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REVIEW ARTICLE

IMPROVING SOLUBILITY OF BCS CLASS II DRUGS USING SOLID DISPERSION: A REVIEW**Sweta Mehta¹, Nisha Mary Joseph^{1*}, Fitsum F. Sahle¹, S. Palani²**

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ABSTRACT

Biopharmaceutics Classification System is important for determining the bioavailability of the drugs. Drug development tool that allows estimation of the three major factors that affect oral drug absorption from immediate release solid oral dosage form is Dissolution, Solubility and Intestinal permeability. The bioavailability issue can be due to insufficient solubility or permeability. Most compounds face the solubility problems. The dissolution rate of drug from its dosage form is considered as an important parameter in the absorption. Dissolution is the rate-limiting step in the absorption of drugs from one solid dosage form especially when the drug is poorly water soluble. Poor wettability of drugs leads to the decrease in their bioavailability. Presently only 8% of new drug candidates have both high solubility and permeability and more than 60% of the products have poor water solubility. As a result the potentially important drugs do not reach the market and are not achieving their full potential. Hence, with the advancement of chemical science, the need of development of pharmaceutical technologies is also increasing. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of many drugs belonging to BCS class II. Solid dispersion has been used over last 20 to 30 years and has been known to give fruitful result in improving the release rate and oral bioavailability of poorly water soluble drugs. Solid dispersion with different polymers and at different ratios is carried out and is known to show good release when compared to the drug alone and the physical mixture. Improvement in dissolution of drug was observed in all the solid dispersions as compared to pure drug.

Keywords: Solid dispersion, eutectic mixtures, isothermal titration calorimetry, kneading method**INTRODUCTION**

Oral route is the most preferred route of administration of the drug due to various reasons like its convenience, good patient acceptance and low medicine production costs¹. The solubility and permeability of the drug is a key determinant for its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge for developing suitable formulation for oral administration². Studies have shown that 40% of the new chemical entities are poorly soluble in water or insoluble in water and up to 50% of the orally administered drug compound suffer from formulation problem related to their low solubility and high lipophilicity. For a drug to be absorbed in the systemic circulation after the oral administration need to be dissolved in the gastric fluid¹. However, a poorly water soluble drug with poor solubility and low dissolution rate in the aqueous gastrointestinal fluid is a reason for its insufficient bioavailability. Solubility of such drugs can be improved by incorporating the drug in a hydrophilic carrier material obtaining a product called solid dispersion³.

In 1961, Sekiguchi and obi first proposed the utilization of solid dispersion in order to increase the dissolution and oral absorption of poorly water soluble drugs⁴. In 1971 Chiou and Riegelman defined Solid dispersion as "dispersion of one or more active ingredients in an inert

carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting solvent method"⁵. The solid dispersion may also be called solid state dispersion, as first used by Mayerson and Gibaldi⁶. Solid dispersion has been used as an effective method to improve the bioavailability and dissolution rate of poorly water soluble drugs⁷.

In the Biopharmaceutical Classification System the class II drugs show low aqueous solubility and high membrane permeability. Thus, Solid dispersion technologies give promising results for improving the oral absorption and bioavailability of the drugs belonging to BCS class II⁸. Though salt formation, particle size reduction, solubilization⁹, and complexation with cyclodextrin⁸ have been used to increase the dissolution rate and thereby the oral absorption and bioavailability of poorly water soluble drugs¹⁰. However these techniques have limitations. On the other hand, solid dispersion formulations offer various processing and excipients an option that allows more flexibility for formulating oral delivery system for poorly water soluble drugs⁸.

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The solubility and bioavailability of poorly water soluble drug can be improved by converting the drug into amorphous state¹¹. The mechanism by which the solid dispersion enhances the solubility and dissolution involves particle size reduction to fine molecular level, conversion of crystalline form to amorphous form and by enhancing wettability¹².

