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SOLID DISPERSION: A STRATEGY FOR SOLUBILITY ENHANCEMENT

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Abstract

Poor water solubility is the major drawback for the various types of drugs and many approaches have been introduced for the solubility enhancement of such drugs. Solid dispersion is one of the techniques adopted for the formulation of such drugs and various methods are used for the preparation of solid dispersion like kneading method, solvent evaporation method, supercritical method, fusion method. Recently various type of carriers like surfactants, disintegrants included in the solid dispersion formulations, named as third generation solid dispersion have also been discussed in this review. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. The review also encompasses the criteria of solvent selection, challenges in formulation of solid dispersion dosage forms, future prospects and various types of marketed preparations.

Keywords: solubility, surfactant, polymers, solid dispersion

1. Introduction:

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelia[1] and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industries[2]. A review of new monograph (1992-1995) in European pharmacopoeia shows that more than 40% of the drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1mg/ml[3, 4].

1.1. Solubility: The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent as given in table 1. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion[5].

1.1.1. Possible Causes for Poor Oral Absorption: Any drug is said to be poorly soluble when:

Aqueous solubility<100µg/ml

High crystal energy (melting point >200 ^{0}C)

Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min,

High molecular weight: (>500), Self association and aggregation[3]

Table 1: definitions of solubility[3].

Definition	**Parts of solvent required for one part of solute**
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Noyes-Whitney equation (1) illustrates how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability:

$$dC/dt * h = AD. (Cs - C) \quad \text{----------} \quad (1)$$

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, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving

compound[6]. Shaikh et al. prepared prolonged release solid dispersions of acetaminophen and theophylline by a simple evaporation method using ethyl cellulose as water–insoluble carrier[7].

1.2. BCS classification:The BCS was first devised in 1995 by Amidon et al.[3]According to the BCS, drug substances can be classified as belonging to one of four classes:

Class 1: high solubility and high permeability

Class 2: low solubility and high permeability

Class 3: high solubility and low permeability

Class 4: low solubility and low permeability[7]

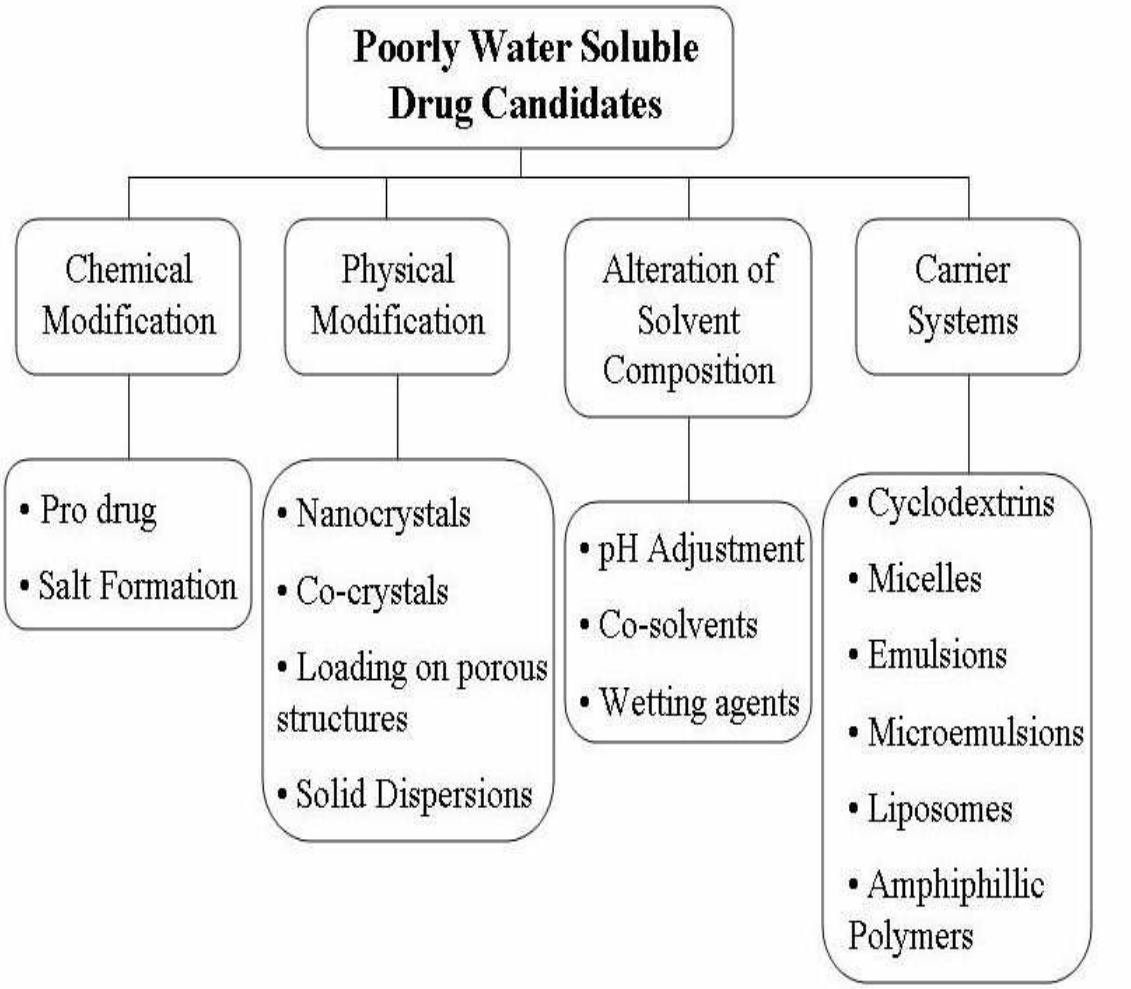
Especially for class II substances according to the Biopharmaceutical Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids[8]. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [9].

