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Solid Dispersions : An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs

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Abstract - Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. This article reviews historical background of solid dispersion technology, limitations, classification, and various preparation techniques with its advantages and disadvantages. This review also discusses the recent advances in the field of solid dispersion technology. Based on the existing results and authors' reflection, this review give rise to reasoning and suggested choices of carrier or matrix and solid dispersion procedure.

Keywords - carrier; dissolution; matrix; poorly soluble drug; solid dispersion; solubility enhancement.

I. INTRODUCTION

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration [1-5]. 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 [6]. Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs [7]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble [8, 9]. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active

molecules can be realized [10]. Therefore lots of efforts have been made to increase dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method [2, 11]. The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960 [12]. Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous [13]. Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinylpyrrolidone (PVPs), Gelucire 44/14, Labrasol,

sugars, and urea [14-16]. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [2]. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi [1]. This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability [13]. Literature reviews on solid dispersion of past four decades suggests that there is an increasing interest in using this approach [5]. Despite an active research interest, the number of marketed products arising from this approach is really disappointing. Only few commercial products were marketed during the last four decades [1, 17, 18]. Several marketed and late stage drugs are designed for improved solubility by solid dispersion are shown in Table I [1, 17-19]. The goal of review is to highlight the historical background of solid dispersion technology, various preparation techniques with emphasis given to their advantages and disadvantages, commonly used carrier in the preparation of solid dispersions and the recent advances in the field of solid dispersion technology.

II. ADVANTAGES OF SOLID DISPERSIONS

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The reasons for solid dispersion or advantages of solid dispersions are as follows:

Particles with reduced particle size : Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium [5]. A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water-soluble drug [20].

Particles with improved wettability : The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion [21].

Particles with higher porosity : Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with SDs that prepared with reticular polymers. More porous nature of the particle results higher dissolution rate [22, 23].

Drugs in amorphous state : Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous

state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process [24, 25].

III. DISADVANTAGES OF SOLID DISPERSIONS

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility [26, 27]. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness [28].

IV. LIMITATIONS OF SOLID DISPERSIONS

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited. Problems of solid dispersion involve (i) the physical and chemical stability of drugs and vehicles, (ii) method of preparation, (iii) reproducibility of its physicochemical properties, (iv) formulation of solid dispersion into dosage forms, and (v) scale-up of manufacturing processes [29].

V. CLASSIFICATION OF SOLID DISPERSIONS

SDs can be classified into simple eutectic mixtures, solid solutions, and physical mixtures of microcrystalline drug dispersed in carriers [30]. A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state but only to very a limited extent in the solid state. A eutectic mixture of a sparingly water soluble drug and a highly water-soluble polymer or carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component and these components are assumed to crystallize simultaneously in very small particulate sizes and thus increases the rate of dissolution of a poorly water-soluble drug [31]. Solid solution consists of a solid solute dissolved in a solid solvent. In solid solution, particle size is reduced to molecular level. Solid solutions of lower drug concentrations generally give faster dissolution rate, and the drug dissolution improves markedly with an increase in molecular weight of a water-soluble polymer such as PEG [31]. Solid solutions can be further classified into three categories based on their miscibility into continuous versus discontinuous solid solutions. As shown in Figure 1, the solid molecules may be dispersed in the solvent in three fashions these are: (i) substitutional crystalline; (ii) interstitial crystalline; and (iii) amorphous solid solutions [30].

