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Research Article

SOLID DISPERSION: AN EVER GREEN METHOD FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Most of the new chemical entities (NCE) near about 40% are poorly water soluble drugs. The solubility behaviour of the drugs remain one of the most challenging aspects in formulation development and it is key determinant to its oral bioavailability and it is the rate limiting step to absorption of drugs from gastrointestinal tract. This results in important products not reaching the market or not achieving their full potential. Solid dispersion has attracted considerable interest as an efficient means of improving the dissolution rate and bioavailability of hydrophobic drugs. This article reviews the mechanism, ideal candidates, classification, manufacturing process, selection of carriers, characterization and limitations of solid dispersion have been discussed.

INTRODUCTION

Most of the new chemical entities (NCE) under development now-a-days are intended to be used as a solid dosage form that originates an effective and reproducible *in vivo* plasma concentration after oral administration due to many advantageous features of this rout like, greater stability, smaller bulk, accurate dosage and easy production[1]. But the fact is most NCEs are poorly water soluble drugs, not well-absorbed after oral administration and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality[2]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water-soluble[3]. To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including Micronization, Nanonisation, Supercritical fluid Recrystalisation, Spray Freezing into Liquid (SFL), Evaporative Precipitation into Aqueous Solution (EPAS), Use of Surfactants, Use of Salt forms, Use of Pecipitation Inhibitors Alternation of PH of Drug Microinvirment, Use of Amorphose, Anhydrates, Solvets and Metastable Polymorphs, Solvent Deposition, Precipitation, Selective Adsorption on Insoluble Carriers, Solid Solution, Eutectic Mixture, Solid Dispersion and Molecular encapsulation with Cyclodextrins[4].However ahead of all, solid dispersion is the most promising method to the scientists due to the ease of preparation, ease of optimization and reproducibility of the manufacturing method[5].

Solid Dispersion -Chiou and Riegelman defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers bymelting of their physical mixtures”[6].The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi *et.al.* Suggested that the drug was present in a eutectic mixture in a microcrystalline state[7], after few years Goldberg *et.al.* reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high. The commercial use of such

systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. The term solid dispersion refers to a group of solid products consisting of at least two different components, generallya hydrophilic matrix and a hydrophobic drug. The matrix can be either crystallineor amorphous. The drug can be dispersed molecularly, in amorphous particles(clusters) or in crystalline particles. Solid dispersion refers to the dispersion of oneor more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohnand Gibaldi[8].

MECHANISM OF ENHANCED DISSOLUTION IN SOLID DISPERSION

The increase in dissolution rate for solid dispersion can be attributed to a number of factor. These include the following

Reduced Particle size or Reduced Agglomeration

Both are related to increase in the exposed surface area of the drug.Size reduction has been considerd to be result of eutectic or solid solution formation. It has also been suggested that the presentation of particles to the dissolution medium as physically seprate entities may reduce aggregation. Many of the carriers used for solid dispersion may have some wetting properties hence it can be suggested that improved watting may lead to reduce agglomeration and increase surface area[9].

Increased solubility or Dissolution rate of the drug

Many of the carriers used may increase the solubility of the drug. There appeare to be two seats of observation with regard to show carrier controlled relese as the rate of relese is controlled by the carrier and is independent of drug properties. Secondly some system show relese behavior that is dependent on the properties of the drug rather the polymer[10].

Transferring the drug from crystalline to amorphous state/Formation of high Energy State:

Amorphous drugs repressant the higher enrgy state and can be considerd as cooled liquids. They have grater aqueous solubility than crystalline forms because the energy required to trancfer a molecule from crystal is greater than required for non crystalline (amorphous) solid. For example the amorphous state of novobiocin is ten time more soluble than crystalline form[11].

Wetting

When a strong affinity exists between a liquid and solid the liquid forms a film over the surface of the solid. When this affinity is nonexistent or weak the liquid has difficulty dispensing the air and there exist an angle of contact between the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions. Those acting at the interfaces between the liquid and vapour phase, at the solid and liquid phase, and at the solid and vapour phases[12].

IDEAL CANDIDATES FOR SOLID DISPERSION

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[13]. In the Biopharmaceutical Classification System (BCS) Class II drugs are those with low aqueous solubility and high membrane permeability[14] and therefore, solid dispersion technologies are particularly promising for improving the oral absorption andbioavailability of BCS Class II drugs. According to the BCS, drug substances are classified in four groups as shown in Table 1[15]. Table 2 represents some BCS Class II drugs on the WHOmodel list of Essential Medicines. The table is adopted fromLindenberg et al., 2004, only for the BCS Class II drugs[16].

