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Review Article

SOLID DISPERSION: STRATEGY TO ENHANCE SOLUBILITYCh. Greeshmika¹, P. Kavya¹, Shaik Sayeeda Sarah¹, B. Hemalatha¹, K. Padmalatha²¹Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for women, Vijayawada., ²Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for women, Vijayawada.**Article Received:** November 2020 **Accepted:** December 2020 **Published:** January 2021**Abstract:**

Solid dispersion is defined as 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. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The focus of this review article on advantages, disadvantages, types and the method of preparation and characterization of the solid dispersion and various types of marketed preparations.

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INTRODUCTION:

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example, parenteral (Dhirendra K *et al.*, 2009).

Although the oral route of administration is preferred, for 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 paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate 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 (Chiou WL and Riegelman S *et al.*, 1971).

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.

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption *in vivo* will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs (Amidon *et al.*, 1995). Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

With recent advances in molecular screening methods for identifying potential drug candidates, an increasing number of poorly water-soluble drugs are being identified as potential therapeutic agents. In fact, it has been estimated that 40% of new chemical entities currently being discovered are poorly water-soluble. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to solubility concerns. It is therefore becoming increasingly more important that methods for overcoming solubility limitations be identified and applied commercially such that the potential therapeutic benefits of these active molecules can be realized (Singh MC *et al.*, 2010).

Definition of solid dispersions:

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 particles (Verma S *et al.*, 2011).

Ideal candidates for solid dispersion (Nadia Saffoon *et al.*, 2011):

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption *in vivo* will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) Class II drugs are those with low aqueous solubility and high membrane permeability and therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances are classified in four groups as shown in Table 1.

Table No – 1: Biopharmaceutical Classification System (BCS)

Class	Permeability	Solubility
Class I	High	High
Class II	High	Low
Class III	Low	High
Class IV	Low	Low

Mechanism involved in enhanced drug solubilization by solid dispersion technique:

Although mechanism is not well understood yet, the basic principle includes complete removal of drug crystallinity and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. This increases surface area of dissolution rate and hence bioavailability of poorly water soluble drugs. Drug in soluble hydrophilic carrier improves the dissolution rate by reducing particle size and increasing the particle porosity. Remaining drug is in amorphous state and Improving wettability and hence possibility bioavailability for poorly water soluble drug. The potential advantage of this technique is enormous. Recently surfactants have been included for betterment of formulation as in many cases. Thermodynamic instability and recrystallisation of drug becomes a problem. Hence surfactants are used to avoid recrystallization and potentiating their solubility (Sakina Sultana *et al.*, 2016).

Rationale behind in using the technique in pharmaceutical industry:

The main reasons to use this technique in pharmaceuticals are

- To improve drug solubility
- To improve drug stability
- To mask the bitter taste of drug
- To obtain required release profile (Kumar S *et al.*, 2011).

Materials used as carrier for solid dispersions (Anupama Kalia *et al.*, 2011):

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drug, since the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, a water-soluble carrier results in a faster release of the drug from the matrix. A poorly soluble or insoluble carrier leads to slower release of a drug from the matrix.

If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from matrix. Various carriers used for preparation of solid dispersions are tabulated in Table 2.

Table No – 2: Materials used as carriers for solid dispersions

S. No.	Category	Carriers	Examples
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose	Rofecoxib from sorbitol and mannitol
2	Acids	Citric acid, succinic acid	Felodipine, rofecoxib
3	Polymeric materials	Polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), hydroxyl propyl methyl cellulose (HPMC), methyl cellulose, hydroxyl ethyl cellulose, cyclodextrin, hydroxyl propyl cellulose, pectin,	Temazepam, felodipine, etoricoxib, rofecoxib
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragit E 100, eudragit RL, eudragit RS, eudragit L 100	Indomethacin from eudragit E100
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, tweens, spans, deoxycholic acid	Felodipin and rofecoxib from poloxamer 188
6	Miscellaneous	Urea, urethane, Hydroxy alkyl xanthins, pentaerythritol	Rofecoxib from urea

Advantages of solid dispersion (Dhirendra K *et al.*, 2017):

a) Particles with reduced particle size:

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply

this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability (Arunachalam A *et al* 2010).

b) Particles with improved wettability:

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions (Karavas *et al.*, 2006). It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts when used, can significantly increase the wettability property of drug.

c) Particles with higher porosity:

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in

a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

d) Drugs in amorphous state:

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. 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 process (Sameer Singh *et al.*, 2011).

Disadvantages of solid dispersions (Dharna Allawadi *et al.*, 2013):

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.