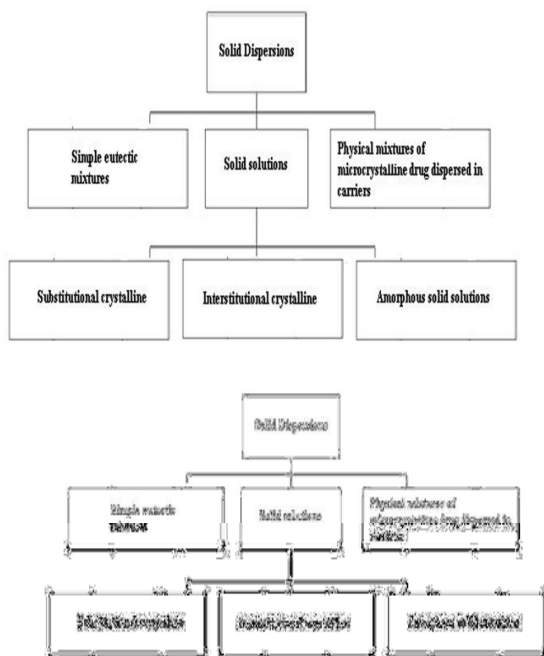


Fig. 1 : The classification of solid dispersions [30].

VI. PREPARATION OF SOLID DISPERSIONS

The fusion (melt), solvent evaporation, spray drying, lyophilization (freeze drying), hot-melt extrusion, electrostatic spinning method, coating on sugar beads using fluidized bed-coating system, supercritical fluid technology, are the methods reported for the preparation of solid dispersions and these methods are discussed below.

Fusion Method : The fusion method is sometimes called melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term “fusion method” is preferred. Fusion or Melting method was first introduced by Sekiguchi et al. in 1961 where the drug was melted in a carrier and after cooling the dry mass obtained was pulverized and sieved to obtain powder. They prepared the SDs of Sulfathiazole in different carriers (e.g. ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide and urea) by the formation of melt of different drug carrier mixtures. Cooling of the drug-carrier melt was done on ice bath with continuous stirring until the dry mass was obtained [1]. Dua et al. in 2010, prepared solid dispersions of aceclofenac with various hydrophilic carriers (urea, mannitol, PVP and PVP/VA-64) in different ratios such as 1:0.5, 1:1 and 1:2 by weight basis using melting or fusion method) with an aim to improve the extent and rate of dissolution. A particular advantage of these carriers for the formation of SDs is

having its good solubility in different organic solvents. Additional attractive features of such carriers include improved compound wettability. This study clearly shows that additions of various hydrophilic carriers like urea, mannitol, PVP and PVP/VA-64 to aceclofenac improves its dissolution rate. Further, all the solid dispersions performed better than the corresponding physical mixtures. The present study also showed that urea, mannitol and PVP/VA-64 yielded solid dispersions with a less improved dissolution rate than PVP as carrier [32]. The melting point of a binary system is dependent upon its composition, i.e., the weight fraction of drug and the carrier present in the system. By proper selection and control, the melting point of a binary system may be much lower than the melting points of its two components. Under such conditions, this melting method can be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point [2].

The main advantages of this method are its simplicity and economy. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be used to prevent oxidation of drug or carrier material. Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method is only applied when the drug and matrix are compatible and when they mix well at the heating temperature. When the drug and matrix are incompatible two liquid phases or suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion and this problem can be prevented by using surfactants. Secondly, another problem may arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, many substances, either drugs or carriers, may decompose during the fusion process at high temperatures [1, 33].

Traditional fusion method usually produces soft, tacky materials with poor flow properties and compressibility. Therefore, Gahoi et al., in 2011, prepared lumefantrine (LMF) solid dispersion by a novel solid dispersion technique ‘Dispersed Fusion’ to improve dissolution rate with particular attention to technological characteristics of granules. This novel ‘Dispersed Fusion’ technique involves spraying of molten drug and hydrophilic inert carrier on diluent in fluidized bed. They found that the drug particle size in agglomerates was significantly reduced in ‘Dispersed Fusion’ technique indicating strong impact of technique [34].

