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SOLID DISPERSION: OVERVIEW OF THE TECHNOLOGY

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ABSTRACT: Up to 40% of new chemical entities (NCEs) discovered today by the pharmaceutical industry through combinatorial chemistry and high through put screening are highly lipophilic or poorly water soluble compounds, so the number of such compounds has dramatically increased and the solubility behaviour of these drugs has become one of the most challenging aspects in formulation development. So amongst the vast majority of strategies (like particle size reduction, use of surfactants, cosolvency, hydrotrophy etc) already reported in the literature to resolve this issue, solid dispersions have emerged as an advanced technique of improving the solubility/dissolution rate and hence, the bioavailability enhancement of a wide range of poorly water-soluble drugs. This review article mainly focuses on solubility ranges, biopharmaceutical classification system (BCS), list of poorly soluble drugs, commercial preparations, classification, types, advantages, limitations, methods of preparation and characterization of solid dispersions. In this review, besides above it is intended to discuss the recent advances and future prospects related to the solid dispersion technology.

INTRODUCTION: Though many routes of drug administration are there but the oral drug delivery is the most preferred route due to ease of administration, patient compliance, flexibility in formulation, etc. However, in case of the oral route there are several bottlenecks such as limited absorption of poorly water soluble drugs from gastrointestinal tract resulting in low bioavailability and poor pharmacological response [1]. Most of the new chemical entities 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 advantages of this route like greater stability, smaller bulk, accurate dosage and easy production [2].

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But what the fact remains is that huge number of new chemical entities are highly lipophillic /poorly water soluble drugs, and are not well absorbed after oral administration, so the oral delivery of such drugs is frequently associated with low bioavailability, high intra/inter-subject variability, and a lack of dose proportionality. To overcome the problem of low solubility associated with such drugs, various strategies till date have been applied to enhance solubility including pro-drug formation, β-CD complexation, use of surfactants, micro-nization, salt formation, etc [3]. One such formulation approach that has significantly enhanced solubility/ dissolution of such drugs is solid dispersion (SD) technology.

The term ‘Solid Dispersion’ refers to a group of solid products consisting of at least two different components, generally ‘a Hydrophobic Drug and a Hydrophilic Carrier’. The carrier can be either crystalline or amorphous. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug gets released as fine colloidal particles and as a result there is

enhancement of solubility/dissolution rate of poorly water soluble drugs [4].

Hydrophobic Drug + Hydrophilic Carrier

Solid Dispersion

FDA Approved Commercial/marketed Solid Dispersion Dosage Forms.

TABLE 1: SOLUBILITY RANGES

	Solubility term	Solute to be dissolved (g)	Solvent needed to dissolve (L)
Solubility Decreasing	Very Soluble	1	< 0.001
	Freely Soluble	1	0.001 to 0.01
	Soluble	1	0.01 to 0.03
	Sparingly Soluble	1	0.03 to 0.1
	Slightly Soluble	1	0.1 to 1
	Very Slightly Soluble	1	1 to 10
	Insoluble	1	>10

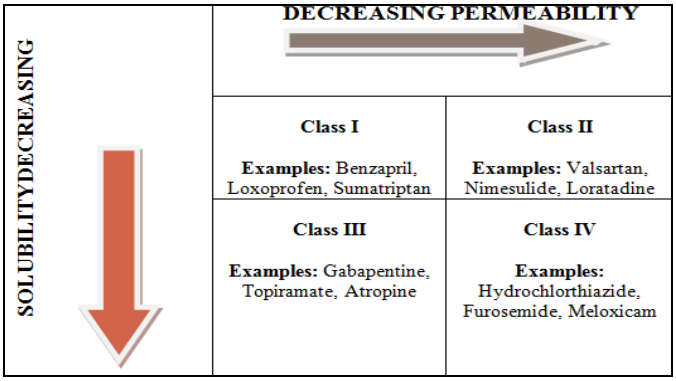
TABLE 2: EXAMPLES OF COMMERCIALLY AVAILABLE SOLID DISPERSIONS [5]

