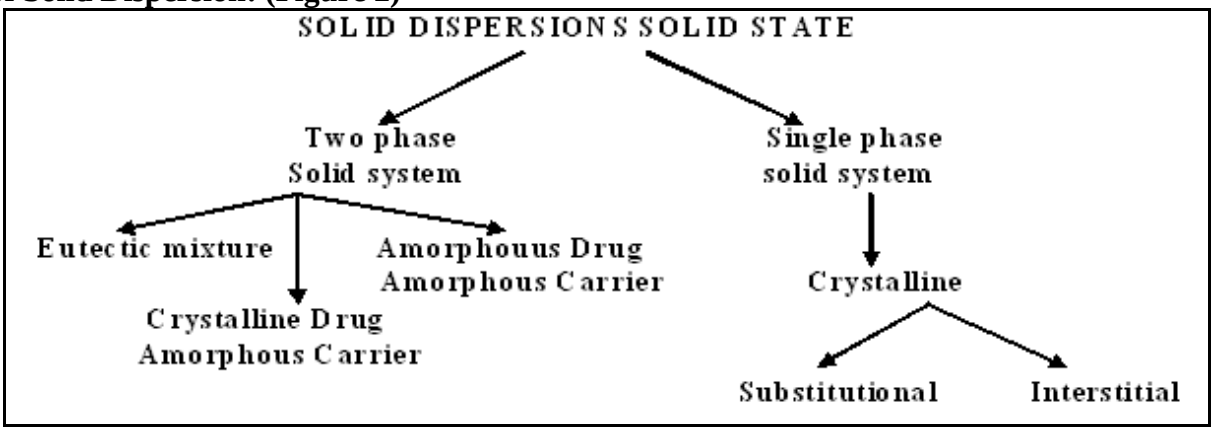

FIGURE 2: TYPES OF SOLID DISPERSION

1. **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 Sekiguchi K, Obi N, Studies on Absorption of Eutectic Mixture as shown in **figure 3** [6, 7].

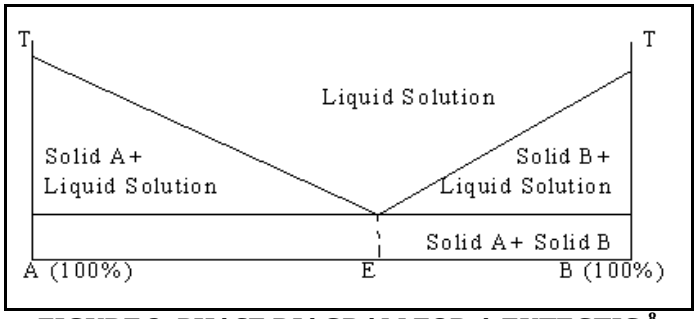

FIGURE 3: PHASE DIAGRAM FOR A EUTECTIC [8]

2. **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 [9].

3. **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 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).

   a. **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.

b. **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 [10] that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Phase diagram is shown in **figure 4**.

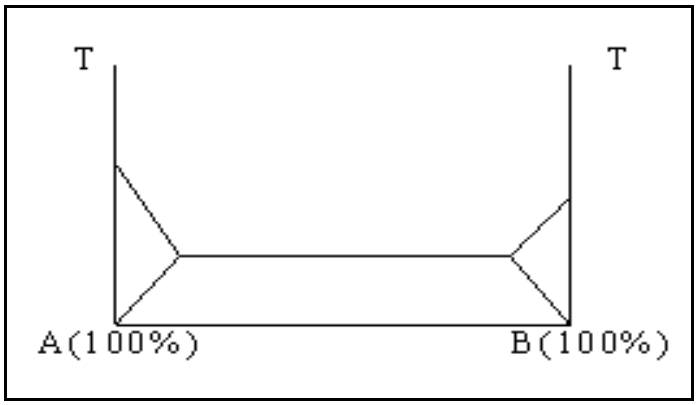

FIGURE 4: PHASE DIAGRAM FOR A DISCONTINUOUS SOLID SOLUTION.

c. **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 [11]. 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 as shown in **figure 5**.