TYPES OF SOLID DISPERSIONS (Dharna Allawadi *et al.*, 2013):

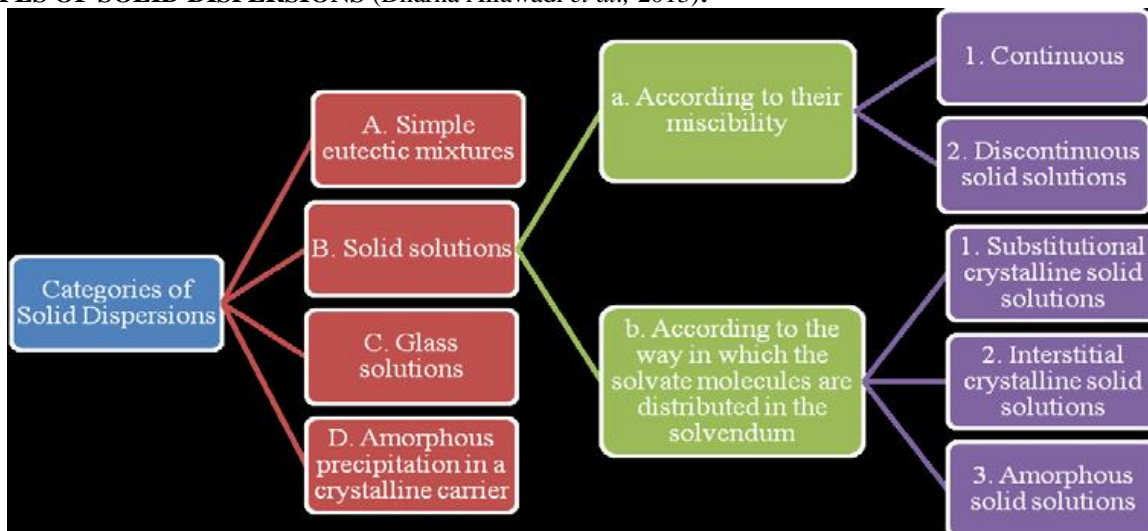


Figure No – 1: Types of solid dispersions

A. 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. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components (Dharna Allawadi *et al.*, 2013).

B. Amorphous precipitation in crystalline matrix:

This type of solid dispersion is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous form. In a simple eutectic mixture, the drug is precipitated out in a crystalline form.

C. 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).

i) 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 (Leuner C *et al.*, 2000).

ii) Discontinuous solid solutions:

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

iii) Interstitial solid solutions (Rahul M. Patil *et al.*, 2011):

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

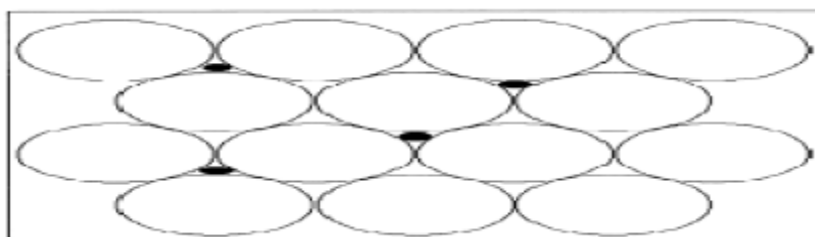


Figure No – 2: Interstitial crystalline solid solution

iv) Substitutional solid solutions (Rahul M. Patil *et al.*, 2011):

Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

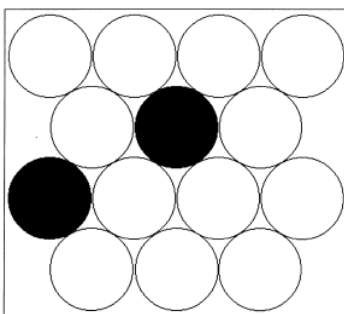


Figure No - 3: Substitutional crystalline solid solution

D. Glass Solutions and Suspensions (Xitiz dogra *et al.*, 2015):

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy carrier. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points. Instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions.

