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Review Article

SOLID DISPERSIONS: AN APPROACH TOWARDS ENHANCING DISSOLUTION RATE

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ABSTRACT

A success of formulation depends on how efficiently it makes the drug available at the site of action. Among all the newly discovered chemical entities, about 40-45% drugs fail to reach market due to their poor water solubility. Because of solubility problem, bioavailability of drugs gets affected and hence solubility enhancement becomes necessary. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of drugs. This article reviews the various preparation techniques, carriers used, advantages and limitations of solid dispersions and compiles some of the recent advances. The experience with solid dispersions over the last 10-15 years indicates that this is a very fruitful approach in improving the release rate and oral bioavailability of poorly water soluble drugs. Hence, this approach is expected to form a basis for the commercialization of many poorly water-soluble and water-insoluble drugs in their solid-dispersion formulations in the near future.

Keywords: Solid dispersion, Poorly soluble drug, Solubility, Bioavailability.

INTRODUCTION

In Pharmaceutical companies major work is going on in the field of drug discovery, in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas. Among the five key physicochemical properties in the early compound screening including pKa, solubility, permeability, stability and lipophilicity, poor solubility tops the list of undesirable compound properties[1]. Compounds with insufficient solubility carry a higher risk of failure during discovery and development, since insufficient solubility may compromise other properties of compound and add undesirable properties, can influence both pharmacokinetic and pharmacodynamic properties of the compound and finally may affect the bioavailability of the compound. Therefore, there is need of a new approach for enhancing solubility of drug. Although most of the drugs have encouraging experimental data obtained *in vitro*, the *in vivo* results have been disappointing.

The attributes may include:

- Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration
- Drug distribution to other tissues with high drug toxicities (anticancer drugs)
- Poor solubility of drugs, and
- Fluctuations in plasma levels owing to unpredictable bioavailability

The simplest and easiest way of administering the drug is oral drug delivery system[2, 3]. Because of the greater stability, smaller bulk, accurate dosage and easy production; solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract[4]. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. Model list of Essential Medicines of the World Health Organization (WHO) has assigned BCS (Biopharmaceutics Classification System) classification on the basis of data available in the public domain. Out of 130 orally administered drugs on the WHO list, 61 could be classified with certainty.

84% of these drugs belong to class I (highly soluble, highly permeable)

17% to class II (poorly soluble, highly permeable)

39% to class III (highly soluble, poorly permeable) and

10% to class IV (poorly soluble, poorly permeable)

The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility[5, 6]. Thus, a greater understanding of dissolution and absorption behaviour of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Table 1: Various methods to increase the solubility of drugs

Physical Modification									
a.	Particle size reduction	b.	Modification of the crystal habit	c.	Drug dispersion in carriers	d.	Complexation	e.	Solubilisation by surfactants
1	Micronization	1.	Polymorphs	1.	Eutectic mixtures	1.	Use of complexing agents	1	Microemulsions
2	Nanosuspension	2.	Pseudo Polymorphs	•	Hot plate method	•	Inorganic Coordination	2	Self microemulsifying drug delivery systems
•	Homogenization			•	Solvent evaporation method	•	Chelates		
•	Wet milling			•	Hot-melt extrusion	•	Metal-olefin		
3	Sonocrystallization			•	Melting-solvent method	•	Inclusion		
4	Supercritical fluid process					•	Molecular complexes		
5	Spray drying								
Chemical Modification									
a.	Soluble prodrugs	b.	Salt formation						
Other Techniques									
a.	Co-crystallisation	b.	Cosolvency	c.	Hydrotrophy	d.	Solubilizing agents	e.	Nanotechnology approaches

Although various method as shown in Table 1, have been commonly used to increase dissolution rate of the drug, there are few practical limitation with these techniques i.e., the desired bioavailability enhancement may not always be achieved[7,8]. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance dissolution of such drugs is to formulate solid dispersions.

Solid dispersion systems can increase dissolution rate and bioavailability of water insoluble drugs as when these are exposed to aqueous media, the carrier dissolves, and the drug is released as very fine colloidal particles. This greatly reduces particle size and increases surface area, which results in improved dissolution rates and per oral absorption. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers[9,10].

This approach has been used for a variety of poorly soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, carbamazepine, celecoxib and albendazole. Various hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), gums, sugar, mannitol, urea, hydroxypropylmethyl cellulose phthalate, gelucires, eudragits and chitosan have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[11].