Brand name	Manufacturer	Drug	Carrier	Dosage Form
Gris-PEG	Pedinol	Griseofulvin	PEG-6000	Tablet
Cesamet	Valeant	Nabilone	PVP	Tablet
Sporanox	Janssen	Itraconazole	HPMC	Capsule
Intelence	Tibotec	Etravirin	HPMC	Tablet
Certican	Novartis	Everolimus	HPMC	Tablet
Isoptin SR-E	Abbott	Verapamil	HPC/ HPMC	Tablet
Nivadil	Fujisawa	Nivaldipine	HPMC	Tablet
Prograf	Fujisawa	Tacrolimus	HPMC	Capsule
Rezulin	Parke Davis	Troglitazone	HPMC	Tablet
Afeditab	Elan	Nifedipine	Poloxamer/PVP	Tablet

PVP - polyvinylpyrrolidone; HPC - hydroxypropylcellulose;
PVPVA - polyvinyl pyrrolidone-co-vinylacetate; HPMC – hydroxypropylmethylcellulose

Biopharmaceutical Classification System: A drug is orally active if it dissolves into the gastrointestinal fluids, then permeates the gut wall, passes through the liver without being inactivated and finally enters the systemic blood flow. But amongst the various hurdles solubility is the major problem for highly lipophillic and poorly water soluble new chemical entities. Amidon *et al.*, classified active compounds into four classes according to their solubility and permeability. This is known as the Biopharmaceutical Classification System (BCS) [6].

- **Class I** compounds have a high solubility and high permeability; therefore their bioavail-ability will depend solely on the gastric emptying rate.
- **Class II** compounds with a low aqueous solubility and sufficient permeability the dissolution will be the rate limiting step.
- **Class III** compounds have sufficient solubility but poor permeability and hence the absorption rate will be determined by passage through the gut wall.
- **Class IV** compounds have both low solubility and low permeability, the rate limiting step will differ case by case [7].



Classification of Solid Dispersions: Based on the type of carrier used in the production of solid dispersion, the following categories of SDs are

1st Generation SDs: These are prepared with crystalline polymers. Example, Urea, Sugars, Organic acids [8].

2nd Generation SDs: These are prepared with fully synthetic or natural product based polymers. Example, polyvinyl pyrollidones, polyethylene glycols and polymethacrylates, hydroxypropyl

methylcellulose, ethylcellulose, hydroxypropyl cellulose, cyclodextrins [9].

3rd Generation SDs: These are prepared with Surface active self emulsifying polymers. Example, Poloxamer 408, Tween80 and Gelucire 44/14 [10].

Types of Solid Dispersion: The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by melting or solvent method. Therefore, based on their molecular arrangement, different types of solid dispersions can be distinguished (**Table 3**) [11].

TABLE 3: TYPES OF SOLID DISPERSIONS

S. no	Type of SD	Matrix*	Drug**	Remarks	Number of Phases
I	Eutectics	C	C	First type of SD prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Continous	C	M	Miscible at all composition, never prepared	1
	Discontinous	C	M	Partially miscible	2
	Substitutional	C	M	Molecular diameter of drug differs less than 5% from the carrier diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous	1or 2
	Interstitial	C	M	(Solute) molecular diameter of Drug differs less than 59% of carrier diameter. Can be discontinuous only	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1

* A: matrix in the amorphous state; C: matrix in the crystalline state.
**A: drug dispersed as amorphous clusters in the matrix; C: drug dispersed as crystalline particles in the matrix; M: drug dispersed molecularly throughout the matrix

Simple Eutectic Mixtures: A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution [12-15].

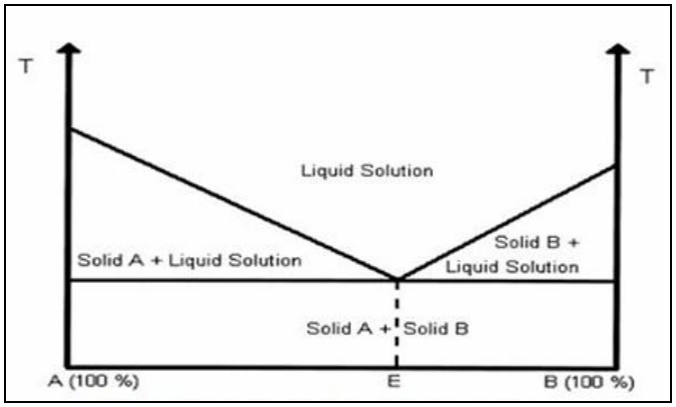


FIG. 1: PHASE DIAGRAM FOR A EUTECTIC SYSTEM

Amorphous Precipitation in Crystalline Matrix: This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form [16, 17].