1.2.1. Class Boundaries Used In BCS:

- A drug substance is considered highly soluble when the highest dose strength is soluble in £ 250 ml water over a pH range 1 to 7.5.
- A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.
- A drug product is considered to dissolve rapidly when 85% of the labeled amount of substance dissolves within 30 minutes, using USP apparatus I or II in a volume of £ 900 ml buffer solution[3]

2. Solid dispersions: Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug [10, 11]. There are different approaches which can be used for increasing the dissolution of the poorly soluble drugs as given in the following figure 1

Figure1. Approaches to Increase solubility/ Dissolution[7].



Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"[12], they classified solid dispersions into the following six representative types: Simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitations in a crystalline carrier, compound or complex formation, and combinations of the previous five types[13] while Corrigan (1985) suggested the definition as being a 'product formed by converting a fluid drug-carrier combination to the solid state'[14] . This strategy includes complete removal of drug crystallinity, and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier[15]. Solid dispersion is a promising approach to improve the dissolution and bioavailability of hydrophobic drugs[16]. The

preparation and storage conditions of solid dispersions are crucial since changes may alter the dissolution characteristics of the active ingredients[17].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 by cosolvents, and particle size reduction.

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and 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[18]. The solid dispersions prepared by using water-soluble carrier such as polyethylene glycol are soft and tacky mass which is difficult to handle, especially in the capsule-filling and tablet making process, e.g., pulverization, sieving and mixing. The surface solid dispersion technique was then introduced in order to overcome these shortcomings. Surface solid dispersion (SSD) was selected as the method of choice for formulating the glimepiride; the carriers used were crospovidone, croscarmellose, sodium starch glycolate, pregelatinized starch, Avicel PH 101 and potato starch [19, 20].

2.1. Simple Eutectic Mixtures: When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug as listed in fig 2. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability[21].

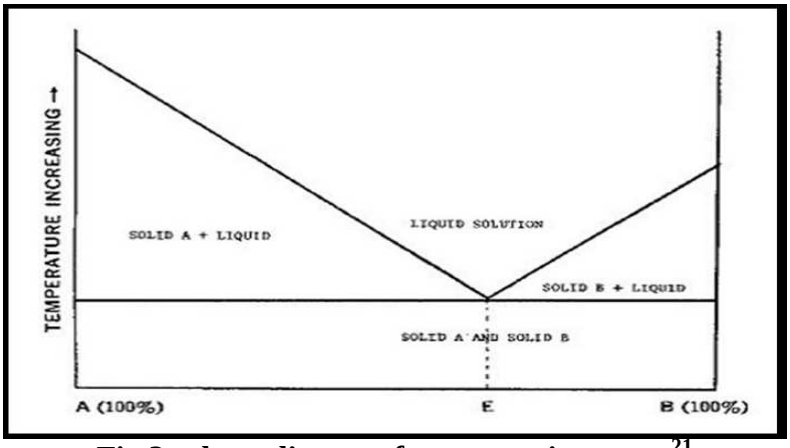


Fig 2: phase diagram for a eutectic system[21]

2.2. Classification: solid dispersion can be classified as shown in fig 3

First generation solid dispersions: The first description of solid dispersions was given from Sekiguchi and Obi in 1961 showed that formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones[22].

Second generation solid dispersions

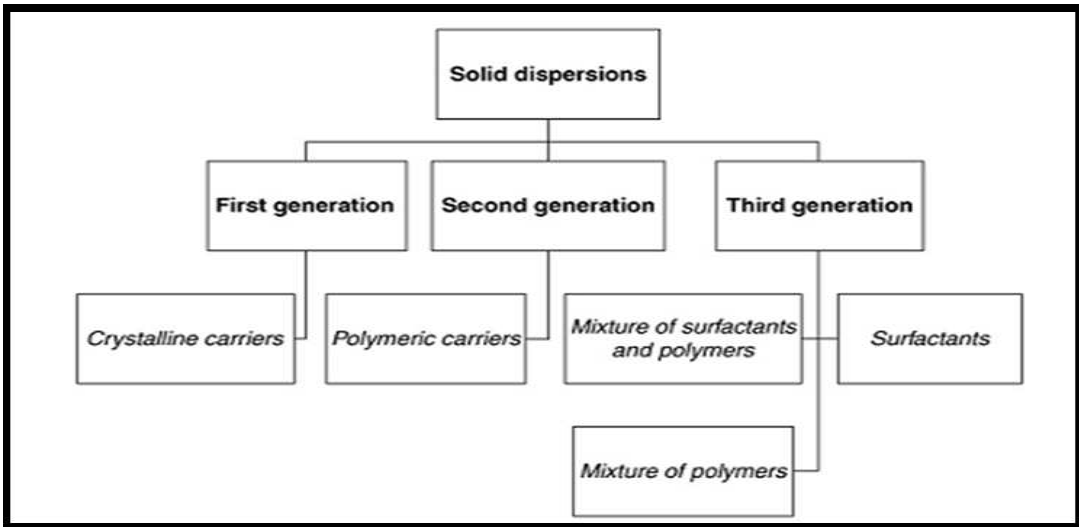
It was noticed in the late sixties (Simonelli et al. 1969; Chiou and Riegelman, 1969), that Solid dispersion with drug in the crystalline state is not as effective as amorphous because they are thermodynamically stable (Simonelli et al. 1969; Vippagunta et al. 2006; Urbanetz, 2006). Therefore, second generations of solid dispersions were introduced having amorphous carriers instead of crystalline. Formerly, the drugs were molecularly dispersed in amorphous carriers which are usually polymers in random pattern (Vilhelmsen et al. 2005)[22].