Table No - 3: Types of solid dispersions

S. No	Solid dispersion type	Matrix*	Drug**	Remarks	No of phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid Solutions				
	Continuous solid solution	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solution	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2
	Substitutional solid solution	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and the matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed	1 or 2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility discontinuous.	2
IV	Glass Suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling /evaporation rate. Many solid dispersions are of this type.	2
VI	Glass solution	A	M	Requires miscibility or solid solubility, complex formation or upon fast cooling or evaporation during preparation, many examples especially with PVP.	1

*A: matrix in the amorphous state, C: matrix in the crystalline state

**A: drug dispersed as amorphous clusters in the matrix.

C: drug dispersed as crystalline particles in the matrix

M: drug molecularly dispersed throughout the matrix

CLASSIFICATION OF SOLID DISPERSION ON THE BASIS OF DEVELOPMENT:

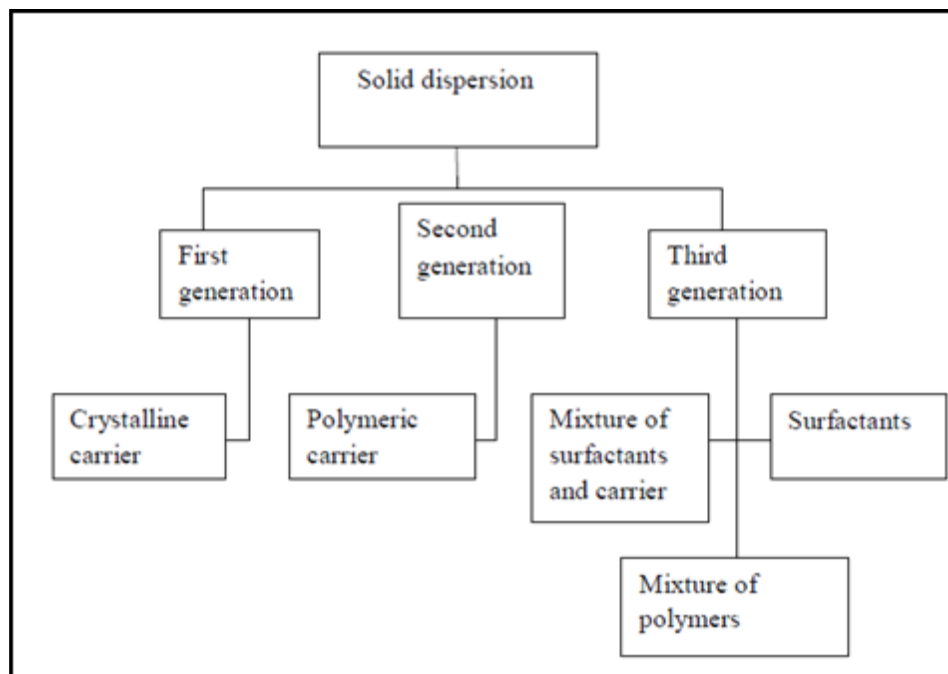


Figure No - 4: Classification of solid dispersion on the basis of development

A. First generation solid dispersions (Sakina Sultana *et al.*, 2016):

The solid dispersions, which could be designed as first generation solid dispersions were prepared using crystalline carriers. Crystalline carriers include urea and sugars, which were the first carriers to be employed in solid dispersions. These have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

B. Second generation solid dispersions (Xitiz Dogra *et al.*, 2015):

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers.

Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP) polyethyleneglycols (PEG) and poly-methacrylates. Natural product based polymers are

mainly composed by cellulose derivatives, such as hydroxyl propyl methyl cellulose (HPMC) ethylcellulose or hydroxypropylcellulose or starch derivatives, like cyclodextrins. Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both. In amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them. In these systems, the drug and carrier interaction energy is extremely high, resulting in a really true solution. The use of polymers in the preparation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved. This type of amorphous solid dispersion is homogeneous on a molecular level. Therefore, only one phase is present.

C. Third generation solid dispersion (Xitiz Dogra *et al.*, 2015):

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared.

These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug re-crystallization.

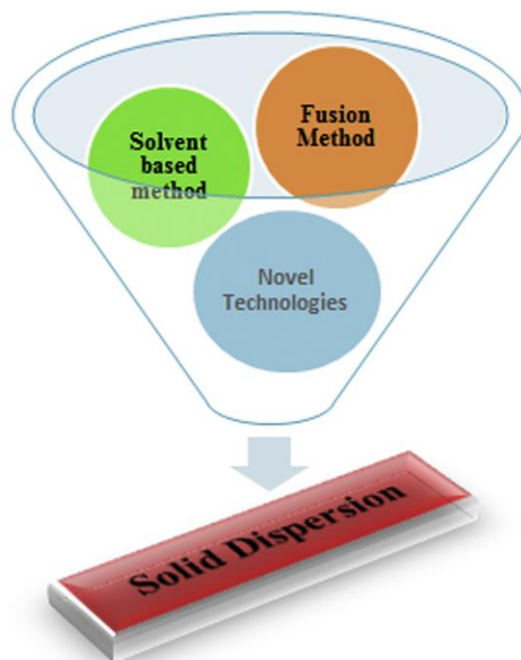
METHOD OF PREPARATION (Shrawan Baghel *et al.*, 2016):