Solvent Evaporation Method: Tachibana and Nakamura were the two researchers who firstly applied solvent evaporation method for the preparation of solid dispersions. Drug (b-carotene) and carrier (PVP) were

dissolved in a common solvent (chloroform) and solvent was evaporated to form the solid mass [35]. Basically, this solvent evaporation method involves two steps and these are: (i) preparation of a solution containing both matrix material or carrier and drug and (ii) the removal of the solvent resulting in the formation of the solid mass [10]. Nature of the solvent used and the rate and temperature of evaporation of the solvent are the critical factors which can affect the formed mass [36]. One of the major advantages of this method is that thermal decomposition of the drugs can be prevented as low temperature is required for the evaporation of the organic solvents. This method has several disadvantages these are: (i) high cost of preparation, (ii) difficulty in selecting a common solvent for both the drug and carrier and complete solvent removal from the product can be a lengthy process, and (iii) crystal forms are difficult to reproduce [2, 37]. Many researchers studied solid dispersion of valdecoxib [38], carbamazepine [39], fexofenadine hydrochloride [40], and glibenclamide [41] using solvent evaporation method. These findings suggest that this method can be employed successfully for the improvement and stability of SDs of poorly water soluble drugs. Manimaran et al., in 2010, prepared the solid dispersion of glibenclamide by the solvent evaporation method using PVP, PEG6000 and Poloxamer as hydrophilic carrier. In this study, they observed that the solid dispersion prepared by using various hydrophilic carriers enhanced the solubility of glibenclamide to a varying degree. All SDs showed increased dissolution rate as compared to pure glibenclamide and PVP was found better than PEG and Poloxamer [41].

Spray Drying : Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent [23]. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drug may be partially crystallized during processing [42, 43]. Polyglycolized glycerides (Gelucire) are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and melting point between 33° and 70°C. Preparation of SDs by conventional spray drying with polyglycolized glycerides has been problematic because a sticky and tacky mass of polyglycolized glycerides is obtained. Therefore, spray drying technique for polyglycolized glycerides has been used with its combination high-melting lipids to solve this problem. Chauhan et al. in 2005, prepared solid dispersions of etoricoxib using spray drying technique with lipid carriers, mainly polyglycolized glycerides (Gelucire 50/13) and high-melting lipids, namely, Compritol (atomized glyceryl dibehenate) or Sterotex K NF (hydrogenated cottonseed

oil). They concluded that SDs of the purely water-soluble drug etoricoxib was successfully prepared by spray drying using lipid carriers [44]. Solid dispersion using polyglycolized glycerides creates some problem as already discussed above and this can be solved by using silicon dioxide as an adsorbent. Due to presence of surface silanol groups, silicon dioxide is able to form hydrogen bond with drug molecule leading to the increase in wettability and consequently enhanced dissolution rate. SD of glibenclamide with Geluride was successfully prepared using silicon dioxide as an adsorbent by spray drying technique with enhanced dissolution rate [45]. Al-Obaidi et al., in 2009, prepared solid dispersions of griseofulvin by using spray drying technology. Spray dried dispersions of griseofulvin (GF), poly[N-(2-hydroxypropyl)methacrylate] (PHPMA) and polyvinylpyrrolidone (PVP) were prepared from acetone and water. The glass transition temperature for the ternary solid dispersion (GF, PHPMA, and PVP) shifted from 83°C (acetone/water) to 103°C for the acetone/methanol system. They found that the SDs that was prepared using lower concentrations of drug and polymers in solutions resulted in the formation of particles that display a lower relaxation rate. Their result also supports the hypothesis that the polymer conformation may significantly change the properties of the solid dispersion [46].

Lyophilization (freeze drying) : An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the SDs. However, the most important advantage is that the risk of phase separation is minimized as soon as the solution is vitrified [47]. Singh et al., in 2011, dissolved some selected solid dispersions in a minimum amount of cyclohexanol. Then this solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After achieving a certain layer thickness, the flask was attached to the vacuum adaptor of the lyophilizer. The solvent was then sublimed under a pressure of 8-10mmHg and condensed onto a -75°C condenser. When the solvent was completely removed, they found that the nature of the powder residue was porous, light and fluffy mass [48]. Lokamatha et al., in 2011, prepared SDs of nevirapine (NVP) with the objective of dissolution enhancement by kneading and freeze drying technique using a novel carrier of low molecular weight dextran (DEX) at varied concentrations of drug:carrier (3:1 and 1:1w/w). They first dispersed NVP and DEX in water, and then the whole solution is stirred for 3 h. The solution is then frozen overnight and then lyophilized over a period of 24 h using a freeze drier. Then the dried powder was sieved through #120 and stored in dessicator. They found that SDs of NVP: DEX, prepared by freeze drying method exhibited a higher release rate than prepared by kneading method [49].

