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Review Article

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Applications of solid dispersions

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ABSTRACT

The Solubility is an inherent property of any solid, liquid or gas. The solubility behaviour of drugs remains one of the most ambitious task in the formulation development. The solubility of drug dictates the ease with which pharmaceutical formulations can be obtained. Solid dispersion is an efficient mean of improving the drug solubility and from last many years it withstands with the objectives of producing improved dissolution rate and bioavailability of hydrophobic drugs. This review describes an overview of solid dispersions technology as a method of improving drug solubility which includes definitions of the various systems, preparation methods, various carriers and characterization methods of solid dispersions.

Key words: Solubility, Solid dispersions, Hydrophobic drugs, Bioavailability.

INTRODUCTION

Solubility of a substance is the amount, which passes into solution when equilibrium is established between the solution and excess (undissolved) substance. The transfer of molecules or ions from a solid state into solution is known as dissolution [1]. Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Formulation development would leads to be failure if drug having poor aqueous solubility [2]. Kapalan (1972) suggested that unless a compound has an aqueous solubility in excess of 1% (10 mg ml^{-1}) over the pH range 1-7 at 37º C, potential bioabsorption problems may occur [3]. If the intrinsic dissolution rate was greater than 1 mg $cm^{-3}min^{-1}$ then absorption was unimpeded thus the solubility of less than 1 mg ml^{-1} indicates the need for a change in drug modification either by physical or chemical process [1]. Consideration of the modified Noyes-Whitney equation provides [4] some hints as to how the dissolution rate of even very poorly water soluble compounds might be improved, to minimize the limitations to oral availability:

$$\frac{dc}{dt} = \frac{AD(C_s - C)}{h}$$

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, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound [5].

Solubilization Techniques [6]:

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are:

(I) Physical Modifications
A. Particle size reduction
(a) Micronization (b) Nanosuspension
B. Modification of the crystal habit
(a) Polymorphs (b) Pseudo polymorphs (including Solvates)

C. Drug dispersion in carriers
(a) Eutectic Mixtures (b) Solid dispersions (non-molecular)
(c) Solid solutions (d) Cryogenic techniques
D. Complexation: Use of complexing agents (Cyclodextrins)
E. Solubilization by surfactants
F. Nanotechnology approaches
(II) Chemical Modifications
(a) Soluble prodrugs (b) Change of pH
(c) Use of buffers (d) Salts
(III) Miscellaneous Methods
(a) Supercritical fluid Methods,
(b) Use of adjuvant, solubilizers, Surfactants, Cosolvency, Hydrotrophy and novel excipients.

Although salt formation, particle size reduction, etc. have commonly been used to increase dissolution rate of the drug, there are practical limitations with these techniques the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water- soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion [7]. The solid dispersion approach was first recognized in 1961; reduces the particle size, therefore increases the dissolution rate and absorption of drugs.

Chiou and Riegalman defined the term Solid Dispersion as "A dispersion involving the formulation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" [8].

Advantages of Solid Dispersion
❖Enhancement of the active agent bioavailability to a desirable extent.
❖Avoiding polymorphic changes and the consequent bioavailability problems.
❖Transformation of liquid or gaseous form of the drug in to solid form is possible.
❖Homogeneous distribution of small amount of drug at solid state is possible to attain [9].

CLASSIFICATION OF SOLID DISPERSIONS

Solid dispersions are classified by various ways viz. on the basis of carrier used and on the basis of their solid state structure as shown in **Figure 1** and **Figure 2** respectively.