Third generation solid dispersions

Third generation of solid dispersions appeared as the dissolution profile could be increased by using carriers having surface activity and self-emulsifying characteristics.

These contain surfactant carriers or a mixture of amorphous polymers and a surfactant as carrier. The third generation solid dispersions stabilize the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce recrystallisation of drug[21]. Surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility[3].

FIG. 3: classification of solid dispersion[3].



2.3. Significant properties of solid dispersion:

There are certain exclusive properties of solid dispersion and that may be given as follows:

1. **Higher Porosity of Drug Particle:** Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity depends on the properties of carriers used, 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 and hence bioavailability.
2. **Reduced Dug Particle Size:** A high surface area is formed, resulting in an increased dissolution rate and consequently, improved bioavailability.
3. **Improved Wettability:** A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface

activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs.

4. **Drugs in Amorphous State:** The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process[4].

3. Carriers:

The properties of the carrier have the major influence on the dissolution profile of the dispersed drug. A carrier should meet the following criteria to meet to be suit for increasing the dissolution rate of drug[23].

Selection of a carrier:

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Freely water-soluble with intrinsic rapid dissolution properties.

2. Non-toxic and pharmacologically inert.

3. Heat stable with a low melting point for the melt method.

4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.

5. Able to preferably increase the aqueous solubility of the drug and

6. Chemically compatible with the drug and not form a strongly bonded complex with the drug[23, 24].

First generation carriers:

Example: Crystalline carriers: Urea, Sugars, Organic acids[6].

Second generation carriers:

Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins[9].

Third generation carriers:

Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14[25].

4. Solvent: Solvent to be included for the formulation of solid dispersion should have the following criteria:

1. Both drug and carrier must be dissolved.
2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration[25].

Class I Solvents (Solvents to be avoided):

Solvents included in this class are not to be taken in to use because of their deleterious environmental effects (table 2).

Table 2 List of some Class I Solvents.

Solvent	Concentration limit(ppm)	Effect
Benzene	2	
Carbon tetrachloride	4	Carcinogen Toxic and environmental hazards Toxic
1,2-dichloroethane	5	Toxic
1,1-dichloroethane	8	Toxic
1,1,1-trichloroethane	1500	Environmental hazards

Class II Solvents (Solvents to be limited):

Theses solvent should be limited used in pharmaceutical products because of their inherent toxicity (table 3).

Table 3 Class II solvents in pharmaceutical products

Solvent	PDE(mg/day)	Concentration limit(ppm)
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-dichloroethene	18.7	1870
Ethylene glycol	6.2	620
Methanol	30.0	3000
Pyridine	2.0	200
Toluene	8.9	890

PDE= Permitted Daily Exposure

Class III Solvents (Solvents with low toxic potential) [7]**:** Solvents included in this class may be regarded as less toxic and have the low risk to human health and as some are given in table 4.

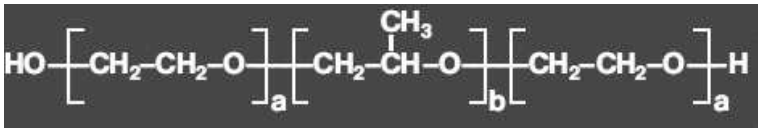
Class IV Solvents (Solvents for which no adequate toxicological data was found): Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products for example Petroleum ether, isopropyl ether. However, no adequate toxicological data on which to base a PDE was found[7].

Table 4 Class III solvents which should be limited by GMP or other quality based requirements[7]

Acetic acid	Heptane
Acetone	Isobutyl acetate
1-Butanol	Isopropyl acetate
2-Butanol	Methyl acetate
Butyl acetate	3-Methyl-1-Butanol
Dimethylsulfoxide	Pentane
Ethanol	1-Pentanol
Ethylacetate	1-Propanol
Ethyl ether	2-Propanol
Formic acid	Propyl acetate

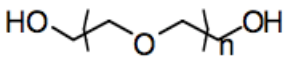
5. Polymers:

1. **Poloxamers:**



Poloxamers are derived from the sequential polymerization of propylene oxide and ethylene oxide. A general formula is shown above in figure[6]. The poloxamers are readily soluble in aqueous, polar and non-polar organic solvents[26].

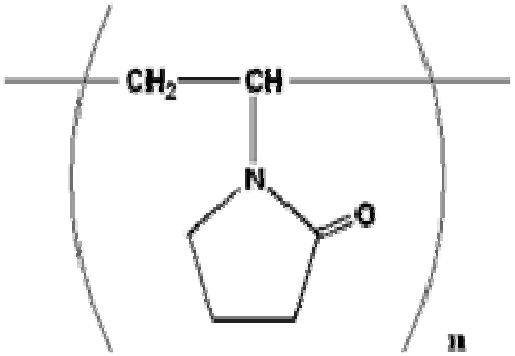
2. **Polyethylene Glycol (PEG):**



Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200±300 000[6]. Chiou and Riegelman, recommended polyethylene glycol, a water soluble polymer, as an

excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs[27, 28]. PEG solid dispersions were formulated using combinations of melting and solvent approach in which the melted drug and carrier mixture were granulated with excipients that result less tacky granulation[29, 30].