Hot-melt extrusion : This technology was first utilized predominantly in the plastic industry and to lesser extent in the food industry since 1930's. Many advantages of hot melt extrusion over conventional solid dosage form manufacturing picked the interest of pharmaceutical industry and researchers for the useful technology to prepare novel drug delivery system [50]. This technique employs the uses of extruders which consists of conveying system, for transportation and mixing of materials, and die system, which shapes the melt into required shape like pellets, granules, or powder [51]. In this method solvents are not used therefore, it is environmentally friendly, economical and no residual solvent in the final product. Advantage of hot melt extrusion technique over melting method is the use of low temperature and short residence time which prevents the drug-carrier mixture from thermal degradation. Another advantage is that production is continuous therefore fewer batches are required and efficient scale-up from laboratory to large-scale production [50, 52]. This method has several disadvantages these are: (i) high shear forces may produce high local temperature in the extruder therefore it may create a problem for heat sensitive materials, (ii) just like traditional fusion method, miscibility of drug and carrier matrix can be a problem [53, 54]. 17β -Estradiol hemihydrate (17β -E2) is a poorly water-soluble drug therefore, Hülsmann et al., in 2000, prepared solid dispersion by melt extrusion technique with an objective to overcome many of the shortcomings of conventional methods. Different compositions of excipients such as PEG 6000, PVP (Kollidon® 30) or a vinylpyrrolidone-vinylacetate-copolymer (Kollidon® VA64) were used as polymers and Sucroester® WE15 or Gelucire® 44/14 as additives during melt extrusion. A 30-fold increase in dissolution rate was obtained from a formulation containing 10% 17β -E2, 50% PVP and 40% Gelucire® 44/14. The SDs was then processed into tablets and the improvement in the dissolution behavior was also maintained with the tablets [52]. Atorvastatin is a selective competitive inhibitor of HMG CoA reductase and its absolute bioavailability is 14% and therefore to increase its solubility solid dispersion was prepared by using this technique. Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with mannitol, PEG 4000 and PVP-K30. They found that the solid dispersions obtained by this method were tacky enough [55].

Some examples of pharmaceutically approved polymeric materials which are used in hot-melt extrusion include vinyl polymers (polyvinylpyrrolidone (PVP), PVP-vinyl acetate (PVP-VA)), polyethylene oxide (PEO), Eudragit® (acrylates), Polyethylene glycol (PEG) and cellulose derivatives [50].

Electrostatic Spinning Method : Electrostatic spinning method involves the introduction of a liquid into an