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[12]. Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. drug–polymer miscibility and stability) and pharmacokinetic (e.g. rate of absorption) constraints[13]. Fig. 1 categorizes various possible categories of solid dispersions. The solid-dispersion components consist mainly of active pharmaceutical ingredients (API), the polymer, plasticizers, stabilizers, and other agents.

Chiou and Riegelman defined the term solid dispersion as[14]:

"A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"

In solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, Solubilization, cosolvency, and particle size reduction[14]. Based on their molecular arrangement, six different types of solid dispersions can be distinguished as described in Table 2. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

Table 2: Types of solid dispersion (Chiou and Riegelman classification) [14]

S. No	Solid dispersion type	Matrix	Drug	Observation	No. of phases
I	Eutectics	Crystalline state	Drug dispersed as crystalline particles in the matrix	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	Crystalline state	A drug dispersed as amorphous clusters in the matrix	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	Crystalline state	Drug molecularly dispersed throughout the matrix	Miscible at all composition, never prepared	1
	Discontinuous solid solutions	Crystalline state	Drug molecularly dispersed throughout the matrix	Partially miscible, 2 phases even though drug is molecularly dispersed	2
	Substitutional solid solutions	Crystalline state	Drug molecularly dispersed throughout the matrix	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter	1 or 2
	Interstitial solid solutions	Crystalline state	Drug molecularly dispersed throughout the matrix	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, Discontinuous. Example: Drug in helical interstitial spaces of PEG	2
IV	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 dispersions are of this type	2
V	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 examples especially with PVP	1

Materials used as carrier for solid dispersions

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[15, 16, 17]. Various carriers used for preparation of solid dispersions are tabulated in Table 3.

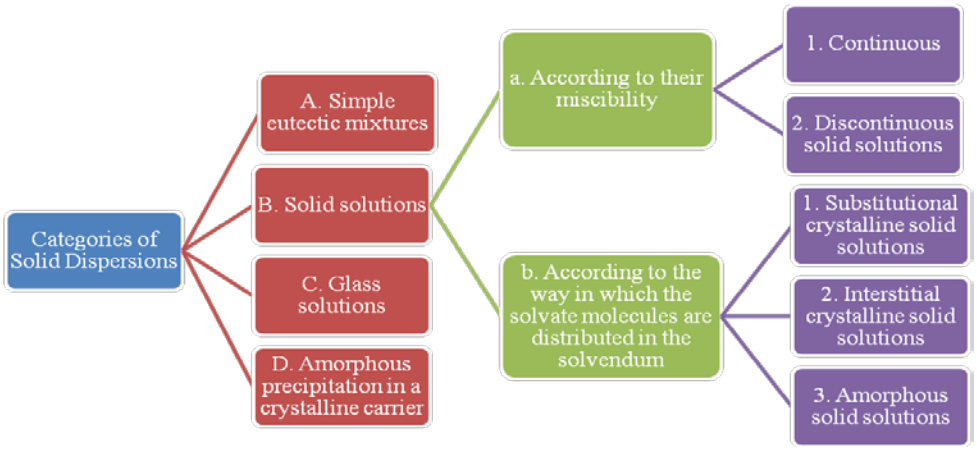

Fig. 1: Categories of solid dispersion

Table 3: Materials used as carrier for solid dispersion

S. No	Category	Carriers	Example
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose	Rofecoxib from sorbitol and mannitol
2	Acids	Citric acid, succinic acid	Felodipine, rofecoxib from citric acid
3	Polymeric materials	Polyvinyl pyrrolidone(PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan	Temazepam , felodipine, etoricoxib rofecoxib from PEG 4000 & 6000 and troglitazone and rofecoxib from PVP K30
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100, eudragit RL, eudragit RS	Indomethacin from eudragit E100
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans	Felodipin and rofecoxib from poloxamer 188
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins	Rofecoxib from urea

Advantages of solid dispersion

The major advantage of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition[18] and results in rapid dissolution rates thereby improving the bioavailability of drug. Along with this, the approach may also offer others advantages which includes[19]:

Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (e.g. PEG) as a solid dispersion to increase its aqueous solubility and dissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water[20].

As a formulation vehicle

Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain[18].

Particles with reduced particle size

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, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability[12].

