Review Article

SOLID DISPERSION: STRATEGY TO ENHANCE SOLUBILITY

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ABSTRACT

The solubility behavior of drugs remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has dramatically increased. Although solid solutions have tremendous potential for improving drug solubility. This article reviews the various preparation techniques for solid dispersion and gives some of the recent technology transfers. Some of the important practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization. New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. In this review, it is intended to discuss the recent advances related on the area of solid dispersions. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. The focus of this review article on the method of preparation, carrier used, characterization, advantages, disadvantages and the application of the solid dispersion.

Keywords: Solid solutions, solubility, solid dispersions, carrier, bioavailability.

1. INTRODUCTION

Oral drug delivery is the most popular, simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms[1]. More than 90% of drugs have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble[2]. After administering a drug orally, it firstly dissolves in gastric and or intestinal fluids before it, and then permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs[3]. Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption in vivo will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs[4]. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

Modified Noyes-Whitney equation[5,6] gives some idea how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$dC / dt = AD (Cs - C) / h$$

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.

Surface area directly proportional to rate of dissolution, it is increased by decreasing the particle size of drug or by optimizing wetting characteristics. Particle size reduction, salt formation, complexation and solubilization of drug in solvent(s) also useful to increase dissolution, however, there are limitations for this techniques. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media[7]. Solid dispersion offers a various preparation method and carrier option that allow the flexibility when formulating oral delivery system for poorly water soluble drugs.

2. SOLID DISPERSION

Solid dispersion, a concept firstly introduced by Sekiguchi and Obi[8]. The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion solvent-method. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[9].

2.1. Types of solid dispersion

2.1.1. Eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution[8, 11].

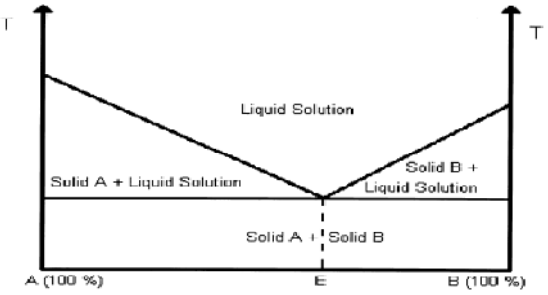

Figure 1: Phase diagram for a eutectic system[12].

2.1.2. Amorphous precipitation in crystalline matrix

This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form[13].

2.1.3. Solid solution

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions[14] and the dissolution rate is determined by the dissolution rate of the carrier. Classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

2.1.3.1. Continuous solid solutions

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

2.1.3.2. Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by Goldberg et al.[14] that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

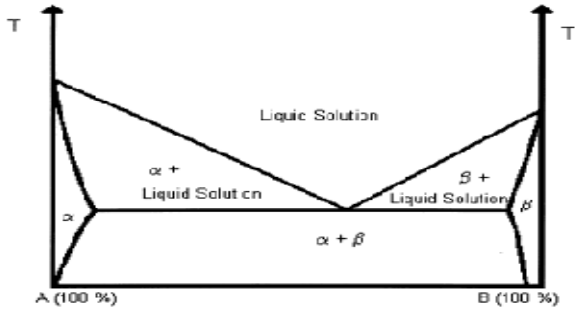

Figure 2: Phase diagram for a discontinuous solid solution[12].

2.1.3.3. Substitutional solid solutions:

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

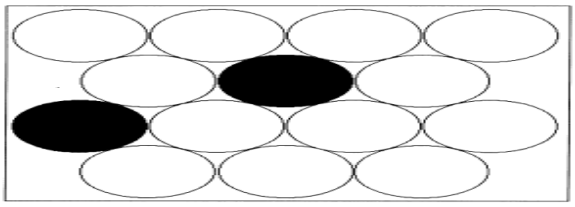

Figure 3: Substitutional crystalline solid solution[9].

2.1.3.4. Interstitial solid solutions:

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter[16].

