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Solid dispersion: A systematic review

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Abstract
Solid dispersion has pulled in extensive popularity as a proficient method for enhancing the dissolution rate and subsequently the bioavailability of a range of poorly water-solvent medications. Solid dispersion of inadequately water-solvent medications with water-soluble bearers has decreased the occurrence of these issues and improved dissolution. The concentration of this review article is on the advantages, limitations, different techniques for effectiveness and portrayal of the solid dispersion. The diverse sorts of solid dispersion in view of their molecular arrangement have been highlighted. A portion of the down to earth angles to be considered for the planning of strong scatterings, for example, determination of carrier and techniques for physicochemical characterization have likewise been discussed. Also, it is planned to examine the future prospects identified with the region of solid dispersion.

Keywords: solid dispersion, carriers, dispersants, solubility, dissolution rate, bioavailability

1. Introduction
Oral drug delivery is by far the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation, etc. However in case of the oral route there are several challenges such as limited drug absorption resulting in poor bioavailability and poor pharmacological response resulting into inadequate and erratic oral absorption. 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 route like greater stability, smaller bulk, accurate dosage and easy production. 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. To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including prodrug formation, complexation, micro capsulation, the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins [1, 2].

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. The technique has been used for a wide variety of poorly aqueous soluble drug. Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract.

$$Dc/dt = AD (C_S - C)/H$$

Where, dC/dt - is the rate of dissolution, A -is the surface area available for dissolution, D - is the diffusion coefficient of the compound, Cs- is the solubility of the compound in the dissolution medium, C -is the concentration of drug in the medium at time t and h - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. To increase the dissolution rate from equation the following approaches are available. To increases the surface area available for dissolution. Decreasing the particle size of drug. Optimizing the wetting characteristics of compound surface. To decrease the boundary layer thickness. Ensure sink condition for dissolution. Improve apparent solubility of drug under physiologically relevant conditions. Drug administered in fed state is a way to improve the dissolution rate [2, 3]. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyesh-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

2. Solid Dispersion
There are various techniques for solubility enhancement. Solid dispersion is one of the best approaches for solubility enhancement. 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; basically amorphous is having good solubility than crystalline substance because no energy is required to break up the crystal lattice of a drug during dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers.

First Generation Solid Dispersions
Solid dispersions were first described by Sekiguchi and Obi in 1961 [3] in which they used concept of eutectic mixtures. They mentioned that the formulation of eutectic mixtures improve the rate of drug release and thus increase bioavailability of poorly soluble drug. Thus first generation solid dispersions were

prepared using crystalline carriers. Eutectic mixtures are binary systems comprising of poorly water soluble drug and highly water soluble carrier and at eutectic point drug crystallizing out simultaneously only in the specific composition. When eutectic mixture is dissolved in aqueous medium, the carrier part will dissolve quickly and drug will be released in the form of fine crystals. The main disadvantage of first generation Solid dispersion is crystalline nature which leads to less solubility as compare to amorphous form, however, they possess good thermodynamic stability. First generation solid dispersion were generally prepared using crystalline carriers like urea, mannitol [3, 4].

Second Generation Solid Dispersions

In second generation instead of crystalline carriers, amorphous carriers were used to disperse drugs which are generally polymers. Polymeric carriers can be of fully synthetic origin like povidone, polyethylene glycols and polymethacrylates whereas natural product based polymers comprises of cellulose derivatives like hydroxypropyl-methylcellulose, ethyl cellulose or starch derivatives, like cyclodextrins. Amorphous solid dispersions are further classified as solid solutions, solid suspension or mixture of both as per molecular interaction of drug and carrier. Amorphous carriers: Polyethyleneglycol, Povidone, Polyvinylacetate, Polymethacrylate, cellulose derivatives

Third Generation Solid Dispersions

In the third generation solid dispersion surfactants carrier or mixture of polymer are used as carrier. If carrier has surface active or self-emulsifying properties, the dissolution profile of poorly soluble drug can be improved and hence result in increased bioavailability. Typically used surfactants as solid dispersion carriers are polaxamer 407, gelucire 44/14, compritol 888 ATO27, inulin.