electric field whereby the liquid is caused to produce fibres. After being drawn from the liquid the fibres harden, which may involve mere cooling, chemical hardening or evaporation of solvent, and then hardened fibres may be collected upon a suitably charged surface. Tubular products comprising polyurethane fibres can be prepared by this electrostatic spinning method. One example of this type of tubular product is a vascular prosthesis, particularly a synthetic blood vessel. Other applications of this type of tubular products include the use of different kinds of ducts, e.g. urinary, air or bile as well as conduit through which for example a wire or other device or structure may pass or lie [56]. The electrostatic spinning method has a few applications in pharmaceutical industry. In this method a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibres with a diameter of micro- or nano-scale. This method is limited to a few matrices because only a few high molecular weight materials are fibre forming materials [57]. In this method electrical forces are used to overcome the surface tension of drug-polymer solution at air interface, the fibres of submicron diameters are formed whose diameter depends upon feeding rate, dielectric constant, surface tension, electric field strength [18]. Verreck et al., in 2003, assessed the application of water-soluble polymer-based nanofibres prepared by electrostatic spinning as a means of altering the dissolution rate of the poorly water-soluble drug, itraconazole. Organic solvent-based solutions of itraconazole/HPMC mixtures were electrostatically spun at 16 and 24 kV. Then the formed nanofibres were collected as a non-woven fabric. Differential scanning calorimetry (DSC) measurements found that the melting endotherm for itraconazole was not present, suggesting the formation of an amorphous solid dispersion or solution. They concluded that the application of electrostatic spinning to pharmaceutical applications resulted in dosage forms with useful and controllable dissolution properties [58]. Verreck et al., in 2003, used electrostatic spinning method for the preparation of drug-laden nonbiodegradable nanofibre for potential use in topical drug administration and wound healing. Itraconazole and ketanserin were selected as model compounds while segmented polyurethane (PU) was selected as the nonbiodegradable polymer. For both itraconazole and ketanserin, an amorphous nanodispersion with PU was obtained when the drug/polymer solutions were electrospun from dimethylformide (DMF) and dimethylacetamide (DMAc), respectively [59].

Coating on sugar beads using fluidized bed-coating system : This method involves a fluidized bed-coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. The method can be applied for both controlled- and immediate-release solid dispersions [29]. Itraconazole (Sporanox oral capsules,

Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering onto sugar beads a solution of a drug and hydroxypropylmethylcellulose (HPMC) in a mixture of suitable solvent system comprises a mixture of methylenechloride and preferably ethanol which may be denatured with butanone. As HPMC does not dissolve completely in methylenechloride, at least 10% alcohol has to be added. A solid solution of drug in HPMC is produced upon coating and controlled drying of coated beads is done in a closed Wurster apparatus [60].

Supercritical Fluid Technology : Supercritical fluid (SCF) technology offers tremendous potential and the low operating conditions (temperature and pressure) make the method more attractive for pharmaceutical research. In the pharmaceutical field, the supercritical fluid technology was industrially applied in the early 1980's. A supercritical fluid exists as a single phase above its critical temperature and pressure [61]. The most commonly used supercritical fluids for a variety of applications include supercritical fluid carbon dioxide, nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia [62]. Carbon dioxide is one of the most commonly used SCFs because of its low critical temperature ($T_c = 31.1^\circ\text{C}$) and pressure ($P_c = 73.8$ bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of CO_2 makes it attractive for processing heat-labile molecules [29]. This technique consists of dissolving the drug and the inert 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 [23]. This SCF technology provides a novel alternative method of preparation of small particles with higher surface area, free flowing property, and a very low content of residual organic solvent and this technology also avoids most of the drawbacks of the traditional methods [29, 63]. A variety of supercritical carbon dioxide techniques have been developed with different working principles, such as rapid expansion of supercritical solutions (RESS), gas antisolvent precipitation (GAS), supercritical antisolvent precipitation (SAS), precipitation with compressed fluid antisolvent (PCA), solution enhanced dispersion by supercritical fluids (SEDS), precipitation from gas-saturated solutions (PGSS), etc [64]. Jun et al., in 2005, prepared cefuroxime axetil (CA) solid dispersions with HPMC 2910/PVP K-30 using solution enhanced dispersion by supercritical fluids (SEDS) in an effort to increase the dissolution rate of poorly water-soluble drugs. FTIR analysis demonstrated that the presence of intermolecular hydrogen bonds between CA and HPMC 2910/PVP K-30 in solid dispersions, result in the formation of amorphous or non-crystalline CA. They concluded that an amorphous or non-crystalline CA solid dispersion prepared using SEDS could be very

useful for the formulation of solid dosage forms [65]. Liu et al., in 2007, investigated the possibility of preparing solid dispersions of the poorly soluble budesonide by supercritical fluid (SCF) technique, using poly (ethylene oxide) (PEO) as a hydrophilic carrier using supercritical carbon dioxide (SC-CO_2) as the processing medium. They found that the enhanced dissolution rates of budesonide were observed from SCF-treated budesonide-PEO mixtures. The amorphous characteristic of the budesonide, the better mixing of drug and PEO powders in the presence of SC-CO_2 , together with the improved wettability of the drug in PEO, produced a remarkable enhancement of the in vitro drug dissolution rate [66].

VII. CONCLUSION

Since the concept of solid dispersion technology was introduced in 1960s, great progresses have been made in solid dispersion technology as solid dispersion offers a variety of opportunities. A single solid dispersion method cannot be universally accepted for a variety of drug materials. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. Most of the solid dispersion work is in lab-scale setups; therefore the manufacturing process requires enough knowledge to scale up to the commercial scale.

REFERENCES

- [1] K. Sekiguchi, and N. Obi, "Studies on absorption of eutectic mixture" I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man," *Chem. Pharm. Bull.*, vol. 9, 1961, pp. 866-872.
- [2] W. L. Chiou, and S. Riegelman, "Pharmaceutical applications of solid dispersion systems," *J. Pharm. Sci.*, vol. 60, no. 9, 1971, pp. 1281-1302, doi: 10.1002/jps.2600600902.
- [3] D. M. Brahmanekar, and S. B. Jaiswal, *Biopharmaceutics and Pharmacokinetics: A Treatise*, 1st ed., Delhi: Vallabh Prakashan, 1995, pp.171-172.
- [4] B. Swarbrick, 2002. *Encyclopedia of Pharmaceutical Technology*, 2nd ed., vol.1, New York: Marcel Dekker Inc, pp. 641-647.
- [5] C. Leuninger, and J. Dressman, "Improving drug solubility for oral delivery using solid dispersions," *Eur. J. Pharm. Biopharm.*, vol. 50, no.1, July 2000, pp. 47-60.

- [6] A. H. Goldberg, M. Gibaldi, and J. L. Kanig, "Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of eutectic mixture: Urea-acetaminophen system," *J. Pharm. Sci.*, vol. 55, issue 5, 1966, pp. 482-487, doi: 10.1002/jps.2600550507.
- [7] G. L. Amidon, H. Lennernas, V. P. Shah, and J. R. Crison, "A theoretical basis for biopharmaceutical drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability," *Pharm. Res.*, vol. 12, no. 3, 1995, pp. 413-420.
- [8] R. A. Prentis, Y. Lis, and S. R. Walker, "Pharmaceutical innovation by seven UK-owned pharmaceutical companies (1964-1985)," *Br. J. Clin. Pharmacol.*, vol. 25, 1988, pp. 387-396.
- [9] C. A. Lipinski, "Avoiding Investment in doomed drugs, is poor solubility an industry wide problem?," *Curr. Drug Dis.*, vol. 4, 2001, pp.17-19.
- [10] A. Arunachalam, M. Karthikeyan, K. Konam, P. H. Prasad, S. Sethuraman, and S. Ashutoshkumar, "Solid dispersions: A review," *Curr. Pharm. Res.*, vol. 1, issue 1, October-December 2010, pp. 82-90.
- [11] J. L. Ford, "The current status of solid dispersions," *Pharm. Acta Helv.*, vol.61, 1986, pp. 69-88.
- [12] R. Dannenfelser, H. He, Y. Joshi, S. Bateman, and A. T. M. Serajuddin, "Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol-polysorbate 80 solid dispersion carrier system," *J. Pharm. Sci.*, vol. 93, 2004, pp. 1165-1175, doi:10.1002/jps.20044.
- [13] T. J. Shah, A. F. Amin, J. R. Parikh, and R. H. Parikh, "Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug," *AAPS PharmSciTech.*, vol. 8, issue 2, Article 29, 2007, pp. E18-E24, doi: [10.1208/pt0802029](https://doi.org/10.1208/pt0802029).
- [14] G. V. D. Mooter, P. Augustijns, N. Bleton, and R. Kinget, "Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30," *Int. J. Pharm.*, vol. 164, 1998, pp. 67-80, doi:10.1016/S0378-5173(97)00401-8.
- [15] D. Law, S. L. Krill, E. A. Schmitt, J. J. Fort, Y. Qiu, W. Wang, and W. R. Porter, "Physicochemical considerations in the preparation of amorphous ritonavir-poly (ethylene glycol) 8000 solid dispersions," *J. Pharm. Sci.*, vol. 90, 2001, pp. 1015-1025, doi:10.1002/jps.1054.
- [16] M. J. Habib, *Pharmaceutical Solid Dispersion Technology*, Washington: CRC, 2000, pp. 35-78.
- [17] D. Q. M. Craig, "The mechanisms of drug release from solid dispersions in water soluble polymers," *Int. J. Pharm.*, vol. 231, issue 2, 2002, pp. 131-144, doi:10.1016/S0378-5173(01)00891-2.
- [18] S. Sethia, "Solid dispersions-revival with greater possibilities and applications in oral drug delivery," *Crit. Rev. Ther. Drug Carrier Syst.*, vol. 20, issues 2-3, 2003, pp. 215-247.
- [19] A. M. Thayer, "Custom manufacturer take on drug solubility issues to help pharmaceutical firms move products through development," *Finding Solutions*, vol. 88, no. 22, 2010, pp. 13-18.
- [20] S. Prabhu, M. Ortega, and C. Ma, "Novel lipid-based formulations enhancing the in vitro and permeability characteristics of a poorly water-soluble model drug, piroxicam," *Int. J. Pharm.*, vol. 301, issues 1-2, 2005, pp. 209-216, doi:10.1016/j.ijpharm.2005.05.032.
- [21] E. Karavas, G. Ktistis, A. Xenakis, E. Georgarakis, "Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone," *Eur. J. Pharm Biopharm.*, vol. 63, issue 2, 2006, pp. 103-114, doi:10.1016/j.ejpb.2006.01.016.
- [22] R. Ghaderi, P. Artursson, and J. Carlfors, "Preparation of biodegradable microparticles using solution-enhanced dispersion by supercritical fluids (SEDS)," *Pharm. Res.*, vol. 16, issue 5, 1999, pp. 676-681, doi 10.1023/A:1018868423309.
- [23] T. Vasconcelos, B. Sarmiento, and P. Costa, "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs," *Drug Discov. Today*, vol. 12 issues 23-24, 2007, pp. 1068-1075, doi:10.1016/j.drudis.2007.09.005.
- [24] V. B. Pokharkar, L. P. Mandpe, M. N. Padamwar, A. A. Ambike, K. R. Mahadik, and A. Paradkar, "Development, characterization and stabilization of amorphous form of a low Tg drug," *Powder Technol.*, vol.167, issue 1, 2006, pp. 20-25, doi:10.1016/j.powtec.2006.05.012.

- [25] L. S. Taylor, and G. Zografi, "Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions," *Pharm. Res.*, vol. 14, no. 12, 1997, pp. 1691-1698, doi: 10.1023/A:1012167410376.
- [26] X. Wang, A. Michel, and G. Van den Mooter, "Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole," *Int. J. Pharm.*, vol. 303, issues 1-2, 2005, pp. 54-61, doi:10.1016/j.ijpharm.2005.07.002.
- [27] G. Van den Mooter, L. Weuts, T. D. Ridder, and N. Blaton, "Evaluation of inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs," *Int. J. Pharm.*, vol. 316, issues 1-2, 2006, pp. 1-6, doi:10.1016/j.ijpharm.2006.02.025.
- [28] N. S. Seth, "Formulation and evaluation of solid dispersion of olanzepine," *Int. J. Pharm. Sci. Res.*, vol. 2, issue 3, 2011, pp. 