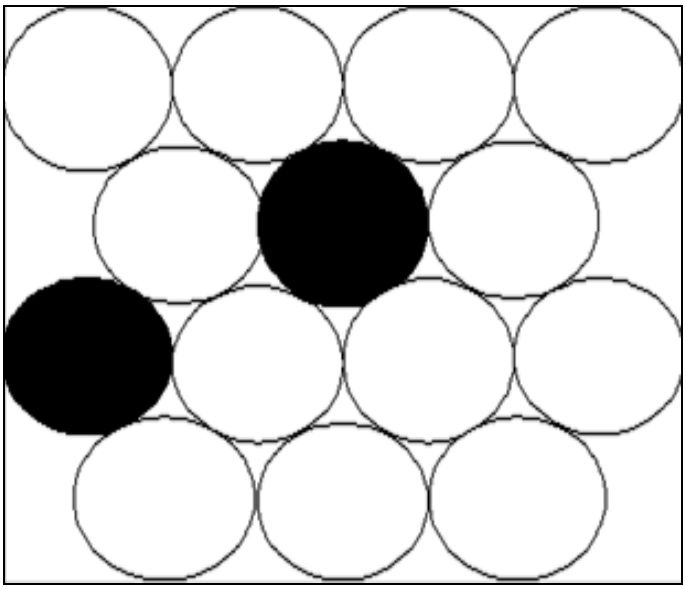

FIGURE 5: SUBSTITUTIONAL CRYSTALLINE SOLID SOLUTION

d. **Interstitial solid solutions:** In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice as shown in **figure 6**. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter [12].

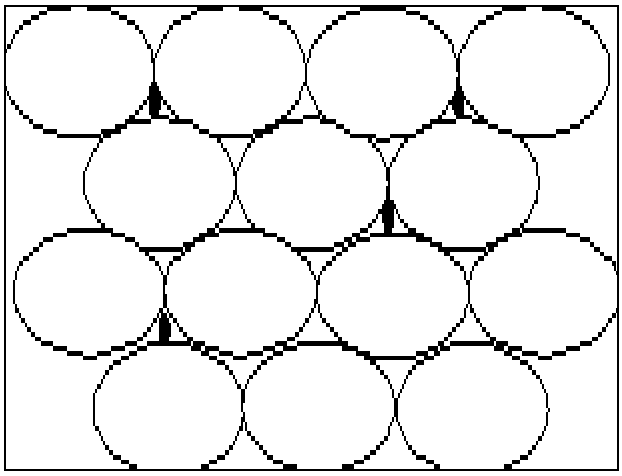

FIGURE 6: INTERSTITIAL CRYSTALLINE SOLID SOLUTION

4. **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.

Methods of preparation of Solid Dispersion: Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.

1. **Melting method:** In this method drug is dissolved in a suitable liquid solvent. Then, the solution is incorporated directly into the melt of polyethylene glycol obtainable below 70°c, without removing the liquid solvent. It has been shown that 5-10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property [10].

   The melting method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it is melted. The final solid mass is crushed, and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a stainless steel

plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures [11]. This process is also known as fusion process. However many substances, either drugs or carriers, may decompose or evaporate during the process due to high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier [12].

2. **Melt agglomeration method:** 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 [13]. It is prepared by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carriers [14]. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor [15]. This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersion are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles [16].

3. **Solvent evaporation method:** The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated [17, 18]. In this method (**figure 7**), the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature [19]. 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 [20, 21].

