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Solid Dispersions An Advancement in Solubility Improvement; Strategy, Mechanism and Characterization

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ABSTRACT

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system**.** Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. This is true for parenterally, topically and orally administered solutions. The solubility of drugs is defined according to (bio-pharmaceutical classification system) BCS classification system which divides drugs to different class according to its solubility. Solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier or matrix known as solid dispersion. Solid dispersion reduces the particle size and changes the micro environment of the drug particle, increases the rate of dissolution and absorption and thus changes the biopharmaceutical properties of poorly water soluble drugs. The solid dispersion method, by which a drug is dispersed in a carrier to make it amorphous, is one of the pharmaceutical approaches most commonly employed to enhance bioavailability of poorly water soluble drugs. Various pharmaceutical approaches for the preparation of SDs, including co-precipitation, lyophilization, spray drying, solvent evaporation, fusion and powder mixing methods, have been reported. It's a new and efficient technique to improve the solubility of poorly soluble drugs.

Keywords: Solubility enhancement, dissolution enhancement, carriers, mechanisms, characterization.

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INTRODUCTION

Solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion [1] Solubilization may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphiphilic components. The mechanism of solubilization involves the property of surface active agents to form colloidal aggregates known as "micelles". For a drug to enter the systemic circulation to exert a therapeutic effect, it must be in solution. Relatively insoluble compounds often exhibit incomplete or erratic absorption. Recent technologies innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility. The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. If exact solubilities are not known, the Pharmacopoeia provides general terms to describe a given range [4] (Table-1).

Table 1: Solubility Expression

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
very Slightly soluble	From 1000-10000
Insoluble or practically insoluble	More than 10000

TECHNIQUES/APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS:

The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes (Figure 1).

Now a days Solid dispersion technique was successfully applied for low dose water-insoluble drugs. However, formulation of the high dose insoluble-drugs as liquisolid tablets is one of the limitations of the liquisolid technique. In fact, when the therapeutic dose of drug is more than 50 mg, dissolution enhancement in the presence of low levels of hydrophilic carrier and coating material is not significant. But by adding some materials such as polyvinyl pyrrolidone (PVP) to liquid medication (microsystems), it would be possible to produce dry powder formulations containing liquid with high concentration of drug. By adding such materials to the liquid

medication, low amount of carrier is required to obtain dry powder with free flowability and good compatibility [2,3].

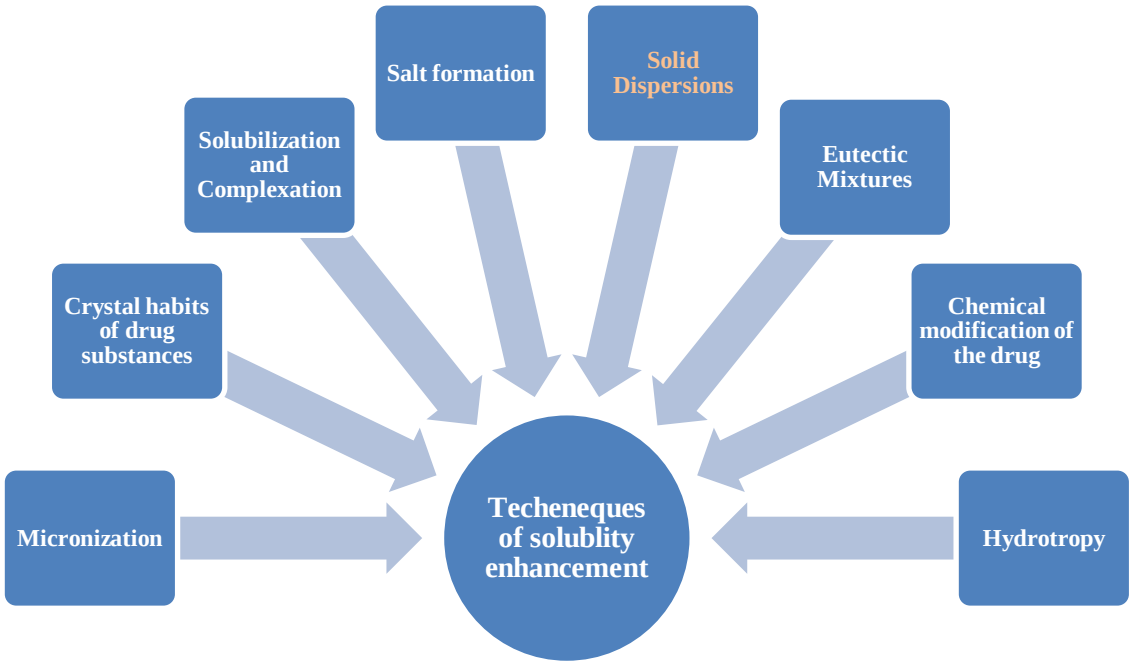

Figure 1: Techniques/Approaches for solubility enhancement

Solubility enhancement of poorly water-soluble drugs by Solid Dispersions:

Solid dispersion (SD) is defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion method, solvent evaporation method and fusion-solvent method. SD reduces the particle size and changes the micro environment of the drug particle, increases the rate of dissolution and absorption and thus changes the biopharmaceutical properties of poorly water soluble drugs. The solid dispersion method, by which a drug is dispersed in a carrier to make it amorphous, is one of the pharmaceutical approaches most commonly employed to enhance bioavailability of poorly water soluble drugs. Various pharmaceutical approaches for the preparation of SDs, including co-precipitation, lyophilization, spray drying, solvent evaporation, fusion and powder mixing methods, have been reported (Figure 2). The enhanced dissolution rate of drugs from solid dispersions is mainly based on four different mechanisms:

- Wetting of the drug is improved by direct contact of the drug with the hydrophilic matrix.
- The saturation concentration around small particles is higher than around large particles.
- The surface area is increased.
- The drug has higher energy in the amorphous state than in the crystalline state, through which the saturation concentration is increased.

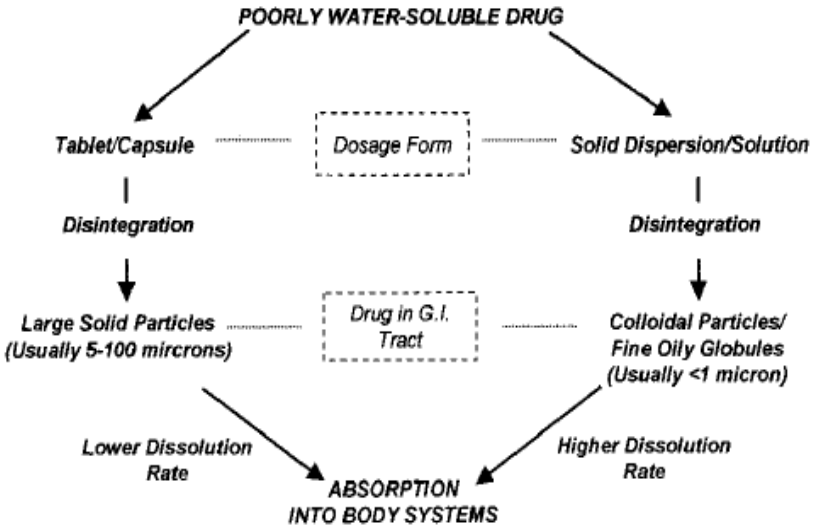

Figure 2: A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

Table 2: Classification of Solid Dispersions

Type of Solid Dispersion	Matrix*	Drug**	Remarks	Ref.
Eutectics	C	C	The first type of solid dispersions prepared	[5]
Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	[6,7]
Solid solutions				
Continuous solid solutions	C	M	Miscible at all compositions, never prepared	[8]
Discontinuous Solid solutions	C	M	Partially miscible	[9]
Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitution. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	[10,11]
Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	[5,12]
Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	[5,13]
Glass Suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate much solid dispersion is of this type.	[5,13]
Glass solution	A	M	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP.	[14]

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

- An important mechanism is the reduction of the drugs particle size to the micro-crystalline or molecular level for rapid dissolution and absorption.

Classification of Solid Dispersions: given in Table 2.

Disadvantages of Solid Dispersions

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization [15,16,17].

Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate [18]. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during *in-vivo* performance. Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

Pharmaceutical applications of Solid Dispersion:

The pharmaceutical applications of solid dispersions technique are numerous. They may be employed-

1. To enhance the absorption of drug;
2. To obtain a homogeneous distribution of a small amount of drug in solid state;
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.;
4. To dispense liquid or gaseous compounds;
5. To formulate a fast release priming dose in a sustained release dosage form;
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier;
7. 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;
8. To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension;

9. To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g., unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc.

MECHANISMS OF ENHANCED DISSOLUTION IN SOLID DISPERSIONS

Solid dispersions have attracted considerable interest as a mean of improving the dissolution rate, hence possibly bioavailability of a range of hydrophobic drugs. The increase in dissolution rate for solid dispersion can be attributed to a number of factors. These include the following –

Reduced particle size or reduced agglomeration

These may be usefully considered together as both are related to increases in the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area [19].