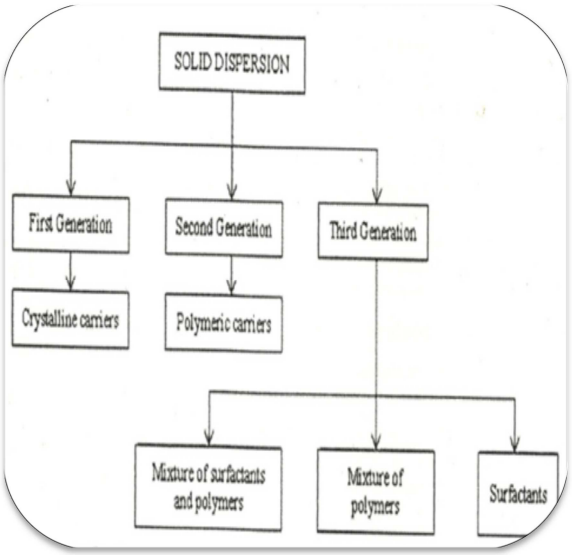

Figure 1: Classification of Solid Dispersion on the Basis of Carrier used

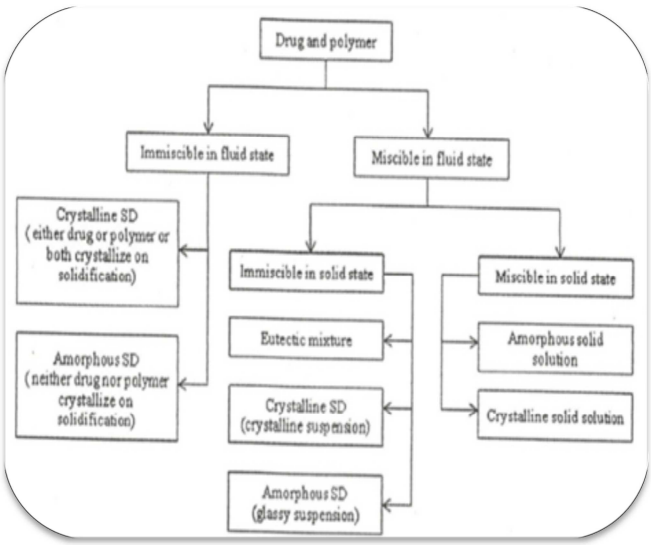

Figure 2: Classification of Solid Dispersion on the Basis of Miscibility of Drug and Polymers in Fluid and Solid State

(1) On the Basis of Carrier used:

(i). First generation: In First generation Solid dispersions crystalline carriers such as urea and sugar, used in the Solid dispersion preparation. These solid dispersions are thermodynamically more stable and did not release the drug as quickly as amorphous ones.

(ii). Second generation: In second generation amorphous carriers are used which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethylene glycols (PEG) and polymethacrylates, hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropoylcellulose or starch derivatives like cyclodextrins.

(iii). Third generation: Surfactants are introduced in the third generation. These carriers have surface activity and self-emulsifying properties. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers were shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability [10].

(2) On the Basis of Solid State Structure:

(i). Drug and polymer exhibiting immiscibility in fluid state: If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture. Such immiscible systems may be regarded as similar to their corresponding physical mixtures and any enhancement in dissolution performance may be because of modification in morphology of drug and/or polymer due to physical transformation (i.e., solid to liquid state and back), intimate drug-polymer mixing, and/or enhanced surface area. Formation of crystalline or amorphous Solid dispersions can be biased by the rate of solidification of mixture and the rate of crystallization of drug and/or polymer [11].

(ii) Drug and polymer exhibiting miscibility in fluid state: If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of Solid dispersion [11, 12].

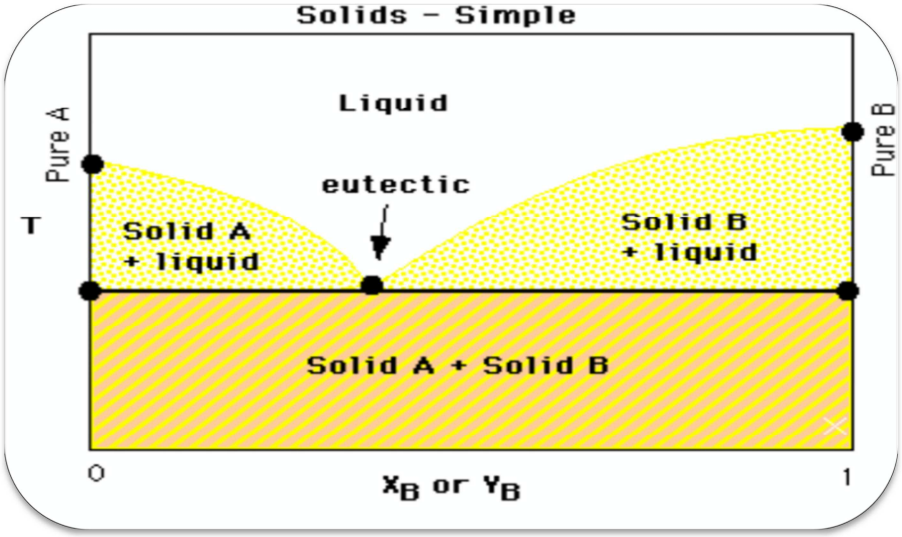

Figure 3 : Eutectic Mixtures

(a) Eutectic mixtures: The term eutectic comes from the greek ‘eutektos’, meaning “easily melted”. A eutectic mixture is defined as a mixture of two components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of one component. Eutectic mixtures can be formed between active pharmaceutical ingredients (API), between APIs and excipients or between excipients. Eutectic mixture formation is usually governed by following factors:

❖The components must be miscible in liquid state and mostly immiscible in solid state [13].

❖Intimate contact between eutectic forming materials is necessary for contact induced melting point depression [14].

❖The components should have chemical groups that can interact to form physical bonds such has intermolecular hydrogen bonding etc.

❖The molecules which are in accordance to modified Vant Hoff's equation can form eutectic mixtures [15].

