

REVIEW ARTICLE

CURRENT TRENDS IN SOLID DISPERSION: A REVIEW**Bhasin Nirika*, Nirmala, S.L Hari kumar**

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Corresponding author's Email - Nirika_b@yahoo.co.in*ABSTRACT**

Poor bioavailability of the highly lipophilic drugs is one major challenges being faced in pharmaceutical industry. Poor absorption of drug from the oral dosage form could be a result of low dissolution rate. Therefore many techniques have been introduced for solubility enhancement out of which Solid Dispersion has attracted considerable interest. Solid dispersion is defined as a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. It increases the dissolution rate of highly lipophilic drug which leads to increased solubility and hence bioavailability of the drug. There are various methods of preparation of solid dispersion like fusion method, solvent evaporation, solvent evaporation-deposition, solvent deposition, kneading method, lyophilization, supercritical fluid method. Basically this technique includes a drug with poor aqueous solubility and hydrophilic carrier. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. The present article discusses the basic concept about solid dispersion, various types of solid dispersion, criteria of solvent selection, the methods of preparation, characterization, their advantages, limitations and applications. Also this reviews about the current trends observed in solid dispersion in past few years and its future prospects.

Keywords- Solid dispersion, solubility, bioavailability, carriers, dissolution

INTRODUCTION

The most challenging task for research scientist is to formulate a successful drug product of a poorly soluble drug. This occurs mainly because of poor bioavailability. Improving oral bioavailability of the drugs which are given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems¹. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route². Poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. The rate limiting process for absorption of poorly soluble drugs from the solid dosage form could be a slow dissolution rate. Various factors affecting the drug absorption from gastrointestinal tract are poor aqueous solubility or poor membrane permeability. Therefore, slow dissolution rate can be overcome by adopting various solubility enhancement techniques such as such as use of surfactants, complexation, polymorphism, salt formation, size reduction and emulsification. Among various approaches applied for solubility and bioavailability enhancement of poorly water soluble drugs solid dispersion is one of the most successful method for increasing the drug dissolution rate of the drug.

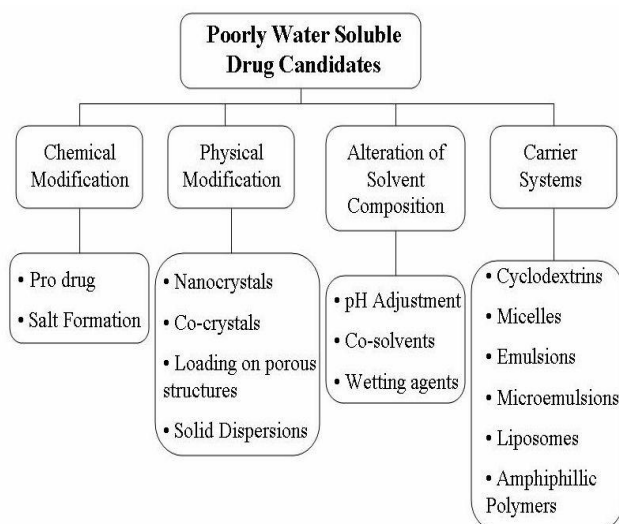
SOLUBLIZATION TECHNIQUES

Solubilization is a process of increasing apparent solubility of poor water soluble drugs. Such techniques mainly includes salt formation, prodrug design, complexation, particle size reduction, and the use of

surface active agents (Micellization), addition of a co-solvent and various other physicochemical techniques. The process of solubilization involves the breaking of intermolecular and or inters ionic bonds in solute, the molecules of solvent separates to provide space for solute which leads to interaction between solute and solvent. Solubility is an important physic chemical property of drug. Solubility behavior of drug forms an important aspect for preformulation studies as well.

Methods to enhance dissolution and absorption rate

1. Methods increasing solubility
 - Pro drug approach
 - Complexation
 - Use of solvates and hydrates
 - Use of salts of weak acids and weak bases
 - Buffering of pH environment
2. Methods increasing surface area
 - Micronization
 - Solid dispersion
 - Solvent deposition
 - Use of surfactants
 - Formulation of dispersible tablets



Solid dispersion improves the dissolution rate of the poorly water soluble drugs by reducing their particle size, improving wettability and forming amorphous particles.