ADVANTAGE OF SOLID DISPERSION

i) Particles with reduced particle size

Molecular dispersion represents the last stage of particle size reduction, solid dispersion uses this principle where the drug is molecularly dispersed in the dissolution medium after the dissolution of the carrier⁸. As a result high surface area is formed and thus increased dissolution and consequently improved bioavailability of poorly water soluble drug¹³.

ii) Particles with improved wettability

Drug solubility enhancement is related to the drug wettability improvement¹³. The use of carriers without surface activity (eg. Urea) and with surface activity (eg. Cholic acid and bile salt) improved drug wettability. Moreover, carriers improve the drug dissolution profile by direct dissolution or co-solvent effect⁸.

iii) Particles with high porosity

The dissolution rate of the solid dispersion increases when carriers with high degree of porosity are used. For example solid dispersion containing linear polymer have larger and more porous particles and thus gives higher dissolution rate¹³.

vi)

iv) Particles in amorphous state

Drugs in amorphous state tend to have higher solubility than the drugs in crystalline state and it requires energy to break the crystal lattice. In solid dispersion the drug exists as supersaturated solution after system dissolution and it is considered when drug precipitate, it exists as a metastable polymorphic form with higher dissolution than the crystal form⁸.

DISADVANTAGE OF SOLID DISPERSION

The major disadvantage of solid dispersion is related to the instability¹³. During storage the effect of moisture on the stability of amorphous pharmaceuticals is of significant concern, as it increases the drug mobility and promotes drug crystallization. An obstacle in solid dispersion method in pharmaceutical development is the amount of carrier needed i.e. more than 50% to 80% is required to achieve desired dissolution. In addition the polymer used for solid dispersion also absorbs moisture which may result in phase separation, crystal growth or conversion to the crystalline form. Thus results in decreased solubility and dissolution rate¹⁴.

Limitations of Solid Dispersion

- i) The physical and chemical stability of drugs and vehicles,
- ii) Method of preparation,
- iii) Reproducibility of its physicochemical properties,¹⁴
- iv) Formulation of solid dispersion into dosage forms, and
- v) Scale-up of manufacturing processes¹³.

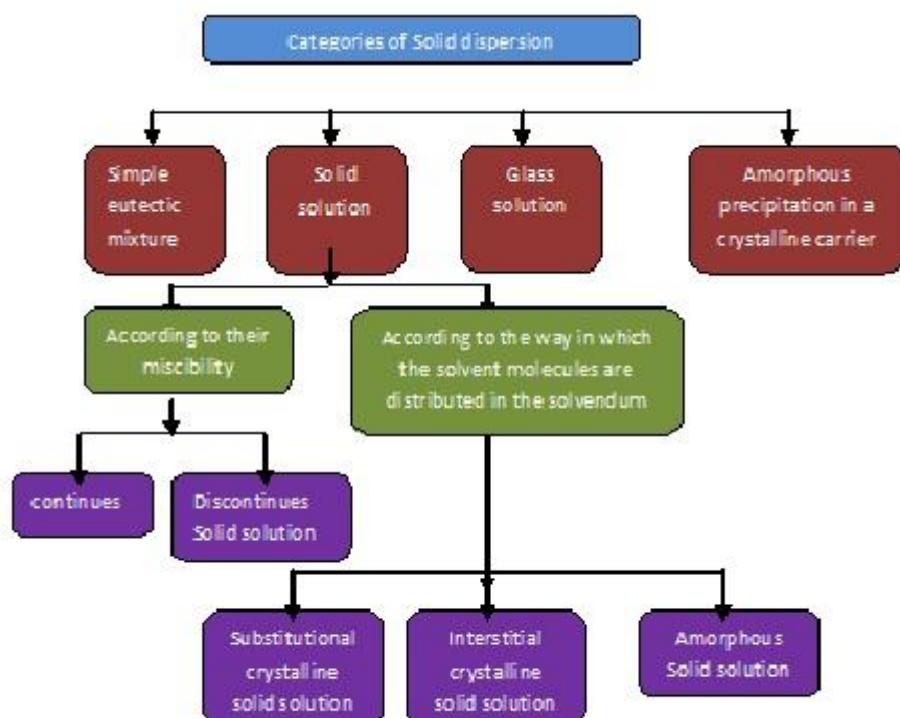


Figure 1: Categories of Solid Dispersion¹⁶

TYPES OF SOLID DISPERSION

a) **Eutectic mixtures:** It consists of two completely miscible compounds in liquid state. However it has very limited miscibility in solid state. It is prepared by rapid solidification of fused melt of two components which has complete liquid miscibility.