3. **Kollicoat IR:** It is a polyvinyl alcohol–polyethylene glycol graft copolymer. It is used as a pharmaceutical excipient that was especially developed as a coating polymer for instant release tablets. The polyvinyl alcohol moiety has good film-forming properties and also act as an internal plasticizer. The molecule is hydrophilic and thus readily soluble in water. It is non-ionic; its solubility does not change when the pH increases or decreases along the gastrointestinal tract. Though the viscosity of aqueous solutions of Kollicoat IR increases with the polymer concentration. A possible disadvantage is its low solubility in non-polar solvents, which may exclude the possibility to prepare solid dispersions of drugs with poor aqueous solubility by solvent methods such as spray drying[31].
4. **Polyvinylpyrrolidone (PVP):** Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersion as a component of binary system for various drugs (Sheu et al.., 1994)[32].



Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3 000 000. These can be classified according to the K value, which is calculated using **Fikentscher's equation**. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given Concentration (Table 5)[6]. The molecular size of PVP K 30 favours the formation of interstitial solid solutions[11].

Table 5: K values of PVP and the corresponding molecular weights[6].

K value	Approximate molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

5. **Polyacrylates and polymethacrylates:** Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mostly used as coatings to modify the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit® [30].

6. **Cellulose Derivatives:** Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β-1, 4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl-(MC),

hydroxypropyl- (HPC), hydroxypropylmethyl (HPMC) and many other semi-synthetic types of cellulose. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP) [6].

7. **Hydroxypropylmethylcellulose (HPMC):** HPMCs are mixed ethers of cellulose, in which 16.5±30% of the hydroxyl groups are methylated and 4±32% are derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane [6, 30].

8. **Hydroxypropylcellulose (HPC):** It exhibits good solubility in a range of solvents, including water (up till 408 ^{0}C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H). The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier[30].

9. **Carboxymethylethylcellulose (CMEC):** CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5±6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol[6].

10. **Cyclodextrin:** Cyclodextrins are used to increase the solubility of water insoluble drugs, through inclusion complexation (Chiou, 1969, Chiou, 1971, Singla, 2002 and Narang, 2002 and Millic et al.., 1997). Cyclodextrins are cyclic (α-1,4)- linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central and hydrophilic outer surface (Hye, 1997)[33, 34, 35].

6. Surfactants:

The utility of the surfactant systems in solubilization is well known. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension. Recently a new class of surfactant known as Gelucires are introduced which identify by melting points and HLB values. Gelucire is widely used in the formulation of semi solid dispersions. Gelucire- 50/13 is a hydrophilic carrier which is frequently used for this purpose; the suffixes 50 and 13 refer to its

melting point and its HLB respectively[36, 37, 38, 39]. Some other surfactants can also be used e.g. tweens, sorbitan esters(span), recently, poloxamers(PXM), a group of block copolymer nonionic surfactants, have attracted considerable attention for application in preparation of solid dispersions. Nine grades of poloxamers have been evaluated by Saettone and coworkers as solubilizers for tropicamide, a poorly water-soluble drug. Solubility was found to increase as the oxyethylene content increased[40, 41]. Surfactants can also be used as plasticizers when they are incorporated into a polymeric material; a plasticizer improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules (Wang et al., 1997)[42].

7. Disintegrants:

As there are many type of drug formulations tailored to elderly patients. Many elderly patients have difficulty in swallowing tablets. So many disintegrants are included in solid dispersion dosage forms. “Primojel”, “Ac-Di- Sol,” and “Kollidon CL” have been used as superdisintegrants, in various ratios by the investigators[43].

8. Characterization of solid dispersions

The methods that have been used to characterize solid dispersions are summarized in Table 6.

- Dissolution testing (particulate or intrinsic): Drugs having intrinsic dissolution rate < 0.1 mg/cm2//min usually exhibit dissolution rate limited absorption.
- Scanning electron microscopy (SEM) polarization microscopy: SEM is used to study the morphology of drug and sometimes the polymorphism of drug.
- Infrared spectroscopy (IR): IR is used to determine the solid state of the drug (molecular dispersion, amorphous, crystalline or a combination). Crytallinities of under 5-10% can not generally be detected.
- Differential Scanning Calorimetry (DSC): as heating is required for the formulation of solid dispersion, physical state may be changed, and the polymer may influence the melting behavior of drug (e.g. melting point depression). Crystallinities under 2% cannot generally be detected[36].

Table 6 Analytic method for characterization of solid forms[6].

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

9. Significant properties of solid dispersion:

There are certain parameters that are given below when successfully controlled, can produce improvements in bioavailability:

1. **Particle size reduction**: Solid dispersion represents the last state of the size reduction. It includes the principle of drug release by creating a mixture of poorly water soluble drug and highly soluble carriers, and after dissolution of carrier, the drug get molecularly dispersed in dissolution medium.
2. **Wettability:** Carriers having surface activity like cholic acid and bile salts, when used, can significantly increase the wettability properties of drug. Recently, in third generation solid dispersion surfactants have been included that is the emerging technique.
3. **Higher porosity:** Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.
4. **Amorphous state of drug particles:** Drug particles in amorphous state have higher solubility.
5. **Approaches for avoiding drug recrystallisation:** Recrystallisation is the major disadvantage of solid dispersions, as we are using amorphous drug particles and they are thermodynamically instable and have the tendency to change to a more stable state. Several polymers are being used for improving the physical stability of the amorphous drugs by increasing the Tg of the miscible mixture[9].