Table 1: Biopharmaceutical Classification System (BCS)

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

Table 2: Some BCS class II drugs on the WHO model list of Essential Medicines. Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs with reliable solubility and permeability

Drug	Used as
Carbamazepin	Antiepileptic
Dapsone	Antirheumatic/leprosy
Griseofulvin	Antifungal
Ibuprofen	Pain relief
Nifedipine*	Ca-channel blocker
Nitrofurantoin	Antibacteria
Phenytoin	Antiepileptic
Sulfamethoxazole	Antibiotic
Trimethoprim	Antibiotic
Valproic acid	Antiepileptic

Table 3: Some BCS class II drugs on the WHO model list of Essential Medicines. Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs for which complete solubility and/or permeability data are lacking

Drug	Used as
Iopanoic acid	Contrast medium
Nalidixic acid	Antibacterial agent
Nevirapine	Antiviral
Praziquantel *	Antihelmentic
Rifampicin*	Antituberculotic

Table 4: Some BCS class II drugs on the WHO model list of Essential Medicines. Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: drugs with inconclusive data

Drug	Used as
Albendazole*#	Antiparasitic
Amitriptyline*¶	Antidepressive
Artemether + Lumefantrine*#	Antimalarial agents
Chlorpromazine*#	Antidepressive
Ciprofloxacin*#	Antibiotic
Clofazimine#	Antibacterial agent
Diloxanide**#	Antiprotozoal agent
Efavirenz#	Antiviral
Folic acid#	Vitamin
Glibenclamide#	Antidiabetic
Haloperidol*#	Neuroleptic
Ivermectin#	Anthelmentic
Lopinavir*#	Antiviral
Mebendazole#	Antihelmentic
Mefloquine#	Antimalarial
Niclosamide#	Anthelmentic
Pyrantel#	Anthelmentic
Pyrimethamine#	Toxoplasmose
Retinol*#	Vitamin
Spironolactone*#	Diuretic
Sulfadiazine#	Antibacterial agent
Sulfasalazine#	Colitis ulcerosa/morbus crohn
Triclabendazole#	Anthelmentic
Verapamil hydrochloride*¶	Ca-channel blocker
Warfarin Sodium¶	Anticoagulant

(* First pass effect; ** Degradation in the GI-Tract; ¶also considered as Class I drug; # also considered as Class IV drug.)

CLASSIFICATION OF SOLID DISPERSION

Solid dispersions are classified by various ways viz. on the basis of carrier used and on the basis of their solid state structure.

1. On the basis of carrier used

First generation

First generation solid dispersions were prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and did not releasethe drug as quickly as amorphous ones.

Second generation

Second generation solid dispersions includeamorphous carriers instead of crystalline carrierswhich are usually polymers. These polymersinclude synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylatesas well as natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethylcellulose, and hydroxypropoylcellulose or starch derivates like cyclodextrins. Different kinds of polymers used in second generation solid dispersions are

1) Fully synthetic polymers – polyvinylpyrrolidone (povidone), polyethylene glycols, polymethacrylates.
2) Natural product based polymers (cellulose derivatives, starch derivatives) – hydroxypropyl-methylcellulose, Ethylcellulose, Hydroxypropylcellulose cyclodextrines.

Third generation

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. The use of surfactant such as inulin, inutec SP1,compritol 888 ATO, gelucire 44/14 and poloxamer407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability[17].

2. On the basis of solid state structure

Drug and polymer exhibiting immiscibility in fluid state

If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixtures and any enhancement in dissolution performance may beowing to modification in morphology of drug and/or polymer due to physical transformation (i.e., solid to liquid state and back), intimate drug–polymer mixing, and/or enhanced surface area. Formation of crystalline or amorphous solid dispersions can be biased by the rate of solidification of mixture and the rate of crystallization of drug and/or polymer.

Drug and polymer exhibiting miscibility in fluid state

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, there by influencing the structure of solid dispersion[18].

Eutectic Mixtures

Eutectic mixture was first described as solid dispersions in 1961 by Sekiguchi & Obi. Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug (A) and a carrier(B) are co-melted at their eutectic composition defined by point ‘e’, as shown schematically in Figure 1, the melting point of the mixture is lower than the melting point of either drug or carrier alone. At the eutectic composition (e), both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug. This was first reported for sulfathiazole-urea[19, 20]. Other examples of eutectic mixture include acetominophen-urea[21] and the dispersion of griseofulvin and tolbutamide in polyethyleneglycol (PEG)-2000[22].

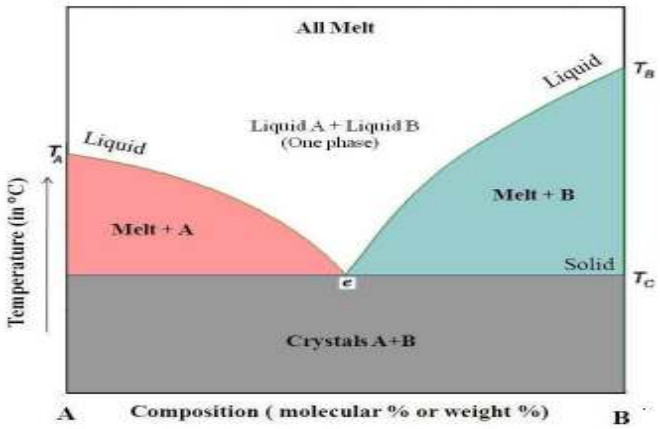


Fig. 1: Phase diagram of a eutectic mixture

Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies.

Amorphous Solid Dispersion

If the drug–polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a "solidified-liquid" state. These types of dispersions have the risk of potential for conversion to a more stable and less soluble crystalline form [18].

Solid Solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. These solid solutions may be either of amorphous or crystalline type. In amorphous solid solutions as the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Amorphous solid solutions have improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility[23]. Crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. Poorly soluble drugs have been incorporated in carrier molecules using crystal inclusion and crystal doping techniques[24], although the usage of such technologies has not yet gained wide spread application in pharmaceutical product development. According to extent of miscibility of the two components, solid solutions are continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are immiscible at intermediate composition, but miscible at extremes of composition are referred to as discontinuous solid solutions. According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional and interstitial. In the substitutional solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice as shown in Figure 2. In this case, the molecular size of the two components should not differ by more than 15%. An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice. For this to occur, the solute molecule diameter should be less than 0.59 than that of solvent molecule[25]. Therefore, the volume of the solute molecule(s) should be less than 20% of the solvent molecule(s). Examples include solid solutions of digitoxin, methyltestosterone, predinsolone acetate and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit faster rate of dissolution

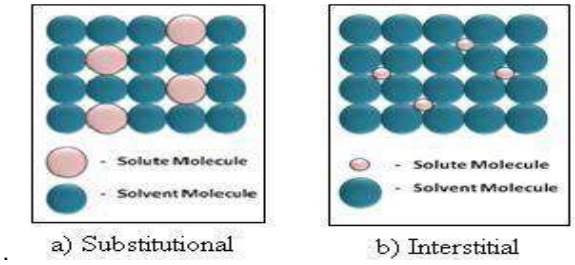
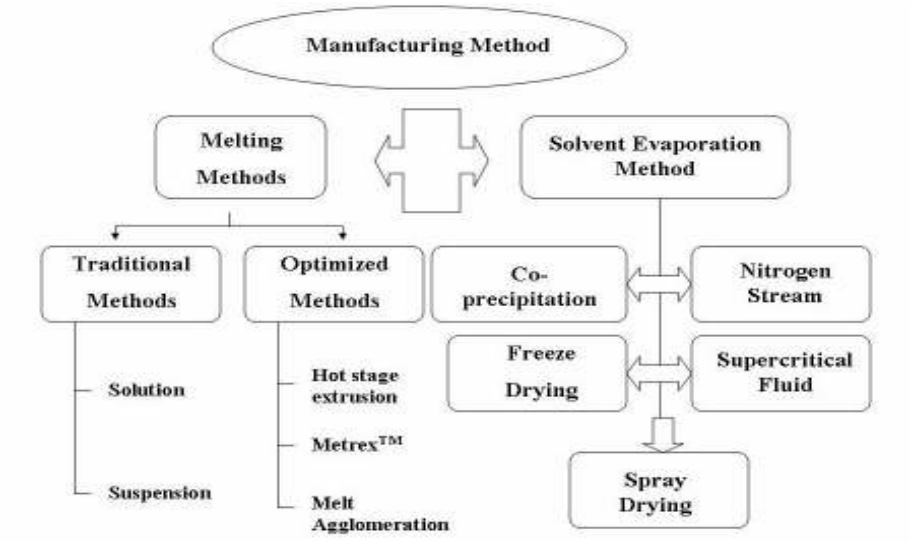


Fig. 2: Schematic representation of substitutional and interstitial solid solutions

Goldberg et al., 1965 discussed the theoretical and practical advantageous of solid solution over eutectic mixtures. The reason for the improvement in dissolution rate is that drug has no crystal structure in solid solution. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolved is not a limitation to the release of the drug from a solid solution. A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug. Even carriers that are not surface active, e.g. urea and citric acid, can improve wetting characteristics. If carriers with surface activity such as cholic acid, bile salts, lecithine, are used the improvement in wetting can be much greater.