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

(c) Amorphous Solid dispersion: If the drug-polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a "solidified-liquid" state. These types of dispersions have the risk of potential for conversion to a more stable and less soluble crystalline form [11].

(d) Solid solutions: "A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent". Since the two components crystallize together in a homogeneous one phase system, solid solution also called as molecular dispersions or mixed crystals or melts [16].

Solid Solution

According to the extent of miscibility of two components	According to molecular size of two molecular size of two molecules of solid solution
i) Continuous solid solution ii) Discontinuous solid solution	i) Substitution solid solution ii) Interstitial 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.

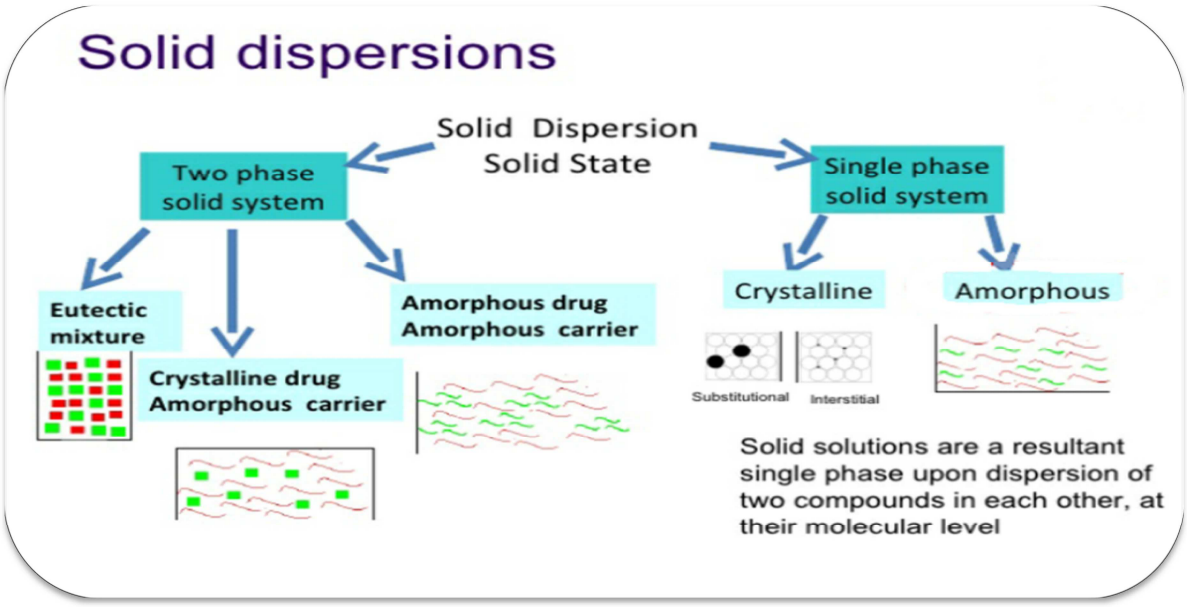

Figure 4: Schematic Diagram of Solid Dispersions Systems

❖**Discontinuous solid solutions:** In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram of discontinuous solid solution is shown in Figure 5 depicts the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. The mutual solubility's of the two components below a certain temperature start to decrease. Goldberg et al [17] suggested that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubility's of the two components but also on the dose of the drug component.

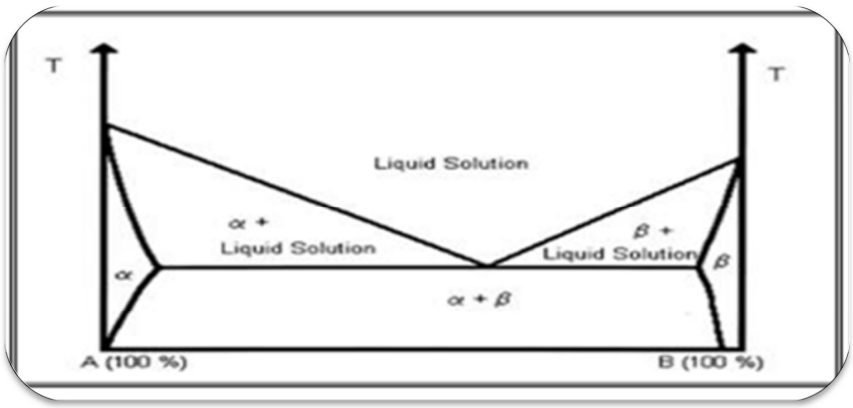

Figure 5: Phase Diagram for Discontinuous Solid Solution

❖**Substitutional crystalline solid solutions:** Classical solid solutions have a 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. A substitutional crystalline solid dispersion is shown in Figure 6 (a). Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [18].