DEFINITION OF SOLID DISPERSION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles¹. Molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which results improved dissolution rates. This technique is one of the oldest and most efficient method of enhancing the solubility and bioavailability of poorly water soluble drugs. Solid dispersion technology affects both specific surface area and solubility.

Sekiguchi and Obi first reported the increased rate and extent of absorption of Sulfathiazole by using solid dispersion technique. Nowadays solid dispersion has attracted considerable interest and has become choice of selection for solubility enhancement of poorly soluble drugs.

Ideal Candidate for Solid Dispersion

According to Biopharmaceutical classification system, Class 2 drugs which have low solubility and high

permeability are the optimum candidates for solid dispersion formulations. This will not only improve solubility of the drug but also enhance oral absorption of the drug.

ADVANTAGES OF SOLID DISPERSION

Various reasons why solid dispersion is chosen as method of solubility enhancement are as following:

➤ Reduction in particle size :

When a molecular dispersion is formed, the polymer/carrier dissolution takes place in a solvent which brings about formation of fine dispersion of drug in medium. This leads to high surface area resulting in increased dissolution rate and bioavailability.

➤ Improves wettability of particles:

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions¹. It is observed that carrier without any surface active leads to increased activity after formation of solid dispersion whereas the carriers with surface activity leads much more increase in dissolution rate after formulation of solid dispersion.

➤ Particles with higher porosity

There is increase in porosity of particles in solid dispersion which mainly depends upon polymer properties being used. Linear polymers produce more porosity than that of reticular polymers. Hence this leads to increase in drug release profile.

➤ Drugs in amorphous state

Drugs in amorphous state show higher solubility than crystalline state. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process³.

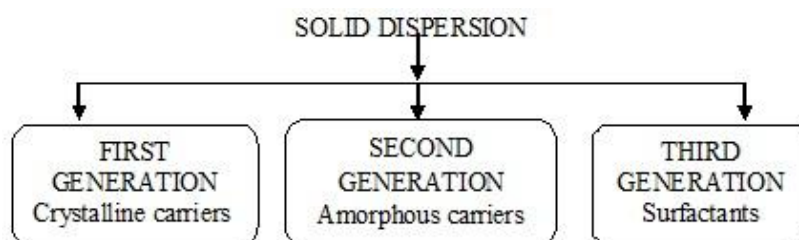
Disadvantages of solid dispersion

Various limitation of this technique is listed below:

- Stability of drug and vehicle
- Difficulty in introducing it into a dosage form
- Laborious and expensive method of preparation
- Reproducibility of physicochemical properties

CLASSIFICATION OF SOLID DISPERSION

According to the type of carrier, solid dispersion can be classified as following:



➤ FIRST GENERATION

First generation solid dispersion uses crystalline carriers in formulation of solid dispersion such as sugars and urea. Major disadvantage of crystalline carrier is that they form thermodynamically more stable form and prevent of the quick release of drug.

➤ SECOND GENERATION

Second generation solid dispersion uses amorphous carriers which are mainly polymers. Polymers maybe synthetic such as PVP and polyethylene glycols or natural based products such as HPMC or starch derivatives like cyclodextrin.

➤ THIRD GENERATION

Third generation solid dispersion utilizes carriers with surface activity. Therefore surfactants are being used such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407, Poloxamer 188.

SELECTION OF CARRIER

In formulation of solid dispersion of a drug, carrier is melted at high temperature and then drug is dispersed in it. The properties of a polymer highly affect the solid dispersion. Therefore, various characteristics which a polymer should possess are as following:

- Physiologically inert
- Readily soluble in water and gastrointestinal fluid
- Melting point should not be much higher than the drug
- Thermal stability at melting temperature
- Low vapor pressure
- Non toxic
- High molecular weight to fulfill the requirement

Various polymers which are generally used are PEG 4000, Polyvinyl pyrrolidone, HPMC, sugars, citric acid etc.