Particles with improved wettability

Enhancement of drug solubility is related to the drug wettability. 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, significantly increase the wettability of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects[12].

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, results in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release rate[12].

Drugs in amorphous state

The enhancement of drug release can usually be achieved if the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that if drugs precipitate it is as a metastable polymorphic form with higher solubility than the most stable crystal form[12].

Disadvantages of Solid Dispersion

Disadvantages of solid dispersions are mainly related to their instability. Basically changes occur in several systems in crystallinity and a decrease in dissolution rate with ageing and system may be destabilized through physical treatment such as pulverization and aging. There is more deteriorating effect of moisture and temperature on solid dispersions than on physical mixtures[21].

Usually solid dispersions are prepared with water soluble low melting point synthetic polymers such as polyvinyl pyrrolidone, mannitol or polyethylene glycol. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/ polymer) ratio.

An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of carrier, i.e., more than 50% to 80% w/w, is required to achieve the desired dissolution.

Solid dispersion is a high energy metastable form. Phase separation, crystal growth or conversion from the amorphous to the crystalline form during storage decrease solubility and dissolution rate and result in variable oral bioavailability.

Applications of Solid Dispersion

Solid dispersion systems can provide numerous additional benefits; some of them are as follows

1. In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion (e.g. Cyclosporine A) for inhalation is prepared. It can avoid many problems like use of local anaesthesia and irritating solvents[22].
2. Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS) where immediacy of action is crucial in relieving acute pain and inflammation.
3. 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 compliance.
4. Solid dispersion systems were also found to reduce food effect on drug absorption, thus increasing the convenience of drug therapy as the need for some drugs to be taken with food was eliminated.
5. Solid dispersion- based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation which thereby improved the convenience of drug therapy by reducing the dosing regime and eliminating the need for refrigerated storage.
6. Improved absorption efficiency demonstrated for solid dispersion systems allows for a reduction in the content of active agent per dose, thus decreasing the cost associated with these drug therapies.
7. It also act as a functional carriers that offer the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption.

These benefits demonstrate the current contributions and future potential of solid dispersion systems toward improving drug therapies for a variety of important medical conditions whose treatment involves poorly water soluble drugs[23].

Methods of Preparation of Solid Dispersions

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. Various preparative methods are shown in Fig. 2.

The brief description of the methods is as follows:

Solvent evaporation method

After complete dissolution of drug and carrier in organic solvent, the solvent is evaporated. The solid mass is ground, sieved and dried. Okonogi et al., prepared solid dispersions of ofloxacin with polyethylene glycol by solvent evaporation method[24].

Modified solvent evaporation method

Drug is dissolved in organic solvent at its saturation solubility with continuous stirring for some time. Polymer is suspended in sufficient amount of water (up to wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried[25].

Melting /Fusion method

This method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or 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[26]. Advantage of melting method is that it is economic and solventless process, however this method is not suitable for the drug or carrier which is unstable at fusion temperature or evaporates at higher temperature. Some of the means to overcome these problems could be by 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. E.g. Albendazole and urea solid dispersions were prepared by this method[27].

Solvent melting method

Accurately weighed drug is dissolved in organic solvent. The solution is incorporated into the melt of mannitol and cooled suddenly and mass is kept in desiccator for complete drying. The solidified mass is crushed, pulverized and passed through sieve [28]. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose (less than 50 mg).

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. Chaulang et al., prepared furosemide and crospovidone solid dispersions by this method[29].

Co-Grinding method

Accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill. A certain number of steel balls are added. The powder mixture is ground. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Nokhodchi prepared chlordiazepoxide and mannitol solid dispersion by this method[30].

Co-precipitation method (co-evaporates)

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[31].

Spray drying method

Accurately weighed amount of drug with lipid carrier are dissolved in methanol to obtain a clear solution. This solution is then spray dried using a laboratory scale dryer. The sample is stored over silica gel in a vacuum desiccator[32].

Gel entrapment technique

Carrier which have tendency to swell is dissolved in suitable organic solvent to form a clear and transparent gel. The drug is then dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved[33].

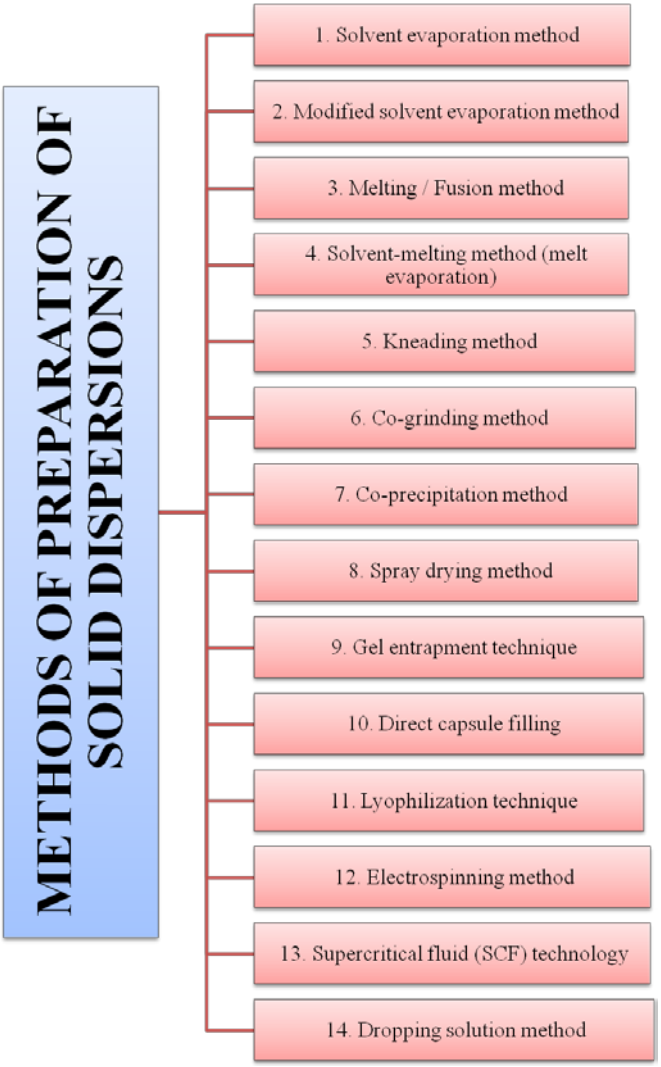

Fig. 2: Method of preparation of solid dispersions

Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug [34]. 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[35].

Lyophilization technique

Lyophilization 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 dispersion[36].

Electrospinning method

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 [37]. 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[38].

Supercritical fluid (SCF) technology

Supercritical CO_2 antisolvent induces the precipitation about 100-fold faster than the liquid antisolvent, not allowing enough time for the drug and the polymer domains to separate out. Thus, supercritical CO_2 precipitation can provide a more dispersed solid mixture. Supercritical CO_2-based precipitation is superior to the liquid based precipitation or the milling process[39]. Moneghini et al., demonstrated a solid dispersion of carbamazepine in polyethyleneglycol (PEG)-4000, produced by CO_2 method, increased the rate and the extent of dissolution of carbamazepine[40]. In this method, a solution of carbamazepine and PEG4000 in acetone was loaded in a pressure vessel, in which supercritical CO_2 was added from the bottom to obtain solvent-free particles.

Conventional methods i.e. spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance[41]. In supercritical fluid antisolvent techniques, CO_2 is used as an antisolvent 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 (ASES), precipitation with a compressed fluid antisolvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS)[42].

Dropping solution method

The dropping method facilitate the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, 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. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.

The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate[43]. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermostable drugs can be used and the physical instability of solid dispersions is a further challenge[44].

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. 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[45]. Table 4 summarizes various methods used to characterize solid dispersions along with their significance.

Table 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 (FTIR) 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 (Tg, temperature recrystallisation) Dynamic vapour sorption Saturated solubility studies	To find out the degree of recrystallization.
5	Amorphous content	Polarized light optical microscopy Hot stage microscopy Humidity stage microscopy DSC (MTDSC) 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.

Mechanisms behind Improved Dissolution

The formulations of solid dispersions results into reduction in particle size, improved wettability and enhancement of the dispersibility of the drug, thereby markedly improving the dissolution rate[46]. The suggested mechanism behind this tremendous increase in dissolution rate may include:

- Partial transformation of crystalline drug to the amorphous state or altering the crystalline morphology
- Formation of solid solution
- Formation of complexes
- Intimate mixing of the drug with hydrophilic excipients
- Reduction of aggregation and agglomeration
- Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer

Review of Solid Dispersion Technology

Till now much research has been done to formulate solid dispersions and fruitful results are obtained. Table 5 summarizes few research findings in the field of solid dispersion along with their results.

Commercial Solid Dispersion Products

In spite of almost several years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far.[13, 62, 63] Amongst these few are mentioned in Table 6.

Table 5: Reseach findings on solid dispersion technology

S. No	Drug used	Polymer and method used	Consequence
1	Griseofulvin	Griseofulvin solid dispersions were prepared using polyethylene glycol 6000 (PEG), talc, and their combination as carriers by the solvent evaporation method[47].	Dispersions of PEG and PEG/talc provided dissolution rates faster than those from dispersions of talc.
2	Nifedipine	The drug to carrier ratios of 1:1 and 1:9 were used for preparing both solid dispersion and physical mixtures by solvent evaporation method.[48]	The dissolution rate of nifedipine was successfully achieved by surface solid dispersion technique.
3	Carbamazepine	Solid dispersions of carbamazepine (CBZ) were formulated by supercritical fluid processing (SCP) and conventional solvent evaporation in polyethylene glycol (PEG) 8000 with either Gelucire 44/14 or vitamin E TPGS NF (d-α-tocopheryl PEG 1000 succinate)[49].	Polymorphic change of CBZ during SCP led to faster dissolution. Therefore, SCP provides advantages over solid dispersions prepared by conventional processes.
4	Albendazole	Solid dispersions were prepared using three different carriers, mixing ratios and methods in an attempt to improve the solubility and dissolution rate of albendazole (ABZ). Carrier includes urea, polyethylene glycol 6000 (PEG) and poloxamer 407 (PXR)[50].	The result showed that PXR system showed the highest dissolution rate with respect to pure drug for all mixing ratios and methods of preparation. However, all carriers showed equivalent efficiency in size reduction of dispersed drug particles. The mixing ratio and method of preparation significantly influenced particle size reduction.
5	Nimodipine	Solid dispersions of the drug nimodipine using polyethylene glycol as carrier were prepared following the hot-melt method. Micro-Raman spectroscopy in conjunction with X-ray powder diffractometry (XRPD) was used for the characterization of the solid structure, including spatial distribution, physical state, and presence of polymorphs, as well as storage stability of nimodipine in its solid formulations[51].	Micro-Raman spectroscopy and XRPD were used to study the effect of storage time on the stability of the drug, and the observed results were in qualitative agreement. Storage period was considerably increased enough for the transformation in the crystalline structure of the drug to occur.
6	Ofloxacin (OFX)	Solid dispersions of a water-insoluble ofloxacin (OFX) with polyethylene glycol (PEG) of different molecular weights, namely binary solid dispersion systems, were prepared at drug to carrier not less than 5:5. Polysorbate 80, a non-ionic surfactant, was incorporated into the binary solid dispersion systems as the third component to obtain the ternary solid dispersion systems. The prepared dispersions were characterized using powder x-ray diffraction and differential scanning calorimetric studies[52].	The result indicated that amorphous OFX existed in the solid dispersions with high drug loading and remarkably improved dissolution of drug from the ternary solid dispersion systems when compared with the binary solid dispersion systems. This might be because of polysorbate80, which improved wettability and solubilized the non–molecularly dispersed or crystalline fraction of OFX.
7	Valdecoxib	Solid dispersions of valdecoxib with mannitol, polyethylene glycol 4000, and polyvinyl pyrrolidone K-12, were prepared to overcome problem of its very low solubility in biological fluids and poor bioavailability after oral administration[53].	The dissolution of valdecoxib has improved considerably from PVP K-12 solid dispersions as compared to mannitol, and PEG-4000 solid dispersions.
8	Chlordiazepoxide	Solid dispersions of chlordiazepoxide were prepared by using three carriers PVP, mannitol and eudragit E by solvent evaporation method[54].	This study showed that addition of PVP to chlordiazepoxide improved its dissolution rates. It also showed that cogrinding technique yield solid dispersions with a less improved dissolution rate than did the solvent deposition/evaporation technique. Results from FT-IR spectroscopy concluded that there was no well-defined interaction between chlordiazepoxide and PVP, mannitol or eudragit E100.
9	Zaleplon	Zaleplon solid dispersion were prepared with poloxamer F68, polyvinylpyrrolidone K30 (PVP K30), and polyethyleneglycol 6000 (PEG 6000) each in 1:1, 1:3 and 1:5 ratios to enhance the dissolution rate using solid dispersion technique with various hydrophilic polymers[55].	The study showed that the dissolution rate of zaleplon can be enhanced to a great extent by solid dispersion technique using solvent evaporation method.
10	Prednisone	Prednisone dispersions were prepared using polyethylene glycol (PEG) 6000 as a carrier at low and high concentration[56].	The results showed a significantly higher prednisone dissolution (80% within 30 minutes) than did conventional tablets prepared without PEG 6000 (<25% within 30 minutes). In addition,

			good disintegration and very good dissolution rate of prednisone without the addition of superdisintegrant were observed.
11	Gliclazide	The solubility and dissolution rate of gliclazide was enhanced by formulating solid dispersions of gliclazide with PVP K90[57].	The solubilization effect of PVP K90, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous form of drug, increased wettability, dispersibility, and development of intermolecular hydrogen bonding were responsible for the enhanced solubility and dissolution rate of gliclazide from its solid dispersion and to some extent in physical mixtures.
12	Meloxicam (MLX)	Solid dispersion were prepared using a hydrophilic polymer, poloxamer 188 (PXM) by kneading technique[58].	The results of the experimental study confirmed that the factors polymer ratio (X_1), and the kneading time (X_2) significantly influences the dependent variables dissolution efficiency at 60 min (%DE60) and yield percent.
13.	Lamotrigine (LMN)	Binary systems of LMN and Hydroxy propyl β-cyclodextrin (HP β-CD) were prepared in different molar ratios (1:1, 1:2, 1:3 and 1:4) by kneading method. The binary systems were characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and powder X-ray diffraction analysis (PXRD)[59].	In kneaded products the entire drug was entrapped inside the HP β-CD cavity and reduction in drug crystallinity also took place, which may be responsible for improved dissolution characteristics as compared to that of the pure drug.
14.	Diazepam	Fast dissolving tablets of diazepam were prepared by wet granulation and direct compression methods using solid dispersion of drug[60].	Solid dispersions of diazepam and PEG-6000 (1:2.5, 1:5 and 1:10) were prepared by using the mentioned methods and it was concluded that it can be used in emergency treatment of anxiety disorder and seizures.
15.	Paracetamol	Solid dispersions of paracetamol were prepared by melting the accurately weighed amounts of carriers (PEG 4000, PEG 6000 and urea) in a water bath and the drug was dispersed in the molten solution using fusion method.[61]	Among Physical mixtures(PM) and solid dispersion(SD) (1:5) the carrier PEG 6000 containing PM and SD showed highest saturation solubility. This may be due to the inherent differences between the carriers in terms of hydration, dissolution and possible complexation of drug with different carriers.

Table 6: Commercially marketed solid dispersions

S. No	Commercial products	Polymer used	Manufacturer Company
1	Gris-PEG® (Griseofulvin)	Polyvinylpyrrolidone (PVP)	VIP Pharma
2	Intelence® (Etravirine)	Hypromellose, and microcrystalline cellulose	Tibotec, Yardley, PA
3	Cesamet® (Nabilone)	Polyvinylpyrrolidone (PVP)	Valeant Pharmaceuticals, Costa Mesa, CA
4	Sporanox® (Itraconazole)	Hydroxypropylmethyl cellulose (HPMC)	Janssen Pharmaceutica, Titusville, NJ
5	lopinavir and ritonavir	Polyvinylpyrrolidone–vinyl acetate copolymer	Abbott Laboratories, Abbott Park, IL

Recent Advances & Future Aspects

Solid dispersion has great potential both for increasing the bioavailability of drug and developing controlled release preparations. Thus, to solve bioavailability issues with respect to poorly water-soluble drugs, solid dispersion technology has grown rapidly[64]. The dosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. There are some major research areas where focus must be given in context to solid dispersion which includes:

Identification of new surface-active carriers and self-emulsifying carriers

A major focus of future research will be identification of new surface-active carriers and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing.

Two new surface active carriers was proposed for enhancement of bioavailability

1. Gelucire 44/14: It is mixture of glycerol & PEG-1500 esters of long chain fatty acid (lauryl monoglycerides). (m.pt - 44°C while HLB value is 14).
2. Vitamin E TPGS NF (D-α-tocopheryl PEG 1000 succinate)

Identification of vehicles

Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention should also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their p-glycoprotein-mediated drug efflux, require careful consideration[65].

Bioavailability enhancement

Solid dispersions have shown promising future for both increasing the bioavailability of drugs and for developing controlled-release preparations. Few successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points[65].

Extended-release dosage forms

To extend the release rate dosage form has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other[66].

Promising Research Approaches

Thermal production methods for the production of solid dispersions without the use of plasticizer

The production of solid dispersions by thermal manufacturing methods frequently require the addition of a plasticizer in order to achieve requisite molten material flow properties when processed by unit operations such as hot melt extrusion. KinetiSol® Dispersing, a rapid high energy thermal manufacturing process, was investigated for the ability to produce amorphous solid dispersions without the aid of a plasticizer.

For this study, itraconazole was used as a model active ingredient, while Eudragit® L100-55 and Carbomer 974P were used as model solid dispersion carriers. Triethyl citrate (TEC) was used as necessary as a model plasticizer. These results demonstrated that KinetiSol® Dispersing could be used for the production of amorphous solid dispersions without the aid of a plasticizer and illustrated the enhanced solid state stability that can be achieved by producing solid dispersions with higher glass transition temperatures[67].

Nanodiamond-mediated delivery for several water-insoluble drugs

Nanodiamond cluster-mediated interactions with several therapeutics to enhance their suspension in water with preserved functionality, thereby enabling novel treatment paradigms. The researchers showed that the water-insoluble compounds interact with the nanodiamonds, a biocompatible material, and formed complexes capable of dispersing the drug in water for sustained periods of time while maintaining the functionality of the drug. Nanodiamond surfaces are functionalized with carboxyl groups to enhance their dispersibility in water. Benefits in drug delivery from the nanodiamond cluster include the capability of trapping more drugs in the nanodiamond cluster compared with conventional drug-delivery methods and facile dissolution of the nanodiamonds in water. Previous studies showed that the surface electrostatic properties of nanodiamonds can promote potent water binding, thereby further enhancing material dispersibility in water.

The researchers reported that nanodiamonds were used to enhance the water dispersion of three anticancer agents:

These therapeutics include[68, 69, 70]

- Purvalanol A, a highly promising compound for hepatocarcinoma (liver cancer) treatment,
- 4-hydroxytamoxifen (4-OHT), an emerging drug for the treatment of breast cancer,
- Dexamethasone, a clinically relevant anti-inflammatory that has addressed an entire spectrum of diseases that span complications from blood and brain cancers to rheumatic and renal disorders.

Given the scalability of nanodiamond processing and functionalization, this novel approach serves as a facile, broadly impacting and significant route to translate water-insoluble compounds toward treatment-relevant scenarios. An application of the solid dispersion method in the controlled release of an extremely high water-soluble drug (oxprenolol hydrochloride, OXP) by polymer blending technique was investigated. Here water-insoluble ethylcellulose (EC) and water soluble hydroxypropylcellulose (HPC) were used as polymer carriers[71].

An appropriate combination of polysorbate 80 & PEG acts as good self-emulsifying system. More recently, solid dispersion explored with insoluble carrier material and in the formulation of sustained release products. A sustained release dosage form of nifedepine was prepared by forming solid dispersion with anionic polymers like HPMC phthalate, methacrylic acid methyl ester co-polymers. It was found to be amorphous in nature and practically insoluble in gastric fluid (pH 1.2) but rapidly dissolves in intestinal fluid (pH 6.8). These dispersions were stable for 6 months under accelerated condition. Similar results for digoxin & dipyridamole were obtained, but additionally its chemical stability in acidic condition increases. Thus solid dispersion has shown great potential and bright future both for increasing the bioavailability of drug and developing controlled release preparations.

CONCLUSION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of drugs, which can subsequently affect the in vivo absorption of drug. Because of solubility problem of many drugs the bioavailability of these gets affected and hence solubility enhancement becomes necessary. Solid dispersions are one of the most attractive processes to improve drug's poor water solubility. Various solubility enhancers like water-soluble carriers, co solvents, surfactants and superdisintegrants via solid dispersion approach (fusion method and solvent evaporation method) aids in solubility enhancement. These significantly help to improve the bioavailability and bioequivalence.

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