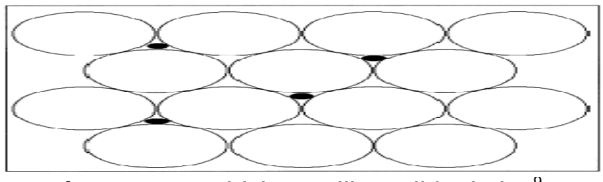

Figure 4: Interstitial crystalline solid solution[9].

2.1.4. Glass solution and suspensions:

Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solution and suspension[13].

3. METHODS OF SOLID DISPERSION PREPARATION

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions[17-20].

3.1. Melting method

Sekiguchi et al.[8] 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. In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation[21]. 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[22].

3.1.1. Hot stage extrusion

Hot stage extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. The hot stage extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the molten state. Hot-stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. Extrusion then collected after cooling at room temperature and milled[23,20,24]. Moreover, it was observed that solid dispersions of itraconazole/Intec SP1 prepared by hot-stage extrusion presented itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying[20].

3.1.2. Melt agglomeration

Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excepients[25]. It is prepare by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier[26]. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor[17].

3.2. Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated[27-29]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature[19]. A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled[28,30].

3.2.1. Spray-drying

Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving[20, 31, 32] or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent[20, 31]. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Van Drooge et al.[33] prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

3.2.2. Freeze-drying

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized[33,21]. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices[34], the technique is poorly exploited for the preparation of solid dispersions[35]. 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.

3.2.3. Supercritical fluid method

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent[36,37]. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel[19]. The use of processes using SCF reduces particle size, residual solvent content, without any degradation and often results in high yield[38, 17, 39].

3.2.4. Co-precipitation method

Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method non-solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried[40]. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator (37^0c) for 12 hrs. Finally it was passed through sieves[41].

3.2.5. Dropping method

This technique may overcome some of the difficulties inherent in the other method and developed by Ulrich et al.[12] to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions A solid dispersion of a melted drug carrier mixture is pipetted and then dropped onto a

plate, where it 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. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. This method also avoids the pulverization, sifting and compressibility difficulties[42].

4. CARRIERS USED IN SOLID DISPERSION

4.1. Polyethylene glycol (PEG)

4.1.1. General characteristics of PEGs: Polyethylene glycols (PEG) are polymers of ethylene oxide, having a molecular weight (MW) in the range 200- 300000. 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. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65^{0}C in every case (e.g. the m.p. of PEG 1000 is 30-40^{0}C, the m.p. of PEG 4000 is 50-58^{0}C and the m.p. of PEG 20000 is 60-63^{0}C)[43]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Dissolution rate of a relatively soluble drug like aspirin can be improved by formulating a solid dispersion in PEG 6000[44].

4.1.2. Influence of the PEG chain length: PEGs of MW 4000-6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50^{0}C. If PEG with low a MW is used, the product changes it's consistency and gives a sticky consistency that is difficult to formulate product[45]. PEGs with higher MW have also been used with success, products containing PEG 8000[46] and 10000[47] showed enhanced dissolution rates compared to the pure drug. Phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW[48].

4.1.3. Influence of drug/PEG ratio: If the percentage of the drug is too high, it will form small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug[49]

4.2. Polyvinylpyrrolidone (PVP)

4.2.1. General characteristics of PVP: Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000000. These can be classified according to the K value, which is calculated using Fikentscher's equation[50]. The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (Tg) is high; for example, PVP K25 has a Tg of 155^{0}C[51]. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. PVP is suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid[52].

4.2.2. Influence of the PVP chain length: 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[50].

4.2.3. Drug/PVP ratio: Solid dispersion prepared with high proportions of PVP tend to exhibit a higher drug solubility and release rate than those with high proportions of drug. For albendazole, for example, it has been shown that an increase in the %PVP in the dispersion leads to an increase in the release rate[53]. When the carrier comprised 81% of the dispersion, no crystalline areas could be detected and the release rate of the compound was rapid. Interestingly, when the %carrier was further increased, the release rate became slower. In the case of piroxicam/PVP solid dispersions[54], the release rate increased with the %PVP up till a ratio of drug/carrier of 1:4, after which it fell again (at ratios of 1:5 and 1:6).