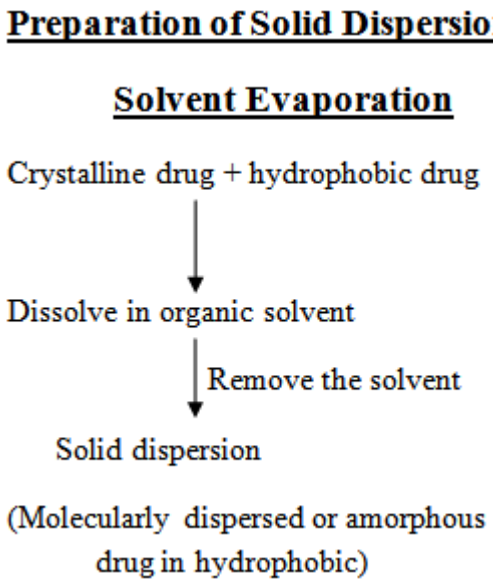

FIGURE 7: PREPARATION OF SOLID DISPERSION BY SOLVENT EVAPORATION METHOD

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods [22].

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

(i) Both drug and carrier must be dissolved.

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

(iii) Ethanol can be used as alternative as it is less toxic.

(iv) Water based systems are preferred.

(v) Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration [23].

Class I Solvents (Solvents to be avoided): Solvents included in this class are not to be taken in to use because of their deleterious environmental effects. Some of the examples are given in **table 2**.

TABLE 2: LIST OF SOME CLASS I SOLVENTS

Solvent	concentration limit (ppm)	Effect
Benzene	2	
Carbon tetrachloride	4	Carcinogenic, toxic , environmental hazards
1,2- dichloroethane	5	Toxic
1,1- dichloroethane	8	Toxic
1, 1,1- trichloroethane	1500	Enviornmental hazards

Class II Solvents (Solvents to be limited): Theses solvent should be limited used in pharmaceutical products because of their inherent toxicity (**table 3**).

TABLE 3: CLASS II SOLVENTS IN PHARMA-CEUTICAL 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

PDE= Permitted Daily Exposure

Class III Solvents (Solvents with low toxic potential) [24]: Solvents included in this class may be regarded as less toxic and have the low risk to human health and as some are given in **table 4**.

TABLE 4: CLASS III SOLVENTS WHICH SHOULD BE LIMITED BY GMP OR OTHER QUALITY BASED REQUIREMENTS [24, 25]

Acetic acid	Ethyl ether
1-butanol	Formic acid
2-butanol	Heptane
Acetone	Isobutyl acetate
Butyl acetate	Isopropyl acetate
Dimethylsulfoxide	Methyl acetate
Ethanol	3-methyl-1-butanol
Ethyl acetate	Pentane
1-propanol	1-pentanol
2-propanol	Propyl acetate

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.

4. **Hot Melt Extrusion method:** In this method extruder is utilized for intense mixing of components. The components of the extruder are barrel, hopper, a kneading screw, heating jacket, and a die. Generally physical mixture of both the carrier and drug is introduced into the hopper then passed through screw and finally it is extruded from the die. The advantage of the method is to get various shapes and designs of the heated drug-matrix mixture into ophthalmic inserts, implants, or oral dosage form.

   Other advantage like continuous production of solid dispersions is possible so that large-scale production can easily be achieved. The product produced by this method can easily be handled because any shape can be adopted. Like other methods, miscibility of drug and matrix also creates problem. Thermo labile compounds can be degraded due to production of heat generated by the extruder.

5. **Fusion method:** Fusion method is the oldest method used for the preparation of solid dispersions as the first solid dispersion created for pharmaceutical application were prepared by the fusion method. It is also referred as the melt method only when the starting materials are in crystalline state. So it is referred as fusion method [2]. The solid dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition. Sekiguchi and obi prepared solid dispersions of sulfathiazole in carriers such as ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, and urea by melting various drug carrier mixtures [26, 27, 28]. The mixture of sulfathiazole and urea which was fused and later cooled to get the final dispersion. The eutectic composition was chosen inorder to obtain simultaneous crystallization of drug and matrix during cooling [29].

6. **Spray-drying:** Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving [30, 31, 32] 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*., [33] prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

7. **Supercritical fluid methods:** The supercritical fluid antisolvent techniques, carbon dioxide are used as an anti-solvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas anti-solvent, solution enhanced dispersion by supercritical fluids, and supercritical antisolvent. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently [34].

   Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent.

   The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier components) [35, 36].

8. **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 [37]. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices [38], the technique is poorly exploited for the preparation of solid dispersions [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 advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.