10. Advantages of solid dispersion:

1. Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic both can lead to the need for lower doses of the drug.
2. Other advantages include transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoidance of polymorphic changes and thereby bio-availability problems), as in the case of nabilone and PVP dispersion, and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption[23].

11. Disadvantages of solid dispersion:

The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abboft) from the market. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness[23].

12. Limitations of solid dispersion:

Serajuddin reported the major limitation in the development of solid dispersions is the lack of suitable manufacturing techniques that could be scaled up to commercial production. The various limitations are:

1. Laborious and expensive methods of preparation,

2. Reproducibility of physicochemical characteristics,

3. Difficulty in incorporating into formulation of dosage forms,

4. scale-up of manufacturing process, and

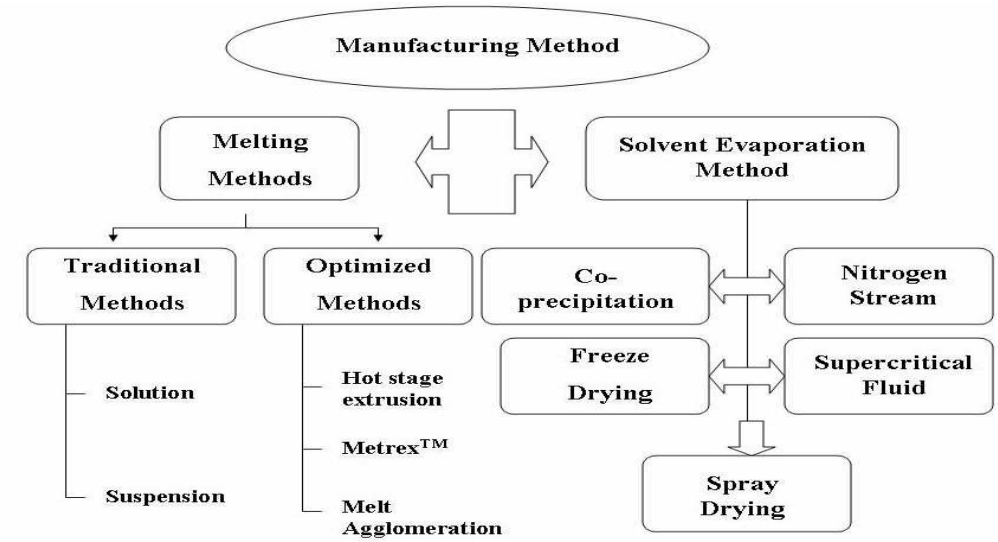
5. Stability of the drug and vehicle[44, 45].

13. Manufacturing methods: (fig.4) Various techniques have been taken in to consideration for manufacturing of solid dispersion and these techniques deal with the challenge of mixing a matrix and a drug, preferably on a molecular level**,** while matrix and drug are generally poorly miscible and during the preparation, de-mixing

(partially or complete), and formation of different phases is observed[45]. This phase separation can be controlled by some approaches that have been given in one of the first studies on solid dispersion and they can be briefly described as follows:

1. Extent of phase separation can be minimized by a rapid cooling procedure.
2. Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation.
3. Phase separation can also be prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible[46].

Figure 4: Methods of preparation of Solid Dispersion[7]



14. Techniques adopted for preparation of solid dispersion:

14.1.1. Solvent evaporation method: (fig 5)

Various investigators have been prepared solid dispersion by using the solvent evaporation method. Tachibechi and Nakumara were the first to dissolve both the drug (β-carotene and the carrier PVP) in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Mayesohn and Gibladi prepared solid dispersion by dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent. The release rate of

griseofulvin form the solid dispersion was 5-11 times higher than that of micronized drug, depending on the drug/ carrier ratio[46].

Note: Although in most other reported studies the volumes of solvents necessary to prepare solid dispersions were not specified, it is possible that they were similarly large[7].

Basic process of preparing solid dispersion consists of dissolving the drug and the polymeric carrier in a common solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some cases, large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier. To minimize the volume of organic solvent required, some investigators have reported the use of cosolvents[46]. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures (23-65^0 C) required for the evaporation of organic solvents. However, solvent methods show many disadvantages such as; expensive, ecological, and difficult to find common and removable solvents, difficulty in completely removing liquid solvent, difficulty of reproducing crystal form[21]. Some other researchers have also used fusion method for preparing solid dispersion formulations as enlisted in table 8.