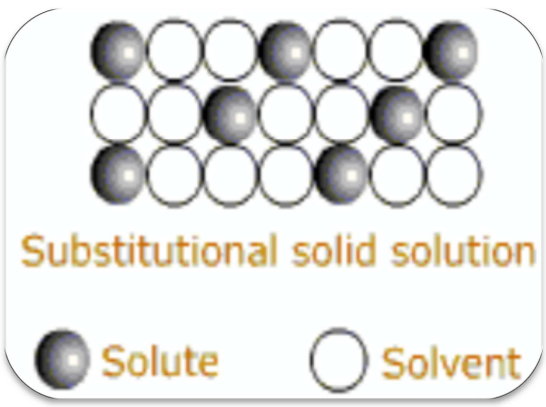

Figure 6:(a)

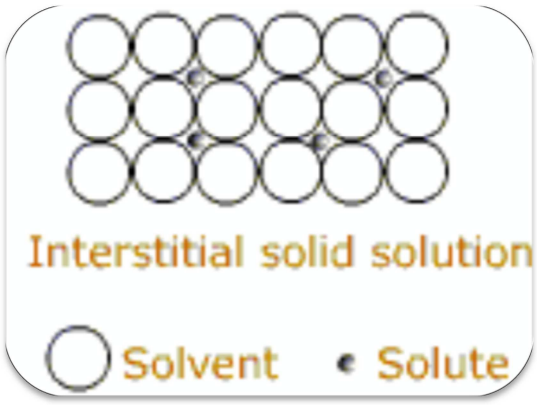

Figure 6: (b)

❖**Interstitial crystalline solid solutions:** In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice Figures 6(b). In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter [19]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

❖

❖**Amorphous solid solutions:** In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Chiou and Riegelman [8] were first to report the formation of an amorphous solid solution to improve a drug's dissolution properties using griseofulvin in citric acid. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

MECHANISM OF INCREASED DISSOLUTION RATE

The higher dissolution rates of Solid dispersions can be described to a number of factors which includes:

❖The formation of higher energy metastable states of the components as a function of the carrier system being used [20].
❖The reduction of particle size to nearly a molecular level [21]. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption [19].
❖Formation of amorphous forms of drug and carriers [22].
❖Carrier prevents aggregation of fine drug particles, thereby providing a larger surface area for dissolution.
❖Carrier with surfactant property reduces interfacial tension between the medium and the drug, hence higher dissolution rates [20].
❖Co-solvent effect on the drug by the water soluble carriers [22].
❖Intermolecular hydrogen bonds formation between drug and carrier [23].
❖Local solubilization effect of carrier at the diffusion layer [24].

Various other factors affecting dissolution of drug from Solid dispersion includes the method of preparation of the Solid dispersion, amount and properties of the polymer carriers, drug polymer contact and drug-polymer interactions.

PREPARATION METHODS OF SOLID DISPERSIONS

(i) Fusion method: Sekiguchi and Obi [16] (1961) prepared the first solid dispersion by the fusion method. In this method, the physical mixture of a drug and a water soluble carrier are heated directly just above its melting point and the drug is incorporated into the matrix. The melted mixture is then cooled and solidified rapidly on ice bath with vigorous stirring. The final solid mass is then crushed, pulverized and sieved which can be further compressed into tablets. In this procedure rapid congelling is desirable, because it results in supersaturation of the drug as a consequence of entrapment of soluble molecule in the solvent matrix by instantaneous solidification [25].

Advantages:
❖It is more convenient and economical method for drugs stable at temperature below 1000 ºC.
❖Technically it is an easier method if the drug and carrier are miscible in the molten state [8].
❖It precludes the use an organic solvent thereby circumventing the enigmas of its removal from the dispersion [10].
❖Dissolution for dispersions obtained by melting technique are much faster than those prepared using solvent techniques [26].

Disadvantages:
❖This method can be applied only when drug and matrix are compatible.
❖A problem can arise during cooling when the drug- matrix miscibility changes. In this case phase separations can occur [27].
❖Degradation of the drug and matrix can occurs during heating temperature necessary to fuse matrix and drug [27].
❖ Solidified melt may be tacky and unhandable [12].

(ii) Solvent-evaporation method: Tachibana and Nakamura were first used this method to prepare solid dispersion. This technique involves a solvent based technique. They use organic solvent to dissolve and intimately disperse the drug and the carrier molecule [28]. In the second step removal of solvents that finally results in product in a form of solid dispersion. The solvent is then evaporated directly on a water bath or hot plate or using a rotavapour. The resulting solid dispersion is stored in the desiccators under vacuum and pulverized to obtain the desired size fraction [12].

An important prerequisite for manufacture of a solid dispersion using the solvent method is that both the drug and carrier are sufficiently soluble in the solvent.

Advantages:
❖Thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents [5].