9. **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 non-solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried [40]. 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 [41].

10. **Dropping method:** This technique may overcome some of the difficulties inherent in the other method and developed [42] 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 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 and compressibility difficulties [43].

Characterization of Solid Dispersion: Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture.

- Thermal analysis.
- X-ray diffraction method.
- Spectroscopic method.
- Modulated temperature differential scanning calorimetry
- Environmental scanning electron microscopy
- Dissolution testing.
- Dissolution rate method.
- Microscopic method.
- Thermodynamic method.

1. **Thermal Analysis Techniques:** Thermal analysis comprises a group of techniques in which a physical property of a substance is measured as a function of temperature, while the substance is subjected to a controlled temperature programme. In deferential thermal analysis, the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat.

    The related technique of deferential scanning calorimetry relies on deference's in energy required to maintain the sample and reference at an identical temperature. Length or volume changes that occur on subjecting materials to heat treatment are detected in dilatometry; X-ray or neutron diffraction can also be used to measure dimensional changes. Both thermogravimetry and evolved gas analysis are techniques which rely on samples which decompose at elevated temperatures. The former monitors changes in the mass of the specimen on heating, whereas the latter is based on the gases evolved on heating the sample.

    Electrical conductivity measurements can be related to changes in the defect density of materials or to study phase transitions [44].

2. **X-ray Crystallography:** X-ray crystallography is a method of determining the arrangement of atoms within a crystal, in which a beam of X-rays strikes a crystal and diffracts into many specific directions. From the angles and intensities of these diffracted beams, a crystallographer can produce a three dimensional picture of the density of electrons within the crystal. From this electron density, the mean positions of the atoms in the crystal can be determined, as well as their chemical bonds, their disorder and various other information.

    Since many materials can form well as various inorganic, organic and biological molecules. X-ray crystallography has been fundamental in the development of many scientific fields. In its first decades of use, this method determined the size of atoms, the lengths and types of chemical bonds, and the atomic-scale differences among various materials, especially minerals and alloys [45].

3. **Spectroscopy:** Spectroscopy was originally the study of the interaction between radiation and matter as a function of wavelength (λ). In fact, historically, spectroscopy referred to the use of visible light dispersed according to its wavelength, e.g. by a prism. Later the concept was expanded greatly to comprise any measurement of a quantity as a function of either wavelength or frequency.

Thus, it also can refer to a response to an alternating field or varying frequency (ν). A further extension of the scope of the definition added energy (E) as a variable; once the very close relationship for photons was realized (h is the Planck constant). The **Planck constant** is a physical constant that is the quantum of action in quantum mechanics. The Planck constant was first described as the proportionality constant between the energy (*E*) of a photon and the frequency (*v*) of its associated electromagnetic wave. This relation between the energy and frequency is called the **Planck relation**:

$$E = h\nu$$

Since the frequency *v*, wavelength λ and speed of light *c*, are related by $\lambda v = c$, the Planck relation can also be expressed as;

$$E = \frac{hc}{\lambda}$$

4. **Modulated temperature Differential Scanning Calorimetry (MDSC):** All spray-dried samples and starting materials were analyzed in triplicate. MDSC measurements perform using DSC equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50 ml/min was used to purge the DSC cell. Open aluminum pans were used for all measurements. The mass of the empty sample pan and the reference pan was taken into account for the calculation of the heat flow. The sample mass varied from 1 to 6 mg. The enthalpic response was calibrated with an Indium standard and the temperature scale was calibrated with Octadecane, Indium and Tin. The heat capacity signal was calibrated by comparing the response of a sapphire disk with the equivalent literature value at 80°C.

5. **Environmental Scanning Electron Microscopy:** The morphology of the spray-dried ternary solid dispersions can be characterized with a Philips XL30 ESEM FEG environmental scanning electron microscope operating at 25 kV accelerating voltage and a vacuum. The samples were sprayed on double-sided carbon tape that was mounted on conventional SEM stubs [46].