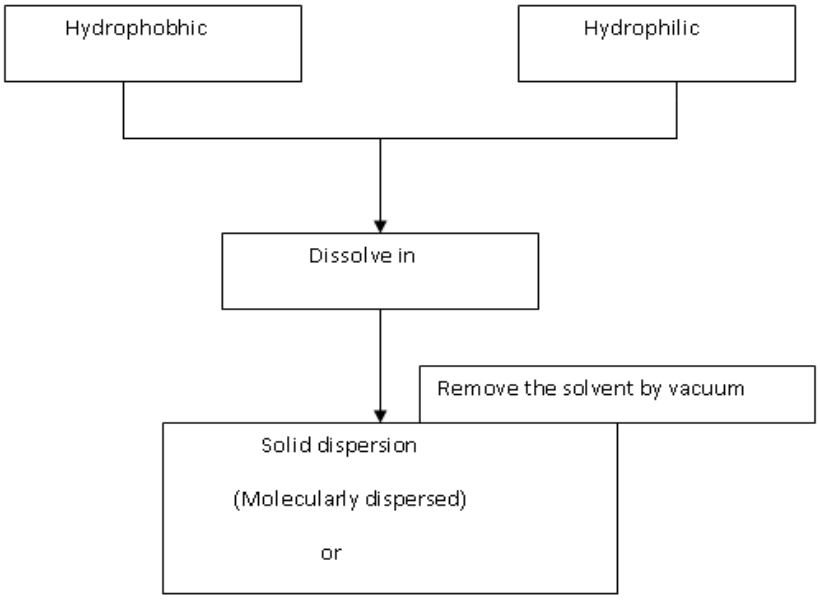


Figure 5: A schematic representation of preparation of solid dispersion by solvent evaporation technique[25]

14.1.2. Fusion method/melting method: The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it get melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg et al. and Chiou and Riegelman. The solidified masses were often found to require storage of 1 or more days in a desiccator at ambient temperatures for hardening and ease of powdering. Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37^0 C or higher temperatures[6]. This method has some limitations:

1. Many drugs can be degraded at such high temperature.
2. Incomplete miscibility between drug and carrier that may occur, because of the high viscosity of a polymeric carrier in the molten state. To avoid the melting method limitations, several modifications, like hot-stage extrusion, Meltrex TM or melt agglomeration were introduced to the original method[3]

Meltrex TM is a patented solid dispersion manufacturing process, also on the basis of the melting process. This technique includes the use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad temperature range. In this process, residence time of drug reduces in the extruder, allowing a continuous mass flow and avoiding thermal stress to the drug and excipients. Additionally, it is possible that the application of this technique to protect drugs susceptible to oxidation and hydrolysis by complete elimination of oxygen and moisture from the mixture[3].

Another modification of the above given method,involves solid dispersion of drug and carrier like troglitazone- polyvinyl pyrrolidone (PVP) k 30 have been prepared by closed melting point method. This method includes controlled mixing of water content to physical mixtures of troglitazone PVPK30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. This method is reported to produce solid dispersion with 0% apparent crystallinity[3]. Some other researchers have also used fusion method for preparing solid dispersion formulations as enlisted in table 9.

14.1.3. Hot melt extrusion: Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms (Follonier et al.., 1994; Zhang and McGinity, 1999, 2000; Ghebre-Sellassie and Martin, 2003). The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces results in to the high local temperature in the extruder and that can be problematic for the heat sensitive materials[3, 47]. There are some advantages over the conventional fusion method and those may be described as follows:

- This technique offers the potential to shape the heated the drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms
- It also offers the possibility of continuous production, which makes it suitable for large scale production.
- It is a fast, simple, continuous, solvent free process requiring fewer processing steps than traditional tabletting techniques.
- When used as a molding technique, there are no requirements for compressibility of the materials used in the formulation (Wu and McGinity, 2003)[30, 48].

14.1.4. Alternative strategies: There are certain other approaches also those may be used for the preparation of solid dispersion as given as follows:

1. **Supercritical fluid technology (SCF):** SCF techniques can be adopted for the preparation of solvent free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Super critical fluid is the one where substances existing as a single fluid phase above their critical temperature and pressure[3]. Methodology includes a very fine dispersion of hydrophobic drug in the hydrophilic carrier. Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable[4, 5, 25].

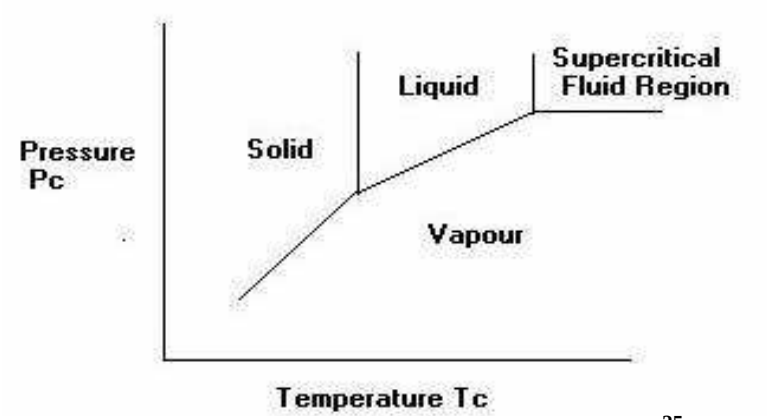


Fig 6: Typical diagram of supercritical region[25]

2. **Co-precipitation method:** In this method, while during constant stirring, a non solvent is added drop wise to the drug and carrier solution and the drug and carrier are co-precipitated to get micro particles, and then this microparticle suspension is filtered and dried.
3. **Electrostatic Spinning Method:** This technology is used in polymer industry wherein it combines solid solution/dispersion technology with nanotechnology. In this process, a potential between 5 and 30 kV is applied on the liquid stream of a drug/polymer solution. And as when the electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameter are formed. After evaporating the solvent, the formed fibers can be collected on a screen[3].
4. **Dropping method:** The dropping method was developed by Bülau and Ulrich (1977) to facilitate the crystallization of different chemicals. This method is a new procedure for producing round particles from melted solid dispersions. Methodology includes that the solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it get 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. As 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 into a spherical shape. The dropping method does not use organic solvents and therefore has none of the problems associated with solvent evaporation[49].