Disadvantages:
❖ To mix both drug and matrix in a common solvent this is difficult, when they differ significantly in polarity.
❖ High cost of preparation.
❖ Complete removal of solvent from the final product is a lengthy process.
❖ Phase separation can occur during drying process.
❖ Adverse effect of small amount of the solvent which is retained in the final product can affect the chemical stability of drug.

(iii) Solvent-melt method: To overcome the problems associated with fusion technique, a blend of fusion and solvent evaporation method has also been proposed. In this technique, the drug is dissolved in an organic solvent and mixed with the melted carrier. The solvent is then evaporated and the resultant product is pulverized to the desired size.

Advantages:
❖Possesses unique advantages of both the fusion and solvent evaporation methods
❖Useful for thermolabile drugs with high melting point [29].

Drawbacks:
❖Technique is limited to drugs with a low therapeutic dose (less than 50 mg).

(iv) Hot melt extrusion method: Hot melt extrusion process solid dispersions are prepared by using the twin screw hot melt extruder. The extruder consists of a hopper, barrel, a die, a kneading screw and heaters as shown in **Figure 7**. The physical mixture is introduced in to the hopper that is forwarded by feed screw and finally is extruded from the die. The effect of screw revolution speed and water content on preparation of solid dispersions should be investigated, since these parameters have profound impact on the quality of solid dispersions [12]. Hot melt extrusion process is same as the fusion method that the mixing of components is done by extruder.

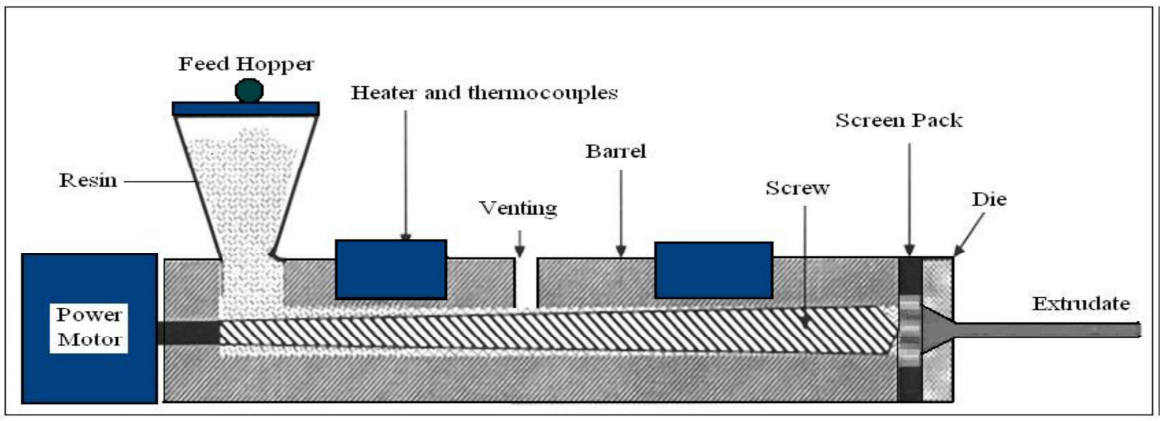

Figure 7: Schematic Diagram Showing Components of a Single Screw Melt Extruder

When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion have the benefit to shape the heated drug- matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Miscibility of drug and matrix can be a problem in this process. Due to high shear forces the high local temperatures in the extruder can be a problem for heat sensitive materials. This technique has the possibility of continuous production, which makes it suitable for large scale production. The product is easy to handle because at the outlet of the extruder shape can be adapted to the next processing step without grinding [27].

(v) Melt agglomeration process: In this method the binder acts as a carrier. This process consists heating the binder, drug and excipients to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipients by using a high shear mixer. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersions by melt agglomeration. It has been investigated that 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 homogeneous distribution of drugs in agglomerate [30].

(vi) Effervescent method: Effervescent solid dispersions includes sodium bicarbonate and organic acids (citric, tartaric or succinic), which react with each other to yield an effervescent mixture. By combining poorly soluble drugs with organic acids, an effervescent solid dispersion, which may increase the dissolution and absorption rates of poorly soluble drugs. Citric acid/sodium bicarbonate was found to be the most effective carrier for releasing prednisone and primidone and sodium bicarbonate/succinic acid was observed to be the best carrier for griseofulvin [31].

(vii) Adsorption on insoluble carriers: These dispersions are also referred to as surface solid dispersions. In this method, the support material is suspended in a solution of the drug followed by evaporation of the solvent. The resulting material contains the drug in a “molecularly micronized” state on the surface of the carrier. Here,

adsorbents maintain the concentration gradient (Cs-Ct), to its maximum, thus increasing the dissolution rate. A special technique under these methods is the fluidized bed system. It involves first preparation of spraying solution by dissolving both drug and carrier and then sugar spheres are charged to fluidized bed granulator and coated. These spheres are fluidized by spraying solution and the coated pellets are dried. Solid dispersion of poorly water-soluble drug nifedipine was prepared in hydroxypropylmethylcellulose (HPMC) on sugar spheres using this technique [32].