6. **Dissolution testing:** Dissolution experiments can be performed in triplicate on the binary and ternary dispersions. The tests were performed according to the USP 24 method 2 in a Hanson SR8plus dissolution apparatus. To simulate the dissolution of a weak basic compound in the stomach, 500mL of simulated gastric fluid without pepsin was used as dissolution medium at a temperature of 37°C and a paddle speed of 100 rpm. An amount of the spray-dried powders, corresponding to drug dose of 100 mg, was added to the dissolution medium. Five-millilitre samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, and 120 min. These samples were filtered with 0.45μm Teflon filters. The first 2ml were discarded. The remainder was diluted with methanol (1/2) to avoid precipitation, and analyzed with HPLC [47].

7. ***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies are done for the find out dissolution behaviour. The *in-vitro* dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through *in- vitro – in- vivo* correlation (IVIVC). On the other hand, if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed *in-vivo* dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately.

Advantages of Solid Dispersions:

1. Improving drug bioavailability by changing their water solubility has been possible by solid dispersion.

2. 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.

3. Increase in dissolution rate & extent of absorption and reduction in Pre systemic metabolism.

4. Transformation of liquid form of drug into solid form.

5. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability [48].

Disadvantages of Solid Dispersions:

1. 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.

2. Drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

Applications of Solid Dispersions: Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used:

1. To obtain a homogeneous distribution of a small amount of drug in solid state.

2. To stabilize the unstable drug.

3. To dispense liquid or gaseous compounds in a solid dosage.

4. To formulate a fast release primary dose in a sustained released dosage form.

1. 5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

2. 6. To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphism, solid solution, eutectic or molecular compounds.

6. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

7. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.

8. To reduce side effect of certain drugs.

9. Masking of unpleasant taste and smell of drugs.

10. Improvement of drug release from ointment, creams and gels.

11. To avoid undesirable incompatibilities.

12. To obtain a homogeneous distribution of a small amount of drug in solid state.

13. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

14. To formulate a fast release primary dose in a sustained released dosage form.

11. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

12. To reduce pre systemic inactivation of drugs like morphine and progesterone.

Challenging future for Solid Dispersion Technique: Since solid dispersions were introduced in 1961, an immense amount of research has been done in this area. However, very few solid dispersion systems have been marketed [49]. Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization. Various issues that impeded the commercial development of solid dispersions include

(a) Inability to scale bench top formulations to manufacturing- sized batches,

(b) Difficulty to control physicochemical properties,

(c) Difficulty in delivering solid dispersion formulations as tablet or capsule dosage forms, and

(d) Physical and chemical instability of the drug and/or the formulation**.**

Marketed Products [50]

Product name	Drug name	Company name
Grispeg	Griseofulvin	Pendinal pharm inc.
Cesamet	Nabilone	Eli lilly
Sproranox	Itraconazole	Janssen
Rezulin	Troglitazone	Pfizer
Hepcure	Hepatitis type b	Cj jeil jedang
Keletra	Lopinavir	Abbott

REFERENCES:

1. Patil RM, Maniyar AH, Kale MT, Akarte AP and Baviskar DT: Solid dispersion: strategy to enhance solubility. International Journal of Pharmaceutical Sciences Review and Research 2011; 8(2) : 66-73.
2. Verma S, Rawat A, Kaul M and Saini S: Solid Dispersion: A Strategy For Solubility Enhancement. International Journal of Pharmacy & Technology 2011; 3(2): 1062-1099.
3. Dau K and Sharma VK: Solid dispersion technology. Pharmabizj 2009; 10, 1-2.
4. Chiou WL and Riegelman S: Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences 1971; 60(9): 1281-1302.
5. Cilurzo F, Minghetti P, Casiraghi A and Montanari L: Characterization of nifedipine solid dispersions. International Journal of Pharmaceutics 2002; 242(1-2): 313-317.
6. Sekiguchi K and Obi N: A comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chemical and Pharmaceutical Bulletin 1961; 9: 866-872.
7. Chiou WL and Riegelman S: Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. Journal of Pharmaceutical Sciences 1969; 58(12): 1505-1510.
8. Lachman L, Liberman HA: Theory and practice of industrial pharmacy. Varghese Publishing House, 3rd edition, 1998.
9. Swarbrick J: Encyclopedia of Pharmaceutical Technology. 3rd edition,2006, 775-777.
10. Patidar K, Kshirsagar MD, Saini V, Joshi PB and Soni M: Solid Dispersion Technology: A Boon for Poor Water Soluble Drugs. Indian Journal of Novel Drug Delivery 2011; 3(2): 83-90.
11. Kim KT, Lee JY, Lee MY, Song CK, Choi J and Kim DD: Solid Dispersions as a Drug Delivery System. Journal of Pharmaceutical Investigation 2011; 41(3): 125-142.
12. Singh S, Baghel RS and Yadav L: A review on solid dispersion. International Journal of Pharmacy & Life Sciences 2011; 2(9): 1078-1095.
13. Gupta MK: Hydrogen Bonding With Adsorbent During Storage Governs Drug Dissolution from Solid-Dispersion Granules. Pharmaceutical Research 2002; 19: 1663–1672.
14. Seo A: The preparation of agglomerates containing solid dispersions of diazepam by melt agglomseration in a high shear mixer. International Journal of Pharmaceutics 2003; 259: 161–171.
15. Vilhelmsen T: Effect of a melt agglomeration process on agglomerates containing solid dispersions. International Journal of Pharmaceutics 2005; 303: 132–142.
16. Horter D and Dressman JB: Physiochemical properties on dissolution of drug in the gastrointestinal tract. Advanced Drug Delivery Review 1997; 25: 3-14.
17. Hasegawa S: Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. International Journal of Pharmaceutics 2003; 302(29): 103–112.
18. Rodier E: A three step supercritical process to improve the dissolution rate of Eflucimibe. European Journal of Pharmaceutical Sciences 2005; 26: 184–193.
19. Won DH: Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical antisolvent precipitation process. International Journal of Pharmaceutics 2005; 301: 199–208.
20. Lloyd GR: A calorimetric investigation into the interaction between paracetamol and polyethlene glycol 4000 in physical mixes and solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics 2003; 48: 59–65.
21. Yoshihashi Y: Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry. Journal of Thermal Analysis and Calorimetric 2006; 85: 689– 692.
22. Goldberg A, Gibaldi M and Kanig L: Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system. Journal of Pharmaceutical Sciences 1996; 55: 482-487.
23. Kamalakkannan V, Puratchikody A, Masilamani K and Senthilnathan B: Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review. Journal of Pharmacy Research 2010; 3: 2314-2321.
24. Tiwari R, Tiwari G, Srivastava B and Rai AK: Solid Dispersions: An Overview to Modify Bioavailability of Poorly Water Soluble Drugs. International Journal of Pharmaceutical Technology and Research 2009; 1: 1338-1349.
25. Leuner C and Dressman J: Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics 2000; 50: 47-60.
26. Singh MC, Sayyad AB and Sawant SD: Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. Journal of Pharmaceutical Research 2010; 3(2): 494-501.
27. Sethia S and Squillente: Solid dispersion: Revival with greater possibilities and applications in oral drug delivery. Critical Review in Therapeutic drug Carrier System 2003; 20: 217-49.
28. Dhirendra K, Lewis S, Udupa N and Atin K: Solid Dispersion: A review, Pakistan Journal of Pharmaceutical Sciences 2009; 22(2): 34-46.
29. Vijay: A basic insight into the stability and manufacturing aspects of solid dispersions. Cronicles of young Scientists 2012; 3(2):95-105.
30. Mooter G: Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. International Journal of Pharmaceutics 2006; 316: 1–6.
31. Chauhan B: Preparation and evaluation of glibenclamide polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. European Journal of Pharmaceutical Sciences 2005; 26: 219–230.
32. Mizuno M: Inhibition of a solid phase reaction among excipients that accelerates drug release from a solid dispersion with aging. International Journal of Pharmaceutics 2005; 305: 37–51.