15. Marketed formulations: There are certain formulations of solid dispersion are available in the market (table 7).

Table 7 : Solid Dispersions: Products[50]

Product	Company	Year Approved	Technology	Reference
GrisPEG	Pedinal Pharm Inc.	1975	Melt process; exact process unknown	Kaur et al.., J Pharm Sci, 69, 1980
Cesamet	Eli Lilly	1985	Process Unknown	Bloch et al.., Pharm Acta Helv, 62, 1987
Sporanox	J&J	1996	Spray dry onto substrate	US Patent 5,663,015
Rezulin	Pfizer	1997	Extrusion	Jan 2005 Arden House
Kaletra	Abbott	2005 (sNDA)	Extrusion	31 Oct 2005 Press Release
Torcetrapib	Pfizer	Ph III	Spray Drying	24 June 2005 Press Release

Table 8: Preparation of solid dispersion of poorly soluble drugs by solvent evaporation method[17]

Drug	Carrier	Solvent	Solvent removal	Reference
ABT-963	Pluronic F-68	Ethanol	Slowly evaporated at ambient condition over one week	51
Aceclofenac	Mannitol,lactose,urea	Dichloroform	Triturated until solvent get evaporated	52
Acyclovir	PEG 6000, PVP K30	Methanol	By evaporation on magnetic stirrer at 40^0C for 1 hr.	53
Allopurinol	gelucire 50/13	Ethanol	under reduced pressure at room temp in dessicator	54
Atorvastatin	PVP K30,MCC(adsorbent)	Methanol	under low pressure	55
Carbamazepine	Glucosamine-hydrochloride	Acetone	at 40 ◦C over a period of 24 h under stirring conditions (200 rpm)	56
Cefixime	Urea	Methanol	evaporated in hot air oven at 40 ^{0}C ± 5^0 C	57
Cefdinir	PVP K 30	Chloroform, DMF	Cefdinir was dissolved in DMF and PVP in	58

			chloroform, mixed together and placed in vacuum oven at 15 lb pressure and 40 ºC temperature for 72 hr	
Cefpodoxime Proxetil	Urea	Methanol	evaporated in hot air oven at 40^0 C ± 5^0 C	59
Cefuroxime axetil	Urea	Methanol	evaporated until a solid mass obtained	60
Celecoxib	Urea	Methanol	evaporated at 40-45^0 C	61
Celecoxib	PVP K 30, crosscarmellose (superdisintegrant)	Methanol	By continuous trituration, mass obtained was further dried at 50^0C for 4 hrs in an oven	62
Chlorodiazepoxide	PVP K30	Ethanol	under reduced pressure at 60°C in a desiccator	63
Curcumin	PVP K 30	Ethanol	Under vacuum in a rotavapor at 65°C and 80rpm for 8h.	64
Diflunisal	Eudragit RS100 and RL100	Ethanol	Under vacuum in a rotary evaporator at 40'c	65
Felodipine	PVP K 30, PEG 4000	Ethanol	solutions were maintained at 40^0 C for 48 h	66
Felodipine	HPMC, poloxamer 188	Ethanol	Was removed by using rotary vacuum evaporator at45^0 C and at 45 rpm for 12 hrs	67
Fenofibrate	PEG 6000: poloxamer(1:1)	Chloroform	Removed using a rotary evaporator	68
Furosemide	PEG 6000 or PVP K30	Ethanol	evaporated under reduced pressure at 40°C, and the resulting residue was dried under vacuum for 3 h	69
Gliclazide	PVP K30	Methanol: acetone (1:1v/v)	removed by evaporation under reduced pressure at 37^0C	70
Glipizide	HPC	Ethanol	evaporated to get dried mass	71
Glipizide	PVP K30	Dichloroform	evaporated at 40'C under reduced pressure	72

			using vacuum evaporator	
Ibuprofen	Eudragit, HPMC	Methanol	Evaporated at 50-60'C for 72 hrs	73
Ketoconazol	PEG 4000, PEG 6000	Methanol	evaporated at 40-45°C with continuous stirring to obtain dry granules	74
KRN 633	PVP	Chloroform	evaporated rapidly by using a rotary evaporator at 60^0 C followed by vacuum drying at 50^0 C.	75
Lovastatin	Locust bean gum	Ethanol	evaporated under reduced pressure at 60°C to 70°C by Rota evaporator with solvent recovery	76
Meloxicam	HEC	N,N'dimethylformamide	evaporated at 50 °C for 30 min	77
Nabumetone	Ethyl cellulose	Methanol	evaporated at 40°C using a thermostatically regulated water bath for about 4 hours	78
Naproxen	β-cyclodextrin	Chloroform	Removed at 40^0 c under vacuum.	79
Nevirapine	PVP K 30	Ethanol : water(1:1)	Dried in oven at 45^0 C until dryness.	11
Nifedipine	PEG 4000	chloroform	Evaporated at 40^0 C under reduced pressure (8 mm Hg. Atm.).	27
Nimesulide	PEG 6000 and talc	Chloroform	The samples were dried at 40ºC for 1 h	29
Nimodipine	Ethyl vinyl acetate (EVA), Eudragit RL (EU RL) 100, and Ethyl Acetate (EC)	Acetone	evaporated to dryness by storing it in a desiccator under vacuum	80
Ofloxacin	PEG 4000 or PEG 20000	Chloroform	Evaporated at 40^0C under reduced pressure using a vacuum dryer	81
Oleanic acid	PVP K30	Ethanol	removed in a water bath at 60ºC.	82
Piroxicam	DMPC(phospholipids), PEG	Chloroform	Under current of N2 gas for a period of 6 hrs	83