MANUFACTURING PROCESSES FOR PREPARATION OFSOLID DISPERSIONS

There are two major methods of preparing solid dispersions; melting method and solvent evaporation method. Fusion method is synonymous to melt method[26].



Melting method

Melting method was first used to prepare simple eutectic mixtures by Sekiguchi and Obi. Leuner and Dress man used to describe melting method as hot melt method. This method consists of melting the drug within the carrier followed by cooling and pulverization of the obtained product. The process has got some limitations like, use of high temperature and chance of degradation of drug during melting, incomplete miscibility between drug and carrier. To avoid these limitations several modifications were introduced to the original process; i.e. hot stage extrusion, Meltrex®, melt agglomeration, injection molding, hot-spin-melting. Though hot melt extrusion was a common processing method in polymer industry it was first adapted for the pharmaceutical purposes.

Solvent evaporation methods

Solvent evaporation method is a simple way to produce solid dispersions where the drug and carrier is solubilized in a volatile solvent. The solvent is later evaporated. Tachibani and Nakumara (1965) were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. The method was then taken up by Mayersohn and Gibaldi (1966). With the discovery of the solvent method, many of the problems associated with the melting method were solved and for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions[27].

SELECTION OF CARRIER(S)

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier ought to meet the following prerequisites for being suitable for increasing the dissolution rate of a drug[28]. It should be

- Freely water soluble with rapid dissolution Properties
- Nontoxic and pharmacologically inert

- Heat stable with a low melting point for the melt method
- Soluble in a variety of solvents
- Preferably enhancing the aqueous solubility of the drug
- Chemically compatible with the drug
- Forming only weakly bounded complex with the drug. The various carries for solid dispersion are enlisted in **Table 5**(29).

Table 5: Carriers used in the preparation of solid dispersion

Chemical class	Examples
Acids	Citric acid, Tartaric acid, Succnic acid
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymer material	Polyvinyl pyrolidone, PEG 4000, PEG 6000, Sodium alginate, Carboxy methylcellulose, Guar gum, Xanthan gum, Methyl cellulose
Surfactant	Polyoxyethylene stearate, Polaxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamin E TPGS NF
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxylakyl xanthenes.

PLAUSIBLE FACTORS INFLUENCING DRUGRELEASE

Nature of carriers

Drug release from solid dispersion is dependent upon the nature of carrier, whether hydrophilic or hydrophobic. Thus, incorporation of poorly water soluble drug into inert and slightly water soluble carrier leads to retardation of drug release from matrix. However, incorporation of poorly water-soluble drug into water-soluble carrier(s) leads to acceleration of drug release.

Drug carrier ratio

The dissolution rate of a drug increases with increase in the proportion of drug carrier. However, this is true only up to a certain limit beyond which the dissolution rate decreases. As much as 38-fold increase in dissolution rate of piroxicam was reported when used as solid dispersion using drug: PVP in the ratio of 1:4. With further increase in PVP concentration, the dissolution rate decreased, attributable to the leaching of carrier during dissolution. This leached out carrier could form a concentrated layer of solution around the drug particle, resulting in lowering of release rate[43]. Accordingly, for the solid dispersion to be effective in enhancing the solubility, an appropriate drug-carrier proportion is desired. It would certainly be more advantageous if carrier is used in minimal amounts. Co-precipitates of flurbiprofen; phospholipids, for instance, when used in the ratio of 20:1, yields 9-fold greater dissolution rate of flurbiprofen. Albeit the proportion of carrier is far less as compared to that of drug, yet it is quite effective in dissolution enhancement. This is because phospholipids spontaneously form liposome bilayer structures in an aqueous media that entrap solutes either in an aqueous phase or bilayer, thereby hastening the dissolution process. Similarly, In case of glipizide the rate of dissolution was increased when the ratio of polymer is increase, about 5-fold greater dissolution rate of glipizide with poloxamer 188 in the ratio of 1:10[31].

Method of preparation

Solid dispersions prepared by melting generally showed faster dissolution rates than those prepared by solvent method. Solid dispersions of griseofulvin-PEG 6000 prepared by solvent method have been reported to yield dissolution rates much slower than the ones obtained using melting method [19]. For example solid dispersion of diazepam-PEG 6000, prepared by melt method with1:10 and 1:5 w/w ratio, showed faster dissolution rates. This rapid release was attributed to very fine state of subdivision of the drug particles, and solubilizing plus wetting effect of the carrier. However, the corresponding solid dispersion prepared by coprecipitation showed slower dissolution owing probably to greater size of diazepam particles[32].

Cooling conditions

In melt technique, drug is incorporated in a molten carrier, and subsequently cooled, forming the dispersion. The method of cooling, whether slow or flash, affects the rate of dissolution. While preparing tolbutamide–PEG 6000 (1:2) dispersion, the melt has cooled by two processes. First process involved flash cooling by placing melt on aluminum and subsequently in a bath of dry ice and acetone. Second process involved slow cooling in oil bath under ambient conditions. More than 15% of drug release was observed in case of flash cooled dispersion as that of slow cooled dispersion due to the difference in particle size, as flash cooled dispersion gives smaller particle size and low crystallinity[33].

Synergistic effect of two carriers used

This has been exemplified in ibuprofen solid dispersions using PEG, talc and PEG-talc as dispersions carriers. It was reported that in 9.1% drug loading, ibuprofen dissolved at the end of 120min was about 66% 73% and 93% from Ibuprofen talc, ibuprofen-PEG and PEG-talc dispersions respectively. Workers attributed this synergism to the partial replacement of PEG with talc. This would cause improved wettability of ibuprofen and hence enhanced solubility of drug by overlapping the diffusion layers between PEG and ibuprofen[34,35].

CHARACTERIZATIN OF SOLID DISPERSION

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion[36].

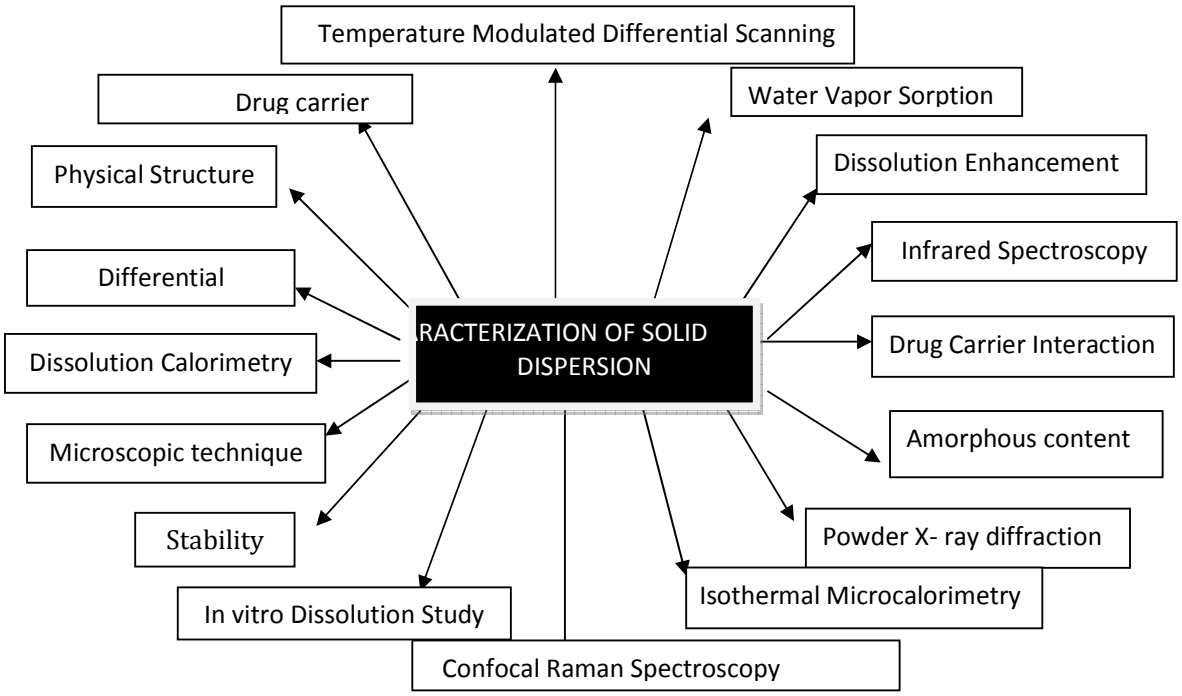


Fig. 3: Characterization of solid dispersion

Drug -carrier miscibility

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

Drug carrier interactions

FT-IR spectroscopy, Raman spectroscopy, Solid state NMR.

Physical Structure
Scanning electron microscopy, Surface area analysis Surface properties, Dynamic vapor sorption Inverse gas chromatography, Atomic force microscopy Raman microscopy.

Amorphous content
Polarized light optical microscopy, Hot stage microscopy Humidity stage microscopy, DSC (MTDSC) ITC, Powder X-ray diffraction.

Stability
Humidity studies, Isothermal Calorimetry DSC (Tg, Temperature recrystallization, Dynamic vapor sorption Saturated solubility studies.

Dissolution enhancement
Dissolution, Intrinsic dissolution Dynamic solubility, Dissolution in bio-relevant media.

Powder X-ray diffraction
Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.

Infrared spectroscopy (IR)
Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material[37].

Water vapor sorption
Water vapors sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different[38]. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

Isothermal Microcalorimetry
Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg)[39]. This technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

Dissolution calorimetry
Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample[40]. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Macroscopic techniques
Macroscopic techniques that measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity for and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additively of these properties in intimately mixed binary solids.

Differential Scanning Calorimetry (DSC)
Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC)[41]. 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 material.

Confocal Raman Spectroscopy
Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than10%was indicative of homogeneous

distribution. Because of the pixel size of 2 μm3, uncertainty remains about the presence of nano-sized amorphous drug particles.

Temperature Modulated Differential Scanning Calorimetry (TMDSC)

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible)are separated from crystallization or relaxation(irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC[42]. Therefore this technique can be used to assess the amount of molecularly dispersed drug[43]. And from that the fraction of drug that is dispersed as separate molecules is calculated.

In Vitro Dissolution Studies

In vitro dissolution studies are done for the find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro – invivo 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. There are some apparatus used in United States pharmacopoeia for dissolution testing these are following[44].

Solubility Studies

Solubility studies are done for the finding out the solubility behavior shown by the solid dispersion system in different types of solvent system and body fluids.

Table 6: Analytic method for characterization of solid forms[45]

Method	Material required per sample
Microscopy	1 mg
Fusion methods(Hot stage microscopy)	1 mg
Infrared spectroscopy	2-20 mg
X-Ray powder diffraction (XRD)	500 mg
Scanning Electron Microscopy	2 mg
Thermo gravimetric analysis	10 mg
Dissolution/Solubility analysis	1mg to 1gm
Differential scanning calorimetry(DSC/DTA)	2-5 mg

ADVANTAGES OF SOLID DISPERSIONS

Generally, solid dispersion is mainly used

- To reduced particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug in to amorphous form.
- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.
- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs.
- To dispense liquid or gaseous compounds.
- To formulate a faster release priming dose in a sustained release dosage form.
- To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or
- Insoluble carriers[46].

LIMITATIONS OF SOLID DISPERSION SYSTEMS

Limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations includes are as follows

- Laborious and expensive methods of preparation,
- Reproducibility of physicochemical characteristics,

- Difficulty in incorporating into formulation of dosage forms,
- Scale-up of manufacturing process, and
- Stability of the drug and vehicle.
- its method of preparation, Various methods have been tried recently to overcome
- the limitation and make the preparation practically feasible. Some of the suggested approaches to overcome the aforementioned problems and lead to industrial scale production are discussed here under alternative strategies[47].

CONCLUSION

The increasing number of poorly water soluble compounds entering pharmaceutical development pipeline in the recent years has prompts the use of several different formulation approaches to enhance oral bioavailability of such compounds. Solid dispersion has set itself as a proven technology for the purpose with unique set of advantages and limitations. The review provides various methodologies of using solid dispersions, and discusses as to why, when, and how to develop them. Proper selection of formulation method and carriers greatly append in solubility enhancement of poorly water soluble drugs. Improved understanding of physical stability of solid dispersions is the main driver for increasing future relevance of solid dispersions. With further expansion in polymer science and a greater perceptive of biopharmaceutical properties prevailing dosage form selection, solid dispersions technique will be widely applied to develop oral dosage form of poorly water-soluble drugs.

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