33. Drooge DJV: Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. International Journal of Pharmaceutics 2006; 310: 220–229.
34. Taki S, Badens E and Charbit G: Controlled release system formed by supercritical anti-solvent coprecipitation of an herbicide and a biodegradable polymer. Journal of Supercritical Fluids 2001; 21: 61-70.
35. Dohrn R, Bertakis E, Behrend O, Voutsas E and Tassios D: Melting point depression by using supercritical CO_2 for a novel melt dispersion micronization process. Journal of Molecular Liquids 2007; 131- 132, 53-59.
36. Vilhelmsen T: Effect of a melt agglomeration process on agglomerates containing solid dispersions. International Journal of Pharmaceutics 2005; 303: 132–142.
37. Drooge, DJV: Characterization of the Mode of Incorporation of Lipophilic Compounds in Solid Dispersions at the Nanoscale Using Fluorescence Resonance Energy Transfer (FRET). Macromolecular Rapid Communications 2006; 27: 1149–1155.
38. Eriksson HJC, Hinrichs WLJ, Veen B, Somsen GW, Jong GJ and Frijlink HW: Investigations into the stabilisation of drugs by sugar glasses: I, Tablets prepared from stabilised alkaline phosphatise. International Journal of Pharmaceutics 2002; 249(1-2): 59-70.
39. Sethia S and Squillante E: Solid dispersions: revival with greater possibilities and applications in oral drug delivery. Critical Reviews of Therapeutic Drug Carrier System 2003; 20(2-3): 215-247.
40. Huang J: Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. International Journal of Pharmaceutics 2006; 319: 44–54.
41. Butler and Matthew J: Method of producing a solid dispersion of a poorly water soluble drug. United States Patent- 5,985,326, Pharmaceutical Patents. 1998.
42. Shah JC, Chen JR and Chow D: 1. Preformulation study of etoposide. 2. Increased solubility and dissolution rate by solid dispersions. International Journal of Pharmaceutics 1995; 113: 103-111.
43. Shaharoodi AB: Dropping Method for Formulating Solid Dispersion. 2003; http:// HYPERLINK http://www. ptemag.com/pharmtecheurope/Solid.www.ptemag.com/pharmtecheurope/SolidDosage/DroppingMethodSolutionfor Formulating SolidDis/Article Standard/Article/detail/83301.
44. Robert CJ, Armas HN and Janssen S: Characterization of ternary solid dispersion of intraconazole PEG 6000. Journal of Pharmaceutical Sciences 2008; 97: 2110-2120.
45. Suzuki H, Miyamoto N, Masada T, Hayakawa E and Ito K: Solid dispersions of benidipine hydrochloride. 1, Preparations using different solvent systems and dissolution properties. Chemical and Pharmaceutical Bulletin 1996; 44: 364-371.
46. Damian F, Blaton N, Naesens L, Balzarini J, Kinget R, Augustijns P and Van Den Mooter G: Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. European Journal of Pharmaceutical Sciences 2000; 10(4): 311-22.
47. HYPERLINK http://www.wikipedia.org/wiki/Lactose
48. Arunachalam A, Karthikeyan M, Konam K, Prasad PH, Sethuraman S and Ashutoshkumar S: Solid Dispersions: A Review. Current Pharmaceutical Research 2010; 1(1): 82-90.
49. Karanth H, Shenoy VS and Murthy RR: Industrially Feasible Alternative Approaches in the AAPS. Pharmaceutical Sciences and Technology 2006; 7: 1-8.
50. Kumar S, Malviya R and Sharma PK: Solid dispersion: Pharmaceutical Technology for the Improvement of Various Characteristics of Active Pharmaceutical Ingredients. African Journal of Basic and Applied Sciences 2011; 3(4): 116-125.

How to cite this article:
Allawadi D, Singh N, Singh S and Arora S: Solid dispersions: A review on Drug delivery system and Solubility enhancement. *Int J Pharm Sci Res* 2013; 4(6); 2094-2105. doi: 10.13040/IJPSR.0975-8232.4(6).2094-05