Prednisone	PEG 6000	Ethanol	evaporated under reduced pressure and dried at 40^0 C until constant weight	84
Rofecoxib	PEG 4000, PEG 6000 and PVP	Chloroform	evaporated at 40-45^0 C with continuous stirring to obtain drug granules	85
Tacrolimus	PEG 6000, PVP, HPMC	DCM: ethanol(1:2)	evaporated under reduced pressure using a vacuum dryer at 40^0C	86
Telmisartan	PVP, PEG 4000	Methanol	Solution was heated until the solvent get evaporated	87
Terbinafine	PVP K 30	Methanol	Solvent was allowed to evaporate in hot air oven at 45'C±10'C	88
Valdecoxib	PEG 4000,PVP K 12	Acetone	solvent was completely evaporated at 40-45^0 C	31
Valsartan	Skimmed milk	Acetone	The mass was dried in Vacuum oven maintained at -1kg/cm^2 at room temperature.	2
Verapamil	Eudragit RLPO or kollidon SR	Acetone	Under vacuum in a rotary evaporator at 50'C	89
Zafirlukast	β-cyclodextrin	Acetone	Evaporated at room temperature.	90
Zaleplon	PEG 6000,PVP K 30	Methanol	Evaporated in vacuum evaporator	91

Table 9: Preparation of solid dispersion by melting method/fusion method:

Drug	**Carrier**	**Melting temperature**	**Reference**
Aceclofenac	Urea, mannitol	80^0 C-85^0 C	92
Albendazole	Poloxamer	63^0 C	93
Atorvastatin	PEG 4000, mannitol	60^0C	55
Cefdinir	PEG 4000	50-58^0C	58
Fenofibrate	PEG 6000, poloxamer 407	60^0C	68
Furosemide	PEG 6000	75^0C	69
Gliclazide	PEG 4000, PEG 6000	----	70
Ibuprofen	PEG 6000	50^0C-60^0C	73
Indomethacin	PEG 4000, gelucire	10^0C above the melting point of each carrier	94

Itraconazol	Euragit E 100	175^0C	95
Ketoconazol	PEG 4000, PEG 6000	80^0 C-85^0 C	74
Nifedipine	PEG 4000	Heated until it get melted	27
Nimodipine	PEG 4000, PVP K 30	10^0C above the melting point of each carrier	96
Paracetamol	PEG 4000, PEG 6000, urea	----	97
Praziquantel	PEG-60 castor oil hydrogenated (CR-60)	136-138^0C	98
Rofecoxib	Poloxamer 188	55^0C±0.5^0C	99
Simvastatin	PEG 4000, PEG 6000	70^0C	100
Tadalafil	Poloxamer 407	60^0C	101
Tenoxicam	Poloxamer 127	55 ºc ±5^0 C	102
Terbinafine	PEG 6000	60^0C	103
Valdecoxib	Mannitol,acetone	165^0C	104

16. Applications of solid dispersion in pharma industries:

The application of solid dispersions for increasing drug bioavailability is by no means a new field of pharmaceutical research. In their early paper on the use of solid dispersions, Chiou and Riegelman observed that, "It is believed that this relatively new field of pharmaceutical techniques and principles will play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms." Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. It is possible that such a technique be used:

- To obtain a homogeneous distribution of a small amount of drug in solid state
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.

- Polymorphs in a given system can be converted into is amorphous, solid solution, eutectic or molecular addition compound[5].

17. Challenging future for solid dispersion technique: Since solid dispersions were introduced in 1961, an immense amount of research has been done in this area. However, very few solid dispersion systems have been marketed[45]. Ritonavir capsules (Norvir, Abbott) has been withdrawn temporarily from the market because of crystallization[18]. Various issues that impeded the commercial development of solid dispersions include

(a) Inability to scale bench top formulations to manufacturing- sized batches,

(b) Difficulty to control physicochemical properties,

(c) Difficulty in delivering solid dispersion formulations as tablet or capsule dosage forms, and

(d) Physical and chemical instability of the drug and/or the formulation itself[25].

18. Exploring characterization tools: Currently, characterization tools of amorphous solid dispersions are poorly developed. Furthermore, a technique is needed to measure the distribution in solid dispersions, i.e. separate molecules, homogeneously distributed, amorphous clusters or crystalline particles. Such a technique should be non-invasive for the sample, maintaining the molecular structure during the measurement.

Conclusion: There are many drugs having poor aqueous solubility and as dissolution of drug is the rate determining step for oral absorption of such drugs, which can subsequently affect the in vivo absorption of drug. So to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those techniques. Many techniques that can be used for the formulation of solid dispersion have already been discussed in the article. Third generation solid dispersions are mainly effective as they use many type of surface active agents, they act as the plasticizers. Many dosage forms can be formulated by using the solid dispersion technology like tablets, capsules. Further research is also required for the better implementation of solid dispersion technology as this is an eminent technique for the solubility enhancement of poorly soluble drugs.

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