Solid Solution: Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum *viz.* the molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier.

Classified as:

- ❖ According to their miscibility: continuous and discontinuous solid solutions.
- ❖ According to the way in which the solvate molecules are distributed in the solvendum: substitutional and interstitial solid solutions.

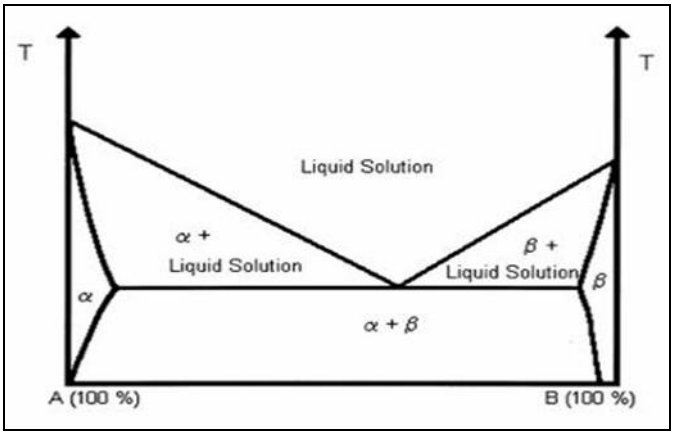


FIG. 2: PHASE DIAGRAM FOR A SOLID SOLUTION

Continuous Solid Solutions: In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical world till date.

Discontinuous Solid Solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by Goldberg *et al.*, [18] that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

Subsitutional Solid Solutions: Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [19]. Classical solid solutions have crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules.

Interstitial Solid Solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter [20].

Glass Suspensions: Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solution and suspension [21].

Glass Solution: Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier.

Selection of the Carrier: The selection of the carrier has huge 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 while as a poorly water 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.

A suitable carrier should meet the following criteria for increasing the solubility/dissolution rate of a drug [22-25].

- ❖ Freely water-soluble with intrinsic rapid dissolution properties.
- ❖ Non-toxic and pharmacologically inert.
- ❖ Heat stable with a low melting point for the melt method.
- ❖ Soluble in different solvents and pass through a vitreous state upon solvent evaporation. Preferably able to increase the aqueous solubility of the drug.
- ❖ Chemically compatible with the drug and should not bond strongly with the drug.

TABLE 4: MATERIALS USED AS CARRIER

Materials used As Carriers	Examples
Sugars	Sorbitol, Mannitol,
Acids	Citric acid, Succinic acid
Polymeric materials	Polyvinyl Pyrollidones (PVP, PVP-K30, PVP-K90), Polyethylene Glycols (PEG-4000, PEG-6000)
Insoluble or enteric polymer	HPMC phthalate, Eudragit (L100, S100, RL, RS)
Surfactants	Tweens, Spans
Surfactant Polymers	Poloxamer 188, Gelucire 44/14, Lutrol F-127, Soluplus
Miscellaneous	Urea

Mechanism of Solubility Enhancement: The following is probable mechanism by which the solubility of poorly water soluble drugs is enhanced by SD technology.

Particles with Reduced Particle Size: Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability [26].

Particles with Improved Wettability: Wettability is improved during solid dispersion production. It has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence, improved wetting may lead to reduced agglomeration and increased surface area [27, 28].

Particles with Higher Porosity: Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile [29].

Drugs in Amorphous State: Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher solubility. Drug in its amorphous state shows higher drug release 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 [30, 31].

Limitations:

- They are not broadly used in commercial products because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization / re-crystallization.
- The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization.
- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a meta-stable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during *in-vivo* performance.