Figure No - 5: Different manufacturing techniques of solid dispersions

A. Fusion Method:

The fusion method, also known as the melt method, was first proposed by Sekiguchi and Obi in 1961. A physical mixture of drug and polymer is heated to form a molten mixture which is then cooled and solidified with rigorous stirring. The resultant solid mass is then crushed, pulverized, and sieved to obtain the desired particle size. Although frequently used, there are a number of challenges in preparing solid dispersion using this method such as lack of drug-polymer miscibility at the heating temperature. The use of surfactants may avoid this problem. Furthermore, drugs and polymers have to be thermally stable at the melting temperature, and consequently, lower processing temperatures are preferred. Also, the fused mixture has to be stable against recrystallization and phase separation on aging over the shelf life of the products.

B. Hot-melt extrusion method:

Hot-melt extrusion method is the modern version of the fusion method in which intense mixing of the components is induced by the extruder. Compared with the traditional fusion method, melt extrusion offers the potential to shape the molten drug-polymer mixture into implants, pellets, or oral dosage forms. This method requires complete miscibility of the drug and polymer in the molten state. Solubility parameter phase diagrams can be used to predict miscibility and to rationally select the compatible polymer.

This technique offers several advantages such as

- (1) solvent free method;
- (2) fewer processing steps as there is no compression of ingredients and no need to dry products which makes this technique simple, continuous, and efficient; and
- (3) thorough mixing at high shear rate and temperature causes the particles to deaggregate and creates a uniform distribution of fine drug particles in the polymer matrix and molecular level dispersion.

Furthermore, compared with the traditional fusion method, this technique offers the possibility of continuous manufacture, which makes it suitable for large-scale production. Some examples of commonly used polymeric materials which are used in hot-melt extrusion include HPMC, HPMCAS, PVP, PVP vinyl acetate, and polyethylene oxide.

C. Co-precipitation method (co-evaporates) (Anupama kalia *et al.*, 2011):

Accurately weighed carrier is dissolved in water and drug is dissolved in organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried.

D. Solvent Method:

The solvent method involves the preparation of a solution of both drug and polymer in a single solvent followed by removal of the solvent to yield a solid dispersion. This technique enables molecular level mixing which is preferred to increase the solubility and stability of the product.

The main advantage of this method is that the thermal decomposition of drug and polymer can be prevented as low temperatures are typically required to evaporate organic solvents. However, formulation scientists face two challenges when using this approach. The first challenge is to mix the drug and the polymer in one solvent which can be difficult if they have significant polarity differences. Sometimes surfactants are used to improve drug or polymer solubility in particular solvents. However, their amount in final dosage form is often significant which reduces the drug loading capacity and may also cause problems if they are not well tolerated in the body. Also, the need to evaporate a large amount of the solvent makes the process expensive. The second challenge is the phase separation which may occur during removal of the solvent. Vacuum drying is frequently used to dry the solution. Sometimes fast drying is achieved by a rotary evaporator. Higher drying temperatures are preferred which reduces the time available for phase separation. However, the high molecular mobility of drugs and polymers at elevated temperatures may accelerate phase separation.

E. Spray drying:

Spray drying has emerged as a popular processing technology for developing solid dispersions of drugs. It is used to convert a solution or suspension into a dry powder in a single step. This technique provides a better control of process variables, producing powders with desired size, shape, density, flow properties, and crystalline forms. Evaporation of solvent occurs at a very fast rate in spray drying, causing a sudden rise in viscosity which leads to the entrapment of drug molecules in the polymer matrix. Drugs with poor aqueous solubility may be spray dried into very small particles provided that they are soluble in certain solvents suitable for spray drying. The nature of the solid particles formed also depends upon chemical properties of the drug, and spray drying may produce amorphous material, crystalline forms, imperfect crystals, or metastable crystals. Indeed, Mahlin *et al.*, and Baird *et al.*, have worked on the different drug compounds and showed that generating an amorphous form depends on the chemical nature of the drugs rather than on the process variables. However, the stability of the amorphous form depends on the process variables.

Spray drying offers great control of the powder characteristics and due to cheaper manufacturing costs, ease of scale-up, and continuous batch manufacture, it has become the most popular solvent-based production method.