b) **Solid solution:** It consists of just one phase irrespective of the number of components. In solid solution the particle size of the drug has been reduced to absolute minimum and the dissolution rate is determined by the dissolution rate of the carrier.

c) **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.

d) **Amorphous precipitation in crystalline matrix:** This is similar to simple eutectic mixtures. However it differs from simple eutectic mixture by that the drug is precipitated out in amorphous form ¹⁵.

Table 1: Types of solid dispersion (Chiou and Riegelman Classification)¹⁷

S.No.	Solid dispersion type	Matrix	Drug	Observation	No. of Phases
1.	Eutectics	Crystalline state	Drug dispersed as crystalline particles in the matrix	The first type of solid dispersion prepared	2
2.	Amorphous precipitation in crystalline matrix	Crystalline state	A drug dispersed as amorphous clusters in the matrix	Rarely encountered	2
3.	Solid solution	-	-	-	-
	Continuous solid solution	Crystalline state	Drug molecularly dispersed throughout the matrix	Miscible at all composition, never prepared	1
	Discontinuous solid solution	Crystalline state	Drug molecularly dispersed throughout the matrix	Partially miscible, 2 phases even though drug is molecularly dispersed	2
	Substitutional solid solution	Crystalline state	Drug molecularly dispersed throughout the matrix	Molecular diameter of drug (solute) differ less than 15% from the matrix (solvent) diameter	1 or 2
	Interstitial solid solution	Crystalline state	Drug molecularly dispersed throughout the matrix	Drug molecular diameter less than 59% of matrix diameter. Usually limited miscibility, Discontinuous. Example: Drug in helical interstitial space of PEG	2
4.	Glass suspension	Amorphous state	A drug dispersed as amorphous clusters in the matrix	Particle size of dispersed phase dependent on cooling/ evaporation rate many solid dispersion are of this type	2
5.	Glass Solution	Amorphous state	Drug molecularly dispersed throughout the matrix	Requires miscibility/ solid solubility or complex formation on fast cooling or evaporation during preparation, many example especially with PVP	1

METHODS OF SOLID DISPERSION

- a) **Fusion method:** it is also known as melt method when the starting materials used are crystalline¹³. Sekiguchi et al. in 1961 were the first to use melting method which involved melting the drug within the carrier followed by cooling and pulverization of the obtained product¹⁷. Ex. Albendazole and urea solid dispersion was prepared by this method¹⁸. The main advantages of this method are its simplicity and economy. However it has few limitations like it is applied only when the drug and the matrix are compatible and when they mix well at the heating temperature. Phase separation may also occur during cooling, the drug matrix miscibility changes¹³.
- b) **Solvent Evaporation method:** the drug and the carrier are completely dissolved in an organic solvent, the solvent is evaporated. The obtained solid mass is ground, sieved and dried. Ex. Solid dispersion of ofloxacin with PEG by solvent evaporation method¹⁶.
- c) **Modified Solvent Evaporation method:** drug is dissolved in organic solvent at its saturation solubility with continuous stirring for some time. The polymer is suspended in sufficient amount of water. The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried¹⁶.
- d) **Melting Solvent method:** it is a combination of two methods which involves dissolving the drug in a suitable solvent and mixing it with molten carrier followed by cooling¹⁵. The solidified mass is crushed, pulverized and passed through sieve. The advantage of this method is it reduces maximum temperature and results in less decomposition of thermolabile drugs.
- e) **Kneading method:** A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved. Ex. furosemide and crospovidone solid dispersion was prepared by this method¹⁹.
- f) **Co-grinding:** the drug and carriers physical mixture is mixed in a blender at a particular speed. It is then charged into a chamber of vibration ball mill. The powder mixture is pulverized and collected at room temperature. Ex chlordiazepoxide and mannitol solid dispersion was prepared by this method¹⁸.
- g) **Co-precipitation method:** the carrier is dissolved in water and drug in organic solvent, then the aqueous solution of carried is poured into organic solution of drug. During the addition of non-solvent the drug and carrier are co-precipitated to form micro particles. The resultant micro particle suspension is filtered and dried (solid dispersion)²⁰.
- h) **Spray drying method:** here the solution of drug substance and carrier is evaporated by spraying the solution as fine droplets in chamber with maintained temperature, humidity and airflow. The principle involved is evaporation of the solvent from the mixture until the desired moisture content is obtained. It is advantageous for weight and volume