(viii) Co-grinding: In this method, accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill for grinding. Strong grinding force gives to solid increases in the activation energy on the surface and in the distortion of the crystal lattice together with communition. Boldyrev et al have termed this process as mechanical activation. Some drugs like griseofulvin lose their crystallinity when ground with microcrystalline cellulose in a vibrational ball mill with subsequent increase in dissolution rate and bioavailability [33].

SELECTION OF CARRIERS

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following prerequisites for increasing the dissolution rate of a drug [19].

- ❖Freely water soluble with rapid dissolution properties.
- ❖Nontoxic and pharmacologically inert.
- ❖Heat stable with a low melting point for the melt method.
- ❖Soluble in a variety of solvents.
- ❖Preferably enhancing the aqueous solubility of the drug.
- ❖Chemically compatible with the drug.
- ❖Forming only weakly bounded complex with the drug.

The various carries for Solid dispersion are enlisted in **Table 1 [**24]:

Table 1: Carriers Used in the Preparation of Solid Dispersion

Chemical Class	Examples
Acids	Citric Acid, Tartaric Acid, Succnic Acid
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymer Material	Polyvinyl Pyrrolidone, PEG 4000, PEG 6000, Sodium Alginate, Carboxy Methylcellulose, Guar Gum, Xantham Gum, Methylcellulose
Surfactant	Polyoxyethylene Stearate, Polaxamer, Deoxycholic Acid, Tweens And Spans, Gelucire 44/14, Vitamin E, TPGS NF
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxy Alkyl Xanthenes

Carriers Used in Solid dispersions:

- **Poloxamers:** The poloxamers are a group of surface active compounds widely used in the pharmaceutical industry. Poloxamers are described as block polymers of the type aba, consisting of a central, hydrophobic block of polypropylene oxide, which is edged by two hydrophilic blocks of polyethylene oxide. The polymers are derived from the sequential polymerization of propylene oxide and ethylene oxide. Due to the possibility to combine blocks of different molecular weights, the properties of the resulting polymers vary in a wide range. Generally, these are waxy, white granules of free-flowing nature and are practically odorless and tasteless. Aqueous solutions of pluronic in presence of acids, alkalis, and metal ions are very stable. The poloxamers are readily soluble in aqueous, polar and non-polar organic solvents and due to this fact they have established themselves as a preferred molecule in the formulation techniques [34, 35].
- **Polymers:** Polymers like polyethylene glycol (PEGs), Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Polyvinylpyrrollidone (PVP) etc. When used in optimum concentration will leads to increase in dissolution rate due to reduction in particle size, solubilization effect of the carriers, increase wettability, increase dispersibility, formation of hydrogen bonds between drug and carrier. When polymers are used in higher proportion these can decrease dissolution rate due to leaching out of the carrier during dissolution which might form a concentration layer of solution around the drug particles so the migration of the released drug particles to the bulk of the dissolution medium slows down [23].
- **Polyethylene glycol (PEG):** The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEG's are polymers of ethylene oxide, with a molecular weight (MW) falling in the range 200-3,00,000. For the manufacture of Solid dispersions and solutions, PEGs with molecular weights of 1500 - 20000 are usually employed. As the MW increases, so does the viscosity of the PEG. At the MW of up to 600 PEGs are fluid, in the range 800-1500 they have a consistency vaseline like, from 2000 to 6000 they are waxy and those with MW of 20,000 and above form hard, brittle crystals at room temperature. Their solubility in water is good, but decreases with MW. One of the advantages of PEGs is that they also have good solubility in many organic solvents. The melting point of PEGs lies under 65˚C in every case [36]. These relatively low melting points are

advantageous for the manufacture of Solid dispersions by the melting method. Additional features of the PEGs include their ability to solubilize some compounds and also to improve compounds wettability [20].

➢ **Polyvinyl pyrrolidone (PVP):** Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weight ranging from 2,500 to 3, 00,000. These can be classified according to the K value, which is calculated using fikentschers equation [37]. **Table** 2 provides an overview of the relationship between the K values and the approximate molecular weight of PVP. K value is dependent not only on its MW but also on the moisture content.

Table 2: K Values of PVP and the Corresponding Molecular Weights [37]

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

In general the glass transition temperature is high for PVP [38], for this reason PVP, has limited application for the preparation of Solid dispersions by the hot melt method. PVP has good solubility in a wide variety of organic solvents; they are particularly suitable for the preparation of Solid dispersion by the solvent method. Similarly to the PGs, PVPs also have good water solubility and can improve the wettability of the dispersed compound in many cases [39]. The chain length of the PVPs has a very significant influence on the dissolution rate of the dispersed drug from the Solid dispersion and the aqueous solubility of the PVPs becomes poorer with increasing chain length. Other disadvantage of the high MW PVPs is their much higher viscosity at a given concentration [38].

➢ Polyvinyl Alcohol (PVA), Polyvinylpyrolidone: Polyvinylacetate copolymer (PVPPVA): All three polymers belong to the polyvinyl group. PVA and vinylpyrrolidone/ vinyl acetate (PVP-PVA) copolymers are both water soluble, crosspovidone swells when dispersed in water [40]. The use of PVA/PVP copolymers as carriers in Solid dispersions has been shown to lead to enormous increases the drug release rate [41].

➢ **Cellulose derivatives**:

(i) Hydroxypropyl methylcellulose (HPMC): HPMCs are mixed ethers of celluloses in which 16.5-30% of the hydroxyl groups are methylated and 4-32% is derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10,000 to 1, 50,000. They are soluble in water, mixtures of ethanol with dichloromethane and methanol with dichloromethane [42].

(ii) HPC (Hydroxypropyl cellulose): It exhibits good solubility in a range of solvents, including water (up till 40ºC), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37000 (Type SSL) to 1, 50,000 (Type H) [37]. The release rate is improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier [43].

(iii) Carboxy methyl ethyl cellulose (CMEC): CMEC also belongs to the cellulose ethers, but unlike many of the others, it is resistant to dissolution under gastric (acidic) conditions, dissolves readily at pH values above 5-6 with lowest dissolution pH being dependant on the grade of the CMEC. CMEC also dissolves readily in acetone, isopropanol 70%, ethanol 60%, 1:1 mixtures of dichloromethane and ethanol [44].

(iv) Hydroxypropyl methylcellulose derivatives (HPMCP): HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5(HP 50) or pH 5.5 (HP 55). Their solubility in organic solvents is also type dependent. Their MWs varies from 20,000 to 2, 00, 000. Various studies demonstrated the potential advantage of using a gastric guide resistant polymer as carrier for poorly soluble drugs [45].

➢ **Polyacrylates and Polymethacrylates:** Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid. 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 ® [46]. Among the eudragit E is often used to improve the release rate since it is soluble in buffer solution at pH values up to 5 swells at higher pHs, while eudragit® L can be used when it is desirable to avoid release in the stomach [47].

➢ **Urea:** Urea is the end product of human protein metabolism has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 100, exhibits good solubility in many common organic solvents [16]. Although urea is not often used as a carrier these days, it has been shown that the dissolution rate of the poorly

soluble compound ofloxacin can be improved by more than threefold by incorporating it in coevaporate with urea [48].

➢ **Sugar, Polypols and their polymers:** Although sugars and related compounds are highly soluble and have very few, if any toxicity issues, but they are less suitable than other carriers for the manufacture of Solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic and their solubility in most organic solvents is poor, making it difficult to prepare coevaporates [49]. Mannitol which has a melting point of 165-168ºC and decomposes only above 250ºC can be employed to prepare dispersions by the hot melt method [50].

➢ **Emulsifiers:** The release behavior of many drugs can be improved by the use of emulsifying agents. There are two possible mechanisms by which emulsifying agent work: improvement of wetting characteristics and solubilization of the drug. Due to their potential toxicity problems; such as damage to mucosal surfaces, they are usually used in combination with another carrier [51]. Inclusion of alkali dodecylsulphate surfactants in carrier systems can lead to conversion of a Solid dispersion to a solid solution [52].
➢ Bile salts and their derivatives are natural surfactants that are built from a steroid skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophillic substances, leading to an increase in the dissolution rate [53].
➢ Organic acids and their derivatives-Organic acids such as succinic acid and citric acid have also been used as carriers in Solid dispersions; originally enhance the release rate of griseofulvin [17, 26].

CHARACTERIZATION OF SOLID DISPERSIONS

(A). Detection of crystallinity in solid dispersions: Characterization of polymorphic and solvated forms involves quantitative analysis of these different physico-chemical properties.

1. Thermal Analysis:

a) Thermo-Microscopic Methods:

This is a visual method of analysis using a polarized microscope with a hot stage to determine the thaw and melting points of solids. The method is advantageous as small amount of sample is required and direct observation of the changes taking place in the sample through the thaw and melt stages. The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems [54].

b) Differential Thermal Analysis (DTA):

This is an effective thermal method for studying the phase equilibrium of pure substance or solid mixture. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transition, evaporation, sublimation, desolvation and other types of changes such as decomposition of the sample can be detected. The method has been used routinely to identify different types of Solid dispersion [54]. The greatest advantage of using this technique is in constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution realest. A sample size of less than 1 mg can be used [8].

c) Differential Scanning Calorimetry (DSC):

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. For characterizing crystal forms, the heat of fusion, ΔH_f, can be obtained from area-under-the-DSC-curve for the melting endotherm. Lack of a melting peak in the DSC of a Solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinity of fewer than 2% cannot generally be detected with DSC [55].

2. X-Ray Diffraction (XRD):

The diffraction method is very important and efficient tool in studying the physical nature of Solid dispersion which has been used in crystal structure studies in two different ways. Sharper diffraction peaks indicate more crystalline material.

- Random orientation of a crystal lattice in a powder sample causes the x-rays to scatter in a reproducible pattern of peak intensities at distinct angles (θ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound.
- An amorphous form does not produce a pattern.
- Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances.

The relationship between wavelength, of the x-ray, the angle of diffraction, θ, and the distance between each set of atomic planes of crystal lattice, d, is given by equation: $M \lambda=2d \sin \theta$, where M represent the order of diffraction [8,54].

3. FT-IR Spectroscopy:

FT-IR spectroscopy used to study the possibility of an interaction between drug and polymer in solid state. Structural changes and lack of crystal structure can lead to changes in bonding between functional group which can be detected by infrared spectroscopy [55, 56]. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix [57]. Sharp vibrational bands indicate crystallinity [58]. Fourier Transformed Infrared spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material [59].

4. Dissolution Rate Determination:

The method involves comparing the *in vitro* dissolution rates of the solute component from constant-surface tablet made from molecular dispersion (i.e., solid or glass solution) with a physical mixture of the same chemical composition [8]. It shows that the Solid dispersion has improved the dissolution rate or not. The degree of crystallinity can also be studied if it is carried out under standard conditions. Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample [59]. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

5. Scanning Electron Microscopy (SEM):

It usually gives primary information of system and hints about the amorphous or crystalline nature of Solid dispersions. The application of the electron microscope technique, however, usually limited to chemicals with high resolution.

6. Thermodynamic Methods:

In this analysis, the phase diagrams of eutectic and solid solution systems give the value of heats of fusion, entropies and partial pressures at various compositions that helps to determine the solubility gap below the solid-liquid equilibrium temperature [8].

7. Water Vapour Sorption Method:

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [60]. This method requires accurate date on the hygroscopicity of both completely crystalline and completely amorphous samples.

8. Isothermal Microcalorimetry Measurement:

Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (T_g) [61]. However, this technique has some limitations'. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

9. Macroscopic Techniques:

Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the activity of these properties in intimately mixed binary solids [27].

(B) Detection of Molecular Structure in Amorphous Solid Dispersions: The properties of a Solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behavior could be different for Solid dispersions that do not contain any crystalline drug particles. Nevertheless, only very few studies focus on the discrimination between amorphous incorporated particles versus molecular distribution or homogeneous mixtures.

1. Confocal Raman Spectroscopy:
It is used to measure the homogeneity of the solid mixture of ibuprofen in PVP [62]. It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2-3 μm, uncertainty remains about the presence of nano-sized amorphous drug particles.

2. Using IR or FTIR:
The extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements [63, 64].

3. Temperature Modulated Differential Scanning Calorimetry (TMDSC):
It is used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the T_g is a function of the composition of the homogeneously mixed Solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC [65]. Therefore this technique can be used to assess the amount of molecularly dispersed drug [66], and from that the fraction of drug that is dispersed as separate molecules is calculated [67].

PHARMACEUTICAL APPLICATIONS OF SOLID DISPERSION

The pharmaceutical applications of Solid dispersions technique are:
❖To enhance the absorption of drug.
❖To obtain a homogeneous distribution of a small amount of drug in solid state.
❖To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
❖To dispense liquid or gaseous compounds.
❖To formulate a fast release priming dose in a sustained release dosage form.
❖To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.
❖To reduce side effects (a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound.
❖To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered by the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension.
❖To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations [68].

Some examples of Solid dispersions in Market:
➢ Sporanox® (itraconazole)
➢ Intelence® (etravirine)
➢ Prograf® (tacrolimus)
➢ Crestor® (rosuvastatin)
➢ Gris-PEG® (griseofulvin)
❖Cesamet® (nabilone)

CONCLUSION

Years of research and development had made the solid dispersion technology an important aspect of pharma industry. The increasing role of solid dispersions in pharmaceutical development is because of growing number of poorly water soluble drugs and improvement in the manufacturing techniques. Hot melt extrusion is particularly important breakthrough for scale-up of solid dispersion manufacture. Now days this technology is also used for the development of fast dissolving tablets and orally disintegrating tablets. Although there are some obstacles in manufacturing commercial applications of solid dispersions in dosage form design but there lies a great future that solid dispersion technology will expedite drug release profile of poorly water soluble drugs.

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