F. Super Critical Fluid Method:

Super critical fluids possess the properties of both liquid and gas. Under supercritical conditions, materials have liquid-like solvent properties and gas like viscosity, diffusivity, and thermal conductivity. Although the solvent properties are beneficial for drug/polymer solubilization, the gas like properties significantly enhance the mass transport characteristics of the fluids. This method is mostly applied using supercritical carbon dioxide (CO₂) either as a solvent for drug and polymer or as an antisolvent. The polymer and drug are dissolved in supercritical CO₂ and sprayed through a nozzle into low-pressure region causing adiabatic expansion of the CO₂ and rapid cooling. Thus, this technique allows the production of drug particles with a greatly reduced particle size. This technique is known as rapid expansion of supercritical solution (RESS). Current SCF methods have demonstrated the potential to create nanoparticulate suspensions of particles with 5-2000 nm diameters. Because this technique is not dependent on the use of organic solvents and the small amount of the residual CO₂ trapped inside the polymer poses no danger to patients, this technique is referred to as environment friendly. Furthermore, the ability of CO₂ to plasticize and swell polymers can also be exploited. However, the low solubility of most pharmaceutical compounds in CO₂ limits the practical application of this approach. Several methods of SCF processing have been developed to address individual aspects of these shortcomings and to improve the solubility. These methods include precipitation with a compressed antisolvent, solution-enhanced dispersion by SCF, supercritical antisolvent processes, gas antisolvent recrystallization, and aerosol supercritical extraction system.

G. Kneading method (Anupama Kalia *et al.*, 2011):

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.

H. Electrospinning method (Anupama Kalia *et al.*, 2011):

The electrospinning technology used in the polymer industry combines solid dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential

between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give an on woven fabric, or they can be collected on a spinning mandrel. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest technique. This technique can be utilized for the preparation of solid dispersions in future.

I. Direct capsule filling (Anupama Kalia *et al.*, 2011):

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.

J. Lyophilization technique (Dharna Allawadi *et al.*, 2013):

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

K. Co-precipitation method (Dharna Allawadi *et al.*, 2013):

Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear

solution. 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. 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.

L. Melt agglomeration method (Dharna Allawadi *et al.*, 2013):

Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excipients. It is prepared by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carriers. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor. 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 (Sethia S and Squillante *et al.*, 2003).

CHARACTERIZATION OF SOLID DISPERSIONS:

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, much effort has been put to differentiate amorphous and crystalline material (Anupama Kalia *et al.*, 2011). For that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of amorphous material can never be measured directly but can be derived from the amount of crystalline material in the sample. It should be noted that through the assessment of crystallinity as the method to determine the amount of amorphous drug, it becomes difficult to reveal whether the drug is present as

amorphous drug particles or as molecularly dispersed molecules. Table No. 4 summarizes various methods

used to characterize solid dispersions along with their significance.

Table No - 4: Various characterization methods to assess solid dispersion

S. No	Characterization	Methods	Significance
1.	Drug-carrier miscibility	Hot stage microscopy (HSM) Differential scanning calorimeter(DSC) X-ray Diffraction(XRD) Nuclear magnetic resonance (NMR)	To find out the complex formation between drug and carrier. To check the degree of amorphization.
2.	Drug-carrier interactions	Fourier transform infrared spectroscopy Raman spectroscopy Solid state NMR studies	To find out the solid state interaction between drug and carrier and formation of inclusion complex.
3.	Surface properties	Dynamic vapour sorption Inverse gas chromatography Atomic force microscopy Raman microscopy	To study the morphology and degree of crystallinity.
4.	Stability	Humidity studies Isothermal calorimeter DSC Dynamic vapour sorption Saturated solubility studies	To find out the degree of recrystallization.
5.	Amorphous content	Polarized light optical microscopy Hot stage microscopy DSC Powder XRD	To find out the amorphous transition.
6.	Dissolution rate	Dissolution studies Intrinsic dissolution Dynamic solubility studies	To find out the rate and extent of drug release.

A. 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.

B. 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, recrystallization, melting or degradation. Furthermore, the melting and recrystallization energy

can be quantified. The melting energy can be used to detect the amount of crystalline material.

C. X-RAY Diffraction (Bhasin Nirika *et al.*, 2014):

The XRD is used 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.

D. In-vitro Dissolution Studies:

In order to determine dissolution behaviour 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 ultimately.

E. 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.

MARKETED PRODUCTS (Dharna Allawadi *et al.*, 2013):

Table No – 5: Marketed products

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

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. Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization (Dharna Allawadi *et al.*, 2013). Various issues that impeded the commercial development of solid dispersions include

- Inability to scale bench top formulations to manufacturing- sized batches,
- Difficulty to control physicochemical properties,
- Difficulty in delivering solid dispersion formulations as tablet or capsule dosage forms, and
- Physical and chemical instability of the drug and/or the formulation (Dharna Allawadi *et al.*, 2013).

CONCLUSION:

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling.

Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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