4.3. Polyvinylalcohol (PVA), crospovidone (PVP-CL), polvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA):

These three polymers belong to the polyvinyl group. Whereas polyvinylalcohol (PVA) and vinylpyrrolidone**/**vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in beagles by a factor of 3.5[55]. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.8[56], in comparison with either the drug powder or a physical mixture of furosemide with crospovidone.

4.4. Cellulose derivatives:

4.4.1. General characteristics of 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 ß-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. Since each glucose unit has three hydroxyl groups that can be derivatized, the

average substitution grade (SG). A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP)[68].

4.4.2. 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 10000 to 1500000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane[57]. A poorly soluble weak base with incomplete bioavailability showed that the release rate and the bioavailability in beagles could be improved through preparation of a solid dispersion in HPMC[58]. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids and benidipine[59].

4.4.3. Hydroxypropylcellulose (HPC): Hydroxypropylmethylcellulose exhibits good solubility in a range of solvents, including water (up till 40^{0}C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37000 (Type SSL) to 1150000 (Type H)[60]. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

4.4.4. 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. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8[61].

4.4.5. Hydroxypropylmethylcellulose phthalate (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 range from 20000 to 2000000[62].

4.5. 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. Commonly they are referred today the trade name Eudragit[65]. Eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pH, while Eudragit L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as a coevaporate with Eudragit E, the rate of dissolution was much higher than from the pure drug powder[59].

4.6. Urea

In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea[8]. Although urea is not often used as a carrier these days. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000[65].

4.7. Sugar, polyols and their polymers

Chitosan a derivative of the polysaccharide chitin which is formed by deacetylation at the N position has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder[68].

4.8. Emulsifiers

Two mechanisms are possible here for release behavior of drug: improvement of wetting characteristics and solubilization of the drug. Bile salts and their derivatives are natural surfactants that are built from a steroidal 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 lipophilic substances, leading to an increase in the dissolution rate[66].

4.9. Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin[10].

4.10. Surface active agents[67]

Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature. , surface active carriers may be included to improve the efficacy or the bioperformance of drug. The properties of surfactant are such that they can alter the thermodynamic activity, solubility, diffusion, disintegration, and dissolution rate of a drug.

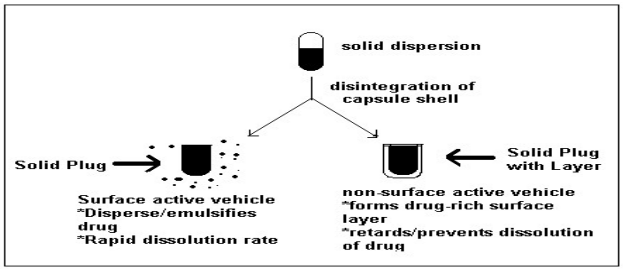

Figure 5: Shows the advantage of a surface-active carrier over a non-surface-active one in the dissolution of drug from a capsule formulation[67].

5. ADVANTAGES OF SOLID DISPERSION[15]

1. Improving drug bioavailability by changing their water solubility has been possible by solid dispersion.

2. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine.

3. Increase in dissolution rate & extent of absorption and reduction in Pre systemic metabolism.

4. Transformation of liquid form of drug into solid form.

5. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

6. DISADVANTAGES OF SOLID DISPERSION[15]

1. 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

2. Drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

7. CHARACTERIZATION OF SOLID DISPERSIONS[68]

The most important methods which are use for characterization are thermo analytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug.

Methods for the characterization of solid dispersions are as following

1. Dissolution testing.

2. Thermo analytical methods: differential thermo analysis and hot stage microscopy.

3. Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change.

4. X-Ray diffraction.

5. Spectroscopic methods, e.g. IR spectroscopy, NMR spectroscopy.

6. Microscopic methods including polarization microscopy and scanning electron microscopys.

8. CONCLUSION

Solid dispersion systems as extremely useful tool in improving the dissolution and solubility enhancement properties of poorly water-soluble drugs. 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. Carriers with or without any surface activity, when used, can significantly increase the wettability properties of drugs. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and increases the solubility of poorly water soluble drug. Solid dispersion has also been used to produce sustained release microsphere using tedious methods. New optimized techniques are also useful in the industries.

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