- Poor scale-up for the purposes of manufacturing.
- Laborious and expensive methods of preparation.
- Reproducibility of physico-chemical characteristics.
- Difficulty in incorporating into formulation of dosage forms.
- Scale-up of manufacturing process.
- Stability of the drug and vehicle

Pharmaceutical Applications: The pharmaceutical applications of solid dispersion include:

- To enhance the bioavailability of poorly water soluble drugs by bringing an increase in the solubility/dissolution rate of such drugs.
- To get uniform distribution of small doses of drug in the solid state.
- To stabilize and protect such drugs which are vulnerable to decomposition by processes like hydrolysis, oxidation, racemization, photo-oxidation etc.
- By making its inclusion complex the binding ability of drugs, for example to the erythrocyte membrane is decreased.
- To reduce side effects by administration as an inclusion compound the damage to the stomach mucous membranes by certain non-steroidal anti- inflammatory drugs can be reduced.
- To mask unpleasant taste and smell and avoid undesirable incompatibilities.
- To convert liquid compounds into formulations. Liquid drugs (*e.g.* unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc.) can be manufactured as solid drug formulations such as powders, capsules or tablets.
- To reduce pre systemic inactivation of drugs like morphine and progesterone [32, 33].

Preparation: The various methods used for preparation of solid dispersions are depicted in **Fig. 2**.

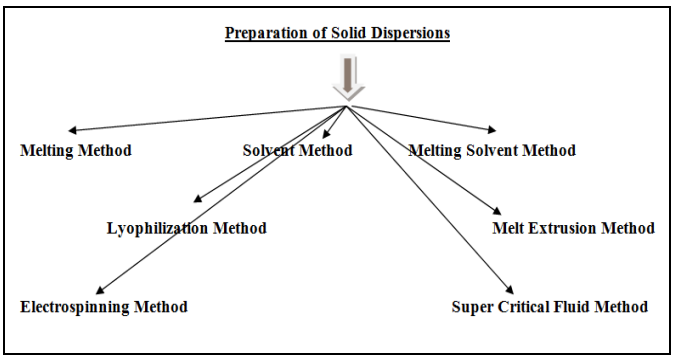


FIG. 3: METHODS OF PREPARATION OF SOLID DISPERSIONS

Melting Method: In this method, the physical mixture of drug and hydrophilic carrier is heated directly until it melts. The melted mixture is then solidified rapidly on an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

The advantages of this method are:

- Simplicity
- Economy

The disadvantages of this method are:

- This method is only applied when the drug and carrier are compatible and when they mix well at the heating temperature.
- This method can bring phase separation during cooling when the drug-carrier miscibility changes.
- Many substances, either drugs or carriers, may decompose during the fusion process at high temperatures.

Solvent Method: The first step in the solvent method is the preparation of a solution containing both hydrophilic carrier and drug. The second step involves the complete removal of solvent(s) resulting in formation of a solid dispersion. The advantage of this method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

Melting-Solvent method: In this method solution is prepared by dissolving drug in a suitable solvent and then incorporation 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. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical stand point, it is only limited to drugs with a low therapeutic dose *e.g.* below 50 mg and particularly useful for drugs that are thermolabile or have high melting points [7].

Lyophilization Method: In this method, drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. This method was proposed as an alternative to solvent evaporation.

The advantages of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized as soon as the solution is vitrified.

Melt Extrusion Method: This method consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed at melting temperature for a small period of time using a co-rotating twin-screw extruder. The drug-carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets.

An important advantage of the melt extrusion method is that the drug-carrier mix is only subjected to an elevated temperature for about one min, which enables drugs that are somewhat thermolabile to be processed. The concentration of drug in the dispersions is always 40% (w/w). Samples are milled for 1 min with a cutting mill and sieved to exclude particles >355µ.

Electrospinning Method: In this method, solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. It 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. This technique has tremendous potential for the preparation of nanofibres and controlling the

release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Super Critical Fluid Method: In this method, carbon dioxide is used as an anti-solvent for the solute but as a solvent with respect to the organic solvent. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. 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 remains trapped inside the polymer; it poses no danger to the patient. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.

Characterization:

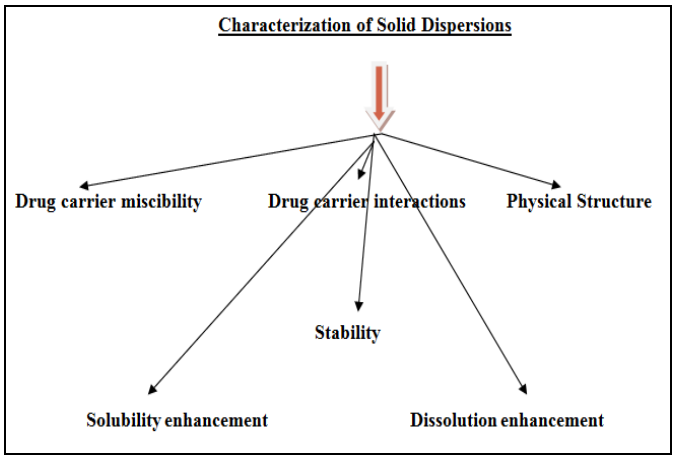


FIG. 4: CHARACTERIZATION OF SOLID DISPERSIONS

Drug-carrier Miscibility:

Differential Scanning Calorimetry (DSC): This technique is often used to detect the amount of crystalline material. In this technique, 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)cry-stallllization energy can be quantified. The melting energy can be used to detect the amount of crystalline material [35, 36].

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

Drug-carrier Interactions:

Fourier Transformed Infrared spectroscopy (FTIR): This technique is used to detect the variation in the energy distribution of interactions between drug and carrier. Sharp vibrational bands indicate crystallinity [37].

Raman Spectroscopy (Confocal): Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2µm, uncertainty remains about the presence of nano-sized amorphous drug particles.

Physical Structure:

Scanning Electron Microscopy (SEM): The shape and surface characteristics of solid dispersion systems were observed by Scanning electron microscopy studies.

Water Vapour Sorption: Water vapour sorption can be used to discriminate amorphous and crystalline material when the hygroscopicity is different.

Stability:

Isothermal Microcalorimetry: This measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) [38].

Temperature Modulated Differential Scanning Calorimetry (TMDSC): The sensitivity of this technique is higher than DSC, so it can be used to assess the amount of molecularly dispersed drug and from that the fraction of drug that is dispersed as separate molecules is calculated. This can also be used to assess the degree of mixing of an incorporated drug. Due to modulation, events like reversible (glass transitions) and irreversible (crystallization or relaxation) can be separated in amorphous materials [39].

Water Vapour Sorption: If hygroscopicity is different water vapour sorption can be used to differentiate between crystalline and amorphous material. It requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

Solubility Enhancement:

Solubility Studies: Solubility studies are done for finding out the solubility behaviour shown by the solid dispersion system in different types of solvent system and body fluids. This can be achieved by either saturation solubility or phase solubility studies.

Dissolution Enhancement

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies are done for finding out dissolution behavior. The *in-vitro* dissolution study can be used to demonstrate the bioavailability or bio-equivalence of the drug product through *in-vitro* / *in-vivo* correlation (IVIVC).

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

Macroscopic Techniques:

Dynamic Mechanical Analysis (DMA): Dynamic Mechanical Analysis (DMA) that measure mechanical properties can be indicative for the degree of crystallinity.

Recent Advances: As we know that solid dispersion technology has tremendous potential for increasing the bioavailability of drug, Successful development has been possible in recent years due to availability of few surface-active and self-emulsifying carriers with relatively low melting points and because of easy manufacturing process filling of drug along with carrier into hard gelatin capsules. Also, the technology has also step in developing controlled release preparations of poorly water soluble drugs.

Future Prospects: Though there are many advantages of solid dispersion technology, but still some issues related to preparation, reproducibility, formulation, scale-up and stability remain unresolved and because of these issues this technology has limited use in commercial dosage forms for poorly-water soluble drugs. Besides above, major focus for research would be the identification of new surface - active / self-emulsifying carriers and vehicles / excipients that will prevent recrystallization of drugs from super-saturated systems and also, physical and chemical stability of both drug and carrier in solid dispersion along with development of extended release dosage forms. Also, a better understanding of dissolution and absorption behaviour of drug with low aqueous solubility is required to successfully formulate them into more soluble and hence bio-available drug product in case of poorly water soluble drug.

CONCLUSION: As from this review, it is clear that the solid dispersion technology is one of the advanced approaches to resolve the problem of solubility of poorly water-soluble drugs. So, prior to developing a new solid dispersion system for a given drug, it is necessary to investigate the physio-chemical properties of the drug and carrier that can best fit with each other. Also, the method of preparation and the ratio of carrier to drug also play a vital role in the solubility/dissolution rate enhancement of drug. We have attempted in bringing all the things in sequence in this article that how to cater all these aspects to achieve this goal.

So in the novel drug delivery applications, solid dispersion technology will continue to develop in future and solve problems associated with the delivery of poorly soluble drugs

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