reduction¹⁵. Rankell et al. prepared solid dispersion of Loperamide with PEG 6000²¹.

- i) **Direct capsule filling:** filling of semisolid material in to and hard gelatin capsule as melt, this method was first described by Francois and Jones¹⁵. The molten dispersion forms a solid plug inside the capsule on cooling at room temperature. This method is advantageous as it reduces cross contamination, exposure in dust free environment, better filling and content uniformity can be obtained²⁰.
- j) **Lyophilization technique:** it has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion²¹.
- k) **Gel entrapment technique:** polymer like HPMC is dissolved in an organic solvent until clear and transparent gel is obtained. The drug is then added to the gel and sonicated for few minutes. The organic solvent is evaporated the solid dispersion obtained is reduced in size and sieved²².

CARRIERS FOR SOLID DISPERSION

Carriers play an important role in influencing the dissolution characteristic of dispersed drug. The carrier needs to meet the following requirement.

Freely soluble in water and with rapid dissolution property.

Soluble in wide variety of solvents

Chemically compatible with the drug

Heat stable with low melting point for melt method.²³

Non toxic and pharmacologically inert²⁴.

First generation carriers: Crystalline carriers: Urea, Sugars, and Organic acids. They have disadvantage of forming crystalline solid dispersion that is thermodynamically more stable and do not release the drug quickly²⁴.

Second generation carriers: Amorphous carriers: Polyethylene glycol, Povidone, Polyvinylacetate, Polymethacrylate, cellulose derivatives²⁵.

Third generation carriers: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, Gelucire 44/14. These carriers have been effective in originating high polymorphic purity and enhanced in vivo bioavailability²⁵.

CHARACTERIZATION OF SOLID DISPERSION

- a) **Physical characterization and saturation solubility**
An excess amount of the physical mixture and solid dispersion is taken in a conical flask and 10 ml of distilled water is added and shaken on rotator shaker for 48 hour at 37°C. Remove the flask and filter it. Suitable amount of aliquot is withdrawn from the filtered solution and the drug content was analyzed after appropriate dilution with distilled water and was compared with pure drug solubility²⁶.
- b) **Fourier Transform Infrared Spectroscopic Analysis**

The interaction between the drug and the carrier in solid dispersion is assessed by FTIR. In the solid dispersion preparation the peak band shows shift in the absorption spectrum for the drug molecule. However, Careful interpretation of the spectrum is required for some of the delicate changes²⁷.

c) Differential Scanning Calorimetry

The calibration of the DSC temperature and enthalpy scale was carried out using Indium/Zinc standards. The sample are taken in an aluminum pan and is hermetically sealed and heated at a constant rate of 20°C per minute over a temperature range of 20 to 150°C. The inert atmosphere was maintained by purging nitrogen gas at flow rate of 50ml/min²⁸.

d) Hyper Differential Scanning Calorimetry (Hyper DSC)

This method employs excess heating rate starting from 100 to 500° C/min. However, in DSC the heating rate ranges from about 1 to 20 ° C/min. Hyper differential scanning calorimetry have number of advantages, which involves its use to prevent recrystallisation during the heating step. Hyper DSC when compared to the standard DSC thermograms can also be used to enhance thermal signals it also have advantage of minimizing and preventing the changes in morphology and interaction during the heating process²⁹.