TYPES OF SOLID DISPERSION

1. Solid Solutions
2. Simple eutectic mixture
3. Glass solutions and suspensions
4. Amorphous precipitation in crystalline carriers

Solid Solutions

In a solid solution the two components crystallize together in a homogeneous one phase system³. As a result molecular size of the particle is reduced which leads to higher dissolution rate. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in the solid state in all proportions³.

Simple Eutectic mixture

Simple eutectic mixtures are prepared by solidifying the melting mixture of two components that show complete liquid miscibility. Thermodynamically, such system is an intimately blended physical mixture of its two crystalline components³.

Glass solutions and Suspensions

A glass solution is a homogeneous system in which a solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent³. Glassy state is brittle and transparent below glass transition temperature.

Amorphous precipitation in crystalline carriers

In this drug is precipitated out in amorphous forms as compared to eutectic mixture. Sulfathiazole was precipitated in the amorphous form in crystalline urea.

Table 1: Classification of carriers

CATEGORY	EXAMPLES
Sugar	Sucrose, lactose, mannitol, dextrose, sorbitol
Citric acid	Succinic acid, Succinic acids
Polymeric materials	Povidone Methylcellulose, HPMC Pectin
Surfactants	Polyoxyethylene stearate, Poloxamer 188 Tweens, Spans
Insoluble enteric polymers	Eudragit RS, Phthalate, HPMC
Miscellaneous	Urea, urethans, Hydroxyalkylxanthins

METHODS OF PREPARATION

There are various methods of preparation of solid dispersion which has been reported in literature. Preparation methods mainly include the mixing of a carrier with the drug at molecular level. During the preparation of solid dispersion formation of different phases and de-mixing is observed. Therefore it was observed that extent of phase separation can be prevented by Rapid cooling procedure. Phase separation can also be prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible⁴.

Various techniques for preparation of solid dispersion are as following:

1. Melting method
2. Solvent method
3. Solvent evaporation-deposition method
4. Solvent deposition
5. Supercritical fluid method
6. Kneading method
7. Lyophilization technique
8. Hot melt extrusion
9. Use of co-solvents
10. Melt solvent method

1. Melting Method

It is also known as Fusion Method. In this method carrier is selected on the basis of preliminary solubility studies. Firstly the carrier is melted in a china dish at 55° - 60° C and the drug is added into the melted carrier with constant stirring. After this the melted mixture is cooled rapidly and stored in desiccators for 24 hours. The solidified mass is crushed pulverized and sieved through mesh for the desired product.

Advantages:

- The main advantage of direct melting method is its simplicity and economy.
- In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier

Disadvantage:

- This method can be applied only when the drug and the carrier are compatible and they mix well at heating temperature.
- Degradation of drug and carrier can occur during heating process,
- Phase separation can occur. When drug is slowly cooled, crystalline form is obtained whereas rapid cooling yields amorphous solid dispersion.

2. Solvent Evaporation Method

The drug and carrier are selected in particular ratios and dissolved in common solvent with constant stirring. The solution is evaporated continuously under pressure to obtain dry mass. The dried mass is pulverized and passed through sieve and stored in desiccators. Two challenges are mainly faced during formulation by solvent evaporation method mainly:

- To dissolve both drug and carrier in same solvent despite of different polarity.
- To minimize drug particle size in solid dispersion, the drug and carrier has to be dispersed in solvent as fine as possible.

Advantages

- Thermal decomposition of the drugs can be prevented because of low temperature required for organic solvents to evaporate.

3. Solvent Evaporation- Deposition Method

The drug and carrier are weighed and transferred into a solvent system. After complete dissolution a water insoluble carrier or an adsorbent is added into the above solution. After the ternary system had been completely mixed, the solvent is evaporated in water bath at 80° C and solid dispersion obtained is crushed, pulverized and sieved and stored in desiccators.

4. Solvent Deposition

The drug is weighed and dissolved in a solvent system. After complete dissolution, an adsorbent is added into it. After complete mixing, the solvent is evaporated at 80°C. The deposits are dried, crushed and sieved to obtain solid dispersion formed.