3. Mechanism of Drug Release

There are two sets of observations with regard to the mechanism of drug release from solid dispersions.

1. Carrier-controlled Release- Corrigan (1986) [5] provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. He found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer
2. Drug-controlled Release- Sjokvist and Nystrom (1991) measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles. In an attempt to reconcile these contradictions Sjokvist-Saers and Craig (1992 used a homologous series of drugs (para-aminobenzoates) in PEG 6000 in an attempt to interrelate the solid state structure, drug solubility and dissolution rate. These noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behaviour as drug-controlled dissolution as opposed to carrier-controlled dissolution. Here the dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself [6].

The resulting enhanced surface area produces higher dissolution rate and enhances bioavailability of poorly water soluble drugs. In addition, 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 advantage of solid dispersions over conventional tablet or capsule is shown schematically in Figure 1 [7, 8].

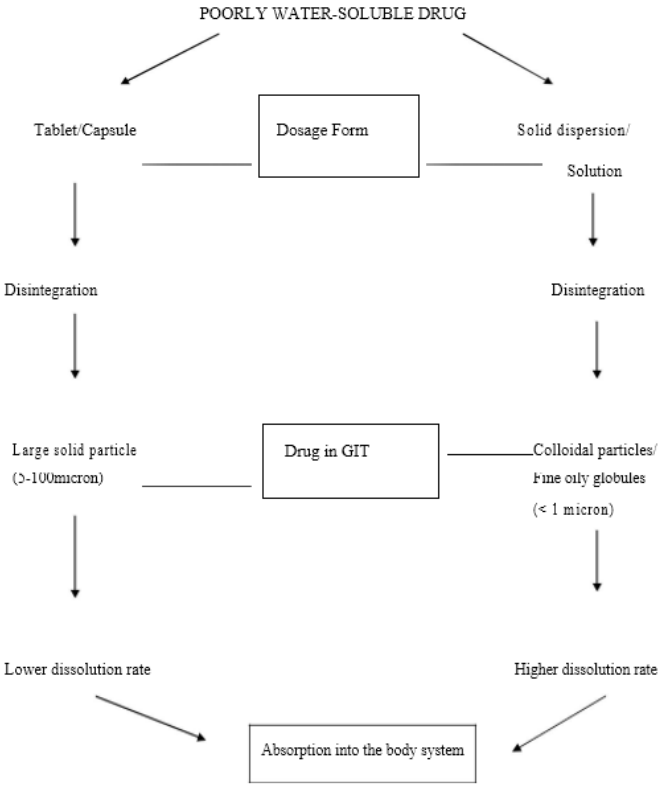


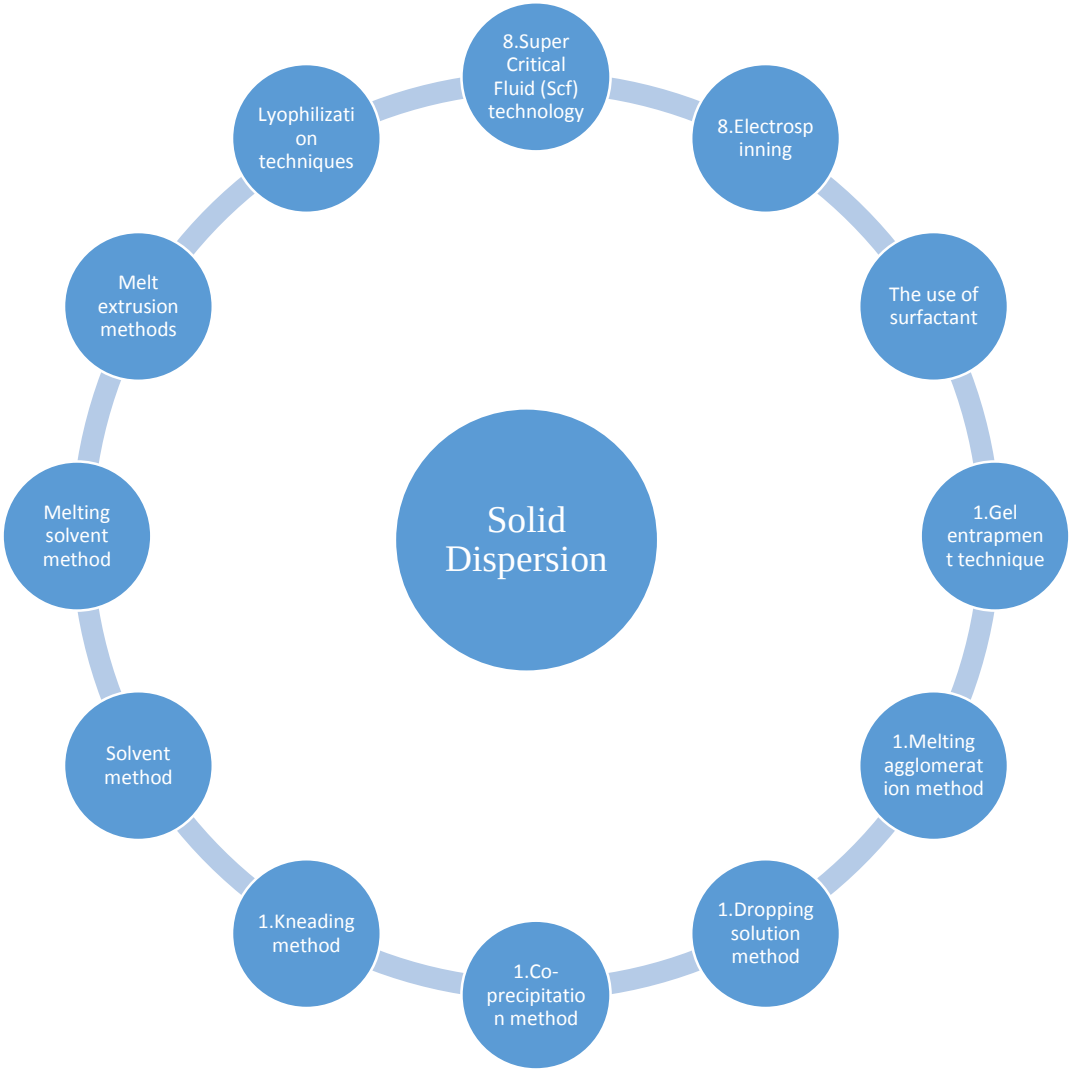
Fig 1: A schematic representation of the bioavailability enhancement of a poorly water- soluble drug by solid dispersion compared with conventional tablet or capsule

Types of Solid Dispersion [9]

Table 1

Types of slid dispersion		Matrix*	Drug**	Remarks	No. of phases
I	Eutectics	C	C	The first type of solid dispersion preparared	2
II	Amporphous percipitation in crystalline matrix	C	A	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Misicible at all compositon, never prepared	1
	Discontinuous solid solutions	C	M	Paratially misicible, 2 phases even though drug is molecularly dispersed	1 or 2
	Substitutional solid solutions	C	M	Molecular diameter of drug differ less than 15% from the matrix diameter. In that case drug and matrix are substitutional.	2
	Intersitial solid solution	C	M	Drug molecular diameter less than 59% of matrix diameter,usually limited miscibility, discontinuous	2
IV	Glass suspension	A	C	Particle size dispersed on colling evaporation rate. Obtained after crystallization of drug in amporphous matrix.	2
V	Glass suspension	A	A	Particle size dispersed on colling evaporation rate,many solid dispersion are of this type	2
VI	Glass solutions	A	M	Requires miscibility,solid solubility,complex formation or upon fast cooling.	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