e) X Ray Powder Diffraction (XRPD)

To characterize the physical form of the drug in the sample X ray diffraction study is carried out. In this method the sample is spread on a glass slide with an

appropriate thickness of 0.5mm. The slide is then placed in X-ray diffractometer vertically at 0° angle so that the x-ray beams falls on it. The results were then recorded over an range of 0 to 90°C³⁰.

f) Scanning electron microscopy

In this method both the pure drug and the solid dispersion sample and mounted on the stub using double sided adhesive tape and coated with gold palladium alloy. The samples are then analyzed using scanning electron microscope for external morphology³¹.

g) In Vitro release Studies

The dissolution a study is carried out using accurately weighed amount of sample. The sample is withdrawn at predetermined time interval and same amount of aliquots is replaced by fresh dissolution medium. The drug release was then analyzed UV spectrophotometrically or HPLC³².

h) Isothermal titration calorimetry (ITC)

It is important method for understanding biological processes at molecular level. In this method a small change of heat during the reaction can be detected. This method is also useful in determining thermodynamic parameters like Gibbs free energy, enthalpy, entropy, binding constant, heat capacity and effective numbers of binding site in the biological reaction. This method has advantages like it is the only technique that can establish all binding site in the biological reaction. It also allows the measurement of heat signals²⁹.

Several Marketed and late stage drugs are designed for improved solubility by solid dispersion

Product/Substance	Dispersion Polymer or Carrier	Technology used	Company
Gris-PEG® (Griseofulvin)	Polyethylene glycol	Melt process; exact process unknown	Novartis
Sproramax capsules (Itraconazole)	Hydroxypropylmethylcellulose (HPMC)	Spray layering	Janseen pharmaceutica
Cesamet® (Nabilone)	Providone	process unknown	Lilly
Kaletra (lopinavir and ritonavir)	Polyvinylpyrrolidone (PVP)/polyvinyl acetate	Melt-extrusion	Abbott Laboratories
Torcetrapib^a	HPMC acetate succinate	Spray drying	Pfizer
Ibuprofen	Various	Melt-extrusion	Soliqs
Isoptin SRE-240 (Verapamil)	Various	Melt-extrusion	Soliqs
Rezulin^b (Troglitazone)	PVP	Melt-extrusion	Pfizer
LCP-Tacrol (Tracrolimus)	HPMC	Melt-granulation	Life Cycle Pharma
Intelence (Etravirine)	HPMC	Spray drying	Tibotec
Certican (Everolimus)	HPMC	Melt or Spray drying	Novartis
Afeditab (Nifedipine)	Poloxomer or PVP	Melt/absorb on carrier	Élan Corp.

a Halted in phase III; b Withdrawn from market.

CURRENT CHALLENGES AND FUTURE PROSPECTS

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailabilities of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use.

One limitation in the development of solid dispersion systems may be the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipophilic in nature, so potential roles of such

carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and *p*-glycoprotein-mediated drug efflux, will require careful consideration.

Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues so future research needs to be directed to address various stability issues. Although, as mentioned earlier, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports on the scale up of the technology. Further studies on scale up and validation of the process will be essential. Many problems and challenges still remain with solid dispersion systems. Nevertheless, as a result of recent breakthroughs, it will continue to be one of the exciting frontiers of drug development.

CONCLUSION

Due to the advantageous features of solid dispersions formulation scientists consider it as one of the most potential method of improving oral bioavailability. But changes in crystal behavior of drug and/or carrier particles during processing and storage limits the method to be commercially applicable. Manufacturing of solid dispersions requires a perfect combination of drug to carrier(s). Carrier molecules play the most important role in enhancing solubility of the resultant dispersion and hence improvement in oral bioavailability. Whatever this technology is also highly potential to formulate controlled release dosage forms as the carriers may enhance or delay drug release.

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