Increased solubility or dissolution rate of the drug

Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in vitro experiments the carriers often elicit minimal solubility increases. There appear to be two sets of observations with regard to the mechanism of drug release from solid dispersions. In the first instance, some systems appear to show carrier-controlled release whereby, at least at low drug loadings, the rate of release is controlled by that of the carrier and is independent of drug properties. Secondly some systems show release behaviour that is dependent on the properties of the drug rather the polymer, even at low drug loadings [19].

Transferring the drug from crystalline to (partially) amorphous state/ formation of high energy states

Amorphous drugs represent the higher energy states and can be considered as cooled liquids. They have greater aqueous solubility than crystalline forms because the energy required to transfer a molecule from crystal is greater than required for non-crystalline (amorphous) solid, for example, the amorphous state of novobiocin is 10 times more soluble than crystalline form. chloramphenicol palmitate, cortisone acetate and phenobarbital are other examples where the amorphous forms exhibit higher water solubility [20].

Wetting

When a strong affinity exists between a liquid and a solid, the liquid may form a film over the surface of the solid. When this affinity is non-existent or weak, however, the liquid has difficulty displacing the air or other substances surrounding the solid, and there exists an angle of contact between the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions, specially, those acting at the interfaces between the liquid and the vapor phases, at the solid and liquid phases, and at the solid and vapor phases. The contact angle concept is important because it affords a method of considering degree of wetting and indicates that surface properties are important [21].

Soluble complex formation in microenvironment

Organic compounds in solutions generally tend to associate with each other to some extent. Frequently, this association is too weak to be detected by standard techniques. In other cases, the intermolecular associations or complex can be readily observed and quantitated by one or more of numerous published techniques. One of more widely used methods, and one that is highly relevant is the solubility analysis technique. Every substance has specific, reproducible equilibrium solubility in given solvent at a given temperature [21].

Saturation of drug in microenvironment

Another mechanism, creation of microenvironment, by hydrophilic carrier has also been reported as mean of solubility enhancement, where in a microenvironment is created where the solubility of the drug particles is increased due to high concentration of hydrophilic carrier in surrounding solution [22].

Solubilization of the hydrophobic drug in presence of the surfactant

Solubilization is thought to occur by virtue of the soluble dissolving in or being adsorbed onto micelle. Thus, the ability of surfactant solutions to dissolve or solubilize water-insoluble materials starts at the critical micelle concentration and increases with the concentration of the micelles. Cholesterol was markedly more soluble in aqueous soap solution than in pure water. Solubilization of prednisolone, methyl-prednisolone and flourometholone, nifedipine was reported as function of surfactant concentration. This resulted in enhanced solubility of hydrophobic drug [16].

METHOD OF PREPARATION

Various preparation methods for solid dispersions have been reported in literature. Some laboratory and industrially feasible methods are summarized here:

Fusion method

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product [9]. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, therefore reducing the process temperature. To cool and solidify the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught, solidification on petri dishes at room temperature, inside a dessicator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a dessicator were used. After cooling, the mixture must be pulverized regarding its handling [23,24,25]. However, the use of high temperatures, and the fact that several drugs can be degraded by the melting process, can be a limitation of this method. The incomplete miscibility between drug and carrier that may occur, because of the high viscosity of a polymeric carrier in the molten state, is another limitation of this process [26,27,28]. To avoid the melting method limitations, several modifications, like hot-stage extrusion, Meltrex TM or melt agglomeration were introduced to the original method.

Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. Second step involves removal of solvent resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties [29,30]. With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermo-labile substances. Likewise, many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities. As a result, for many years the solvent method was the method of choice for polymer-based systems. Using the solvent method, the pharmaceutical engineer faces many challenges. The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Identification of a common solvent for both drug and carrier can be problematic and complete solvent removal from the product can be a lengthy process. Moreover subtle alterations in the concentrations used for solvent evaporation may lead to large changes in the product performance. In addition large volumes of solvents are generally required

which can give rise to toxicological problems.

With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the preparation of solid dispersions. Many investigators studied solid dispersion of felodipine [30,31] meloxicam [32] and nimesulide [33] using solvent evaporation technique.

Hot melt extrusion

Hot melt extrusion (HME) also offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, more possibility of the formation of solid dispersions and improved bioavailability [34]. Hot-stage extrusion (HME) consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled [35,36,37]. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer which broadens the application of hot-stage extrusion to thermally labile compounds. Solid dispersions of itraconazole/PVP [38] were successfully prepared by this technique. An amorphous solid dispersion of itraconazole with HPMC was formed from milled melt extrudate and resulted in a significantly increased dissolution rate compared with the physical mixture; the formulation was found chemically and physically stable for periods in excess of 6 months [39]. The tablets formed by compressing milled melt-extruded glassy powder with additional excipients showed high oral bioavailability [40].

Electrostatic spinning method

In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. Electrospun samples dissolved dependent on the type of formulation and the drug: polymer ratio. The technique has been successfully used in the pharmaceutical industry for the preparation of solid dispersions [41]. Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and non-biodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct

incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared by using this technique [42,43].

Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule-filling machine [44,45]. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (eg, polysorbate 80 with PEG, phosphatidylcholine with PEG [46]. The temperature of the molten solution should not exceed above 70 °C because it might compromise the hard-gelatin capsule shell.

Supercritical fluid (SCF) process

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power [47,48]. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000 nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement [49]. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed anti-solvents process (PCA), solution enhanced-dispersion by SCF (SEDS), supercritical anti-solvents processes (SAS) and aerosol supercritical extraction system (ASES) [50,51].

It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. SCF technology offers tremendous potential, as it is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.

Lyophillization technique

Lyophillization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion [52]. This technique was proposed as an alternative technique to solvent evaporation. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified [53] have successfully investigated the potential applications of lyophilization technique using glyburide, ketoprofen, meloxicam, amylobarbitone in solid dispersion manufacturing. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration [54].

Spray drying

Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications [55,56]. The spray drying technique is a useful method to obtain spherical particle and narrow distribution. The role of porous materials such as calcium silicate, controlled pore glass and porous cellulose is appreciated to formulate solid dosages forms because they confer special characteristics such as decrease of melting point and a decrease in the crystallinity of drug entrapped in pores. In addition, porous material controls polymorphs and stabilizes meta-stable crystals in solid

dispersions under sever storage conditions. Moreover, porous silica has been reported to improve solubility and dissolution rates of indomethacin and tolbutamide [57,58]. The frequent use of the organic solvent in spray drying pose problems such as residues in products, environmental pollution and operational safety as well as corporate problems such as capital investment. Solid dispersion of loperamide and PEG 6000 were prepared by this technique. The prepared SD (s) exhibited higher dissolution rates than that of pure crystalline loperamide [16] studied the suitability of this technique for preparation of SD(s) of glibenclamide with polyglycolized glycerides. This study revealed the improvement in solubility, dissolution rates and in therapeutics efficacy of glibenclamide in SD(s).

Selection of carriers for Solid Dispersions:

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suit for increasing the dissolution rate of a drug: be freely water-soluble with intrinsic rapid dissolution properties; be nontoxic and pharmacologically inert; be heat stable with a low melting point for the melt method; be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method, preferably increase the aqueous solubility of the drug and be chemically compatible with the drug and not form a strongly bonded complex with the drug. Following are the few examples of commonly used pharmaceutical carriers for solid dispersions PEG, sorbitol, mannitol, glycolate, HPMC, HPMC pthlate, sodium starch glycolate, polyvinyl alcohol, cyclodextrins [59].

CHARACTERIZATION OF SOLID DISPERSIONS

Many methods are available which provides an insight into the physical nature of a solid dispersion system and the nature of interaction between the components. Characterization requires pooling of data from several methods of study to finally arrive at conclusion regarding the nature of the solid dispersion.

Thin layer chromatography

Drug-excipient interactions can be studied by thin layer chromatography. When excipients are present it is advisable to set a mixture of the excipients at the same conditions as the drug-excipient mixtures. This will give chromatograms of both systems. If any degradation products are present, the source may be determined more easily [60].

Spectroscopic methods

In the UV studies the spectra of the pure and the dispersed drugs are scanned. Assay of the solid

dispersion and calculation of molar extinction provides evidence of any decomposition of the drug. Hypsochromic or bathochromic shift or increase or decrease in the absorptivity without change in λmax has been considered as evidence for interaction between β–cyclodextrin and drug in the formation of complexes[60].

The Phase solubility analysis

The solubility studies are performed according to a methods described by Higuchi and Connors. An excess quantity of the drug is added to the simulated gastric fluid placed in glass vials, tightly closed and shaken at room temperature up to 24-72 hrs using rotary shaker. After attainment of equilibrium, the contents of each vial are filtered through a 0.45 µm filter and then assayed for the drug content at appropriable wavelength [61].

Microscopic methods

Particle size and morphology of solid dispersions can be observed by microscopy. Scanning electron microscopy can be used for this purpose, wherein, the samples are coated with gold and palladium using a vacuum evaporator and are examined at accelerating voltage with a suitable magnification. This method has been used to study the Naproxen-chitosan systems, Glibenclamide-polyglycolized Glycerides, Naproxen-PVP etc [51].

Thermal analysis

This technique is useful in investigation of solid-state interaction between two or more component systems. It is based on the principle of change of thermal energy as a function of temperature and may be carried out in any of the following ways,

Cooling curve methods

The physical mixtures of various compositions are heated to produce a homogeneous melt. The temperature of each mixture during the cooling process is recorded as a function of time and from a series of temperature - time curves, the phase diagram is established. The method is time consuming, requires relatively large amount of sample and changes in slopes can be missed especially if cooling takes place rapidly. The method cannot be applied to samples that decompose after melting.

Thaw melts methods

A sample of solid dispersion is heated gradually in a capillary tube and the thaw and melting points are noted by visual observation. The principal drawback of this method is that it depends on a subjective observation, and is, therefore, not highly reproducible.

Thermo microscopic methods

This is a simple method in which hot stage microscope is used to study the phase diagrams of

binary systems. The physical mixture or dispersion (approx. 1 mg) on a slide is heated at the rate of 1-5 °C per minute. The thaw and melting points are then recorded by visual observation. This method requires only a small amount of sample but it is limited to thermally stable compounds only. This technique has been used to characterize diflunisal–PEG solid dispersion.

Differential thermal analysis (DTA) and differential scanning calorimetry

Differential scanning calorimetry (DSC) has become the most widely used thermal analysis technique. In this technique, the sample and reference materials are subjected to a precisely programmed change. When a thermal transition (a chemical or physical change that results in the emission or absorption of heat) occurs in the sample, thermal energy is added to either the sample or the reference containers in order to maintain both the sample and reference at the same temperature. Because the energy transferred is exactly equivalent in magnitude to the energy adsorbed or evolved in the transition, the balancing energy yields a direct calorimetric measurement of the transition energy.

In differential thermal analysis (DTA), the difference in temperature between the sample and a thermally inert reference material is measured as a function of temperature (usually the sample temperature). Any transition that the sample undergoes results in liberation or absorption of energy by the sample with a corresponding deviation of its temperature from that of the reference. A plot of the differential temperature versus the programmed temperature indicates the transition temperature and whether the transition temperature is exothermic or endothermic [62].

Zone melting method

In this method, a molten zone affected by a heater, traverses a cylindrical ingot or solidified melt at a rate of about 0.5 - 0.001 cm per hour. A mechanical stirring device is also required for the mixing of the liquid in the molten zone. After zone melting is completed, the bar is sectioned and analysed for its chemical composition. A phase diagram is then constructed from the chemical compositions and freezing temperatures of the corresponding sections. The method is limited to compounds with high thermal stability and low volatility.

Powder X-ray diffraction

As a consequence of the importance of solid drug substance characterization, analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical field. The detection of crystalline phases in mixed systems can be analyzed by powder X-ray diffraction. However, too much Crystallinity causes brittleness. The Crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak. The ratio between these intensities can be used to calculate the amount of Crystallinity in the material[63,64].

Dissolution studies

The dissolution rate method was proposed by Alien and Kwan to study the degree of Crystallinity in solid – solid equilibrium. The method involves comparing the *in-vitro* dissolution rates of the solute component from a constant surface tablet prepared from a solid dispersion, with a physical mixture of the same chemical composition. The method has been shown to be applicable to Indomethacin - PEG 6000 and sulphathiazole - urea systems.

CONCLUSION:

A lot of research has been carried out in this area and for better clinical efficiency, some improvements in solubility and dissolution rate has to be made generally. By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. But solid dispersion techniques play a good role in improving solubility and stability of the drugs.

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