Methods for preparation of solid dispersions

a) Melt solvent method- It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol.
b) Solvent method-In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.
c) Lyophilization technique- Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. 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.
d) Supercritical fluid antisolvent techniques (SAS)- The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remain strapped inside the polymer; it poses no danger to the patient.
e) Kneading technique- Mix drug and polymer with the small amount of the solvent i.e. water to form a thick paste by kneading and hence it is dried at 450C in an oven. Pass the mass through the sieve no. 30 and store in the desiccator.
f) Co-precipitation-Add required amount of drug to the solution of β-cyclodextrins. Keep the system under magnetic agitation with controlled process parameters and protect from the light. Separate the formed precipitate by vacuum filtration and then dry at room temperature in order to avoid the loss of the structure water from the inclusion complex.
g) Spray Drying-Dissolve the various amounts of carriers in water. Then disperse the 10gm of drug, pre-sieved through a 60-mesh screen in the solution. The resulting dispersion is subjected towards the nozzle at a flow rate previously fixed using a peristaltic pump & spray dry it at an inlet temperature of about 1200C & an outlet temperature of about 65-700C.Fix the spray pressure. Maintain the flow rate of drying air at the aspirator. After spray-drying, collect each resulting powders by cyclone separation and transferred to glass vials.
h) Electro spinning- Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone)
i) Melt Agglomeration Process- 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. It has been found that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate [10, 11].

Characterization 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 [11, 12].

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

- Polarised 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

Commercially available solid dispersion [13,14]

Table 2

Commercial products	Dispersant	Manufacturer Company, Country
Afeditab (Nifedipine*)	Poloxamer or Polyvinylpyrrolidone (PVP)	Élan Corp, Ireland
Cesamet (Nabilone*)	Polyvinylpyrrolidone (PVP)	Valeant Pharmaceuticals, Canada
Certican (Everolimus*)	Hydroxypropylmethylcellulose (HPMC)	Novartis, Switzerland
Fenoglide (Fenofibrate*)	Poltethylene glycol (PEG)	Life Cycle Pharma, Denmark
Gris-PEG (Griseofulvin*)	Polyvinylpyrrolidone (PVP)	VIP Pharma, Denmark
Gris-PEG (Griseofulvin*)	Polyethylene glycol	Novartis, Switzerland
Isoptin SRE-240 (Verapamil*)	Various	Soliqs, Germany
Kaletra (Lopinavir* & Ritonavir*)	Polyvinylpyrolidone(PVP) / Polyvinyl acetate	Abbott Laboratories, USA
LCP-Tacro (Tacrolimus*)	HPMC	Life Cycle Pharma, Denmark

*=Drug, a=Withdrawn from market

Applications of Solid Dispersions
1) To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
2) To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo oxidation and other decomposition procedures.
3) To reduce side effect of certain drugs.
4) Masking of unpleasant taste and smell of drugs.
5) Improvement of drug release from ointment creams and gels.
6) To avoid undesirable incompatibilities.
7) To obtain a homogeneous distribution of a small amount of drug in solid state.
8) To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
9) To formulate a fast release primary dose in a sustained released dosage form.
10) To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
11) To reduce pre-systemic inactivation of drugs like morphine and progesterone [14, 15].

Limitations of Solid Dispersions

Although a great research interest in solid dispersion in the past four decades, the commercial. Utilization is very limited. Problems of solid dispersion involve-

i) The physical and chemical stability of drugs and vehicles,
ii) Method of preparation,
iii) Reproducibility of its physicochemical properties,
iv) Formulation of solid dispersion into dosage forms, and
v) Scale-up of manufacturing processes [15, 16].

Future prospects of solid dispersions

Despite many advantages of solid dispersions, issues related to preparation, reproducibility, formulation, scale-up and stability limited its use in commercial dosage forms for poorly water soluble drugs. However, successful development has been feasible in recent years due to availability of surface-active and self-emulsifying carriers with relatively low melting points. The drug along with carrier are filled into hard gelatin capsules because of easy manufacturing process and improved bioavailability and enhanced dissolution rate. One of the major focuses for research would be the identification of new surface-active and self-emulsifying carriers for solid dispersion. The other focus would be on identification of vehicles or excipients that would retard or prevent crystallization of drugs from super-saturated systems along with development of extended release dosage forms and physical and chemical stability of both drug and carrier in solid dispersion [16, 17].

4. Conclusion

The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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