5. Supercritical Fluid Method

In this method CO₂ is used as either solvent in which either drug or matrix is dissolved or either as anti solvent. When supercritical CO₂ is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This method does not require any organic solvent due to which it is considered as solvent-free method. However, the application of this technique is very limited, because the solubility in CO₂ of most pharmaceutical compounds is very low (<0.01wt-%) and decreases with increasing polarity².

6. Kneading Technique⁵

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.

7. Lyophilization Technique

In this technique the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion⁶.

Advantage

- The risk of phase separation is minimized as soon as solution is vitrified.

8. Hot Melt Extrusion Method⁶

Hot-stage extrusion (HME) consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer, which broadens the application of hot-stage extrusion to thermally labile compounds.

9. Use of Co-solvent

Co-solvency is defined as a process in which the solubility of the drug is increased by addition of water miscible solvents. The added solvents are called as co-solvents. The solubilization effect brought about is dependent on the polarity of drug, solvent and co-solvent. Examples of various co-solvents are propylene glycol, polyethylene glycol, ethanol etc. The co-solvents basically enhance the solubility in of the drug and reduce difference between polarity of the drug and water system thereby enhancing the solubility. The mechanism involved in solubility enhancement by co-solvency is reduction in interfacial tension between aqueous solution and hydrophobic solutes and reduces the contact angle between liquid and solid.

10. Melt-Solvent Method

In this method the drug is dissolved in liquid solvent. The solution so formed is incorporated into the melted polymer without removing liquid solvent.

CURRENT TRENDS OF SOLID DISPERSION IN PHARMACEUTICAL INDUSTRY

The development of solid dispersions of various poor water soluble drugs has proved to be an effective technique for solubility enhancement. Despite of various

advantages of this technique, many problems related to preparation, formulation, scale-up and stability has been encountered in commercial production of water insoluble drugs.

Following is the data regarding formulations of solid dispersion of various poor water soluble drugs along with its method of preparation and observations obtained:

Table 2: Data of solid dispersion of various drugs formed with different polymers and different techniques used in formulation

DRUG	SOLID DISPERSION METHOD	POLYMERS USED	RESULTS	Ref
Midazolam	Solvent evaporation Co-grinding method Fusion method	Hydroxypropyl- β -cyclodextrins Poloxamer-188 PEG-4000 PEG-3350+ poloxamer 407	Solid dispersion with poloxamer-188 in ratio 1:5 by co-grinding technique was successful in fast release of drug when compared to pure drug	7
Domperidone	Fusion method Solvent –melt Solvent evaporation	Sodium alginate	Enhanced aqueous solubility, dissolution rate and systemic bioavailability with sodium alginate and formulating solid dispersion of the drug.	8
Pioglitazone HCl	Solvent evaporation	PVP K30, HPMC PEG 6000 Eudragit epo Poloxamer 407	There was 100% drug release with PEG 6000 followed by 75% release with PVP K 30 AND 62% with Poloxamer 407	9
Glimepiride	Solvent evaporation	PVP K 30	Significant increase in solubility of the drug was observed	10
Clonazepam	Solvent evaporation	PEG6000 Poloxamer HPMA 6cps, HPC	Highest improvement in wettability & dissolution rate with PEG 6000.	11
Itraconazole	Hot-melt extrusion	Methocel TM A15, E3LV E15LV, E50LV E4M, K3LV K100LV, K4M grades of methyl cellulose	The technique was effectively utilized to prepare homogenous solid solutions of E50LV-drug characterized as having a single glass transition temperature over a wide range of drug loadings	12
Alprazolam	Solvent evaporation	PEG-6000 PVP K-30	The formulations containing drug and PEG-6000 and PVP-K30 at 1:1 revealed similar dissolution profile as compared to theoretical dissolution	13
Carbamazepine Spironolactone Atorvastatin Furosemide Fenofibrate Etoricoxib Ibuprofen, Glipizide	Solvent evaporation method	HPMC 6CPS PEG-6000	Atorvastatin, Furosemide Carbamazepine, Ibuprofen responded very well against PEG 6000.	14
Mefenamic acid	Solvent evaporation	PEG PVP K-30 HPMC	Dissolution of MA improved significantly in solid dispersion products containing drug: polymer ratio 2:2:10 (85% in 20 minutes).	15
Terbinafine Hydrochloride	Solvent evaporation Melting method	PVP K 30 PEG 6000	Solid dispersion showed improved dissolution rate than pure drug	16
Dihydroartemisinin (DHA)	Solvent evaporation Inclusion complexes	PVPK30, PVPK25, PVPK15) Hydroxypropyl β extrin	DHA solubility was enhanced 84-fold in DHA-HP β CD complexes and 50-times in DHA-PVPK30.	17
Ibuprofen	Melting method Physical mixtures	Poloxamer-188	Ibuprofen was completely released from the solid dispersion	18

CHARACTERIZATION OF SOLID DISPERSION

There are several techniques have been available to investigate the molecular arrangement in solid dispersions. Several different molecular structures of the drug in the matrix can be encountered in solid dispersions¹⁹. There are many techniques available which can detect the amount of crystallinity in dispersion.

1. Physical Structure

- Scanning electron microscopy
- Surface area analysis
- Surface properties
- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

2. Drug Carrier miscibility

- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- NMR 1H Spin lattice relaxation time

3. Drug-Carrier Interaction

- Fourier Transform Infrared Spectroscopy (FTIR)
- Raman Spectroscopy
- Solid State NMR

4. Stability

- Humidity studies
- Isothermal Calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

5. Dissolution enhancement

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

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectroscopy (IR) is used to detect the variation in the energy distribution of interactions between drug and matrix. Presence of sharp vibrational bands indicates crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) can be used to accurately detect crystallinity ranging from 1 to 99% in pure material. It can be carried out using KBr pellet.

Differential Scanning Colorimetry (DSC)

This technique is used to detect the amount of crystalline material. In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting

energy can be used to detect the amount of crystalline material¹⁹.

X-RAY Diffraction

The XRD is use to determine the material qualitatively and the pattern of pure drug exhibits sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The lack of sharp peaks in the diffractograms of solid dispersions indicates that the drug is in the amorphous form in the dispersions.

In-Vitro Dissolution Studies

In order to determine dissolution behavior of the drug , in-vitro dissolution studies are carried out. This study demonstrates 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 ultimately¹⁹. Dissolution studies are performed using USP dissolution apparatus, generally paddle apparatus in dissolution medium which may be, distilled water²⁸ or 0.1 N HCl with or without surfactant or Simulated Gastric Fluid pH1.2 or Phosphate buffer. Then dissolution rate is estimated²⁰.

Scanning Electron Microscopy (SEM)

This technique is used to determine the external morphology of the sample. SEM indicates crystallization processes and determines the size that with increase with an increasing drug content. The disappearance of large crystals of drug indicates decrease in crystallinity or conversion to amorphous form.

APPLICATIONS OF SOLID DISPERSION

There are numerous pharmaceutical applications of solid dispersions. The various applications are as following:

1. To reduce pre-systematic inactivation of drugs like morphine and progesterone.
2. In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion for inhalation is prepared. It can avoid many problems like use of local anesthesia and irritating solvents²¹.
3. Solid dispersion system accelerates the onset action of drugs which require immediate action like NSAIDS.
4. Dosage forms containing solid dispersions increases greater drug loading per dose and increases the stability of some drugs
5. Solid dispersion systems were shown to provide bio available oral dosage forms for anti-cancer drugs, which could be substituted for standard injections to improve patient comfort and compliance²¹.
6. A solid dispersion system improves absorption efficiency thereby reducing in the content of active

agent per dose, thus decreasing the cost associated with these drug therapies.

CONCLUSION

Solid dispersion is one of the latest and most effective techniques used for enhancement of solubility of poorly water soluble drug. Various Methods of preparations as

described above can be used for formulating the solid dispersion. Currently hydrophilic polymers are being used in formulation of solid dispersion to achieve the goal of solubility enhancement. Solid dispersion has a lot of future scope and novel applications in drug delivery system which will help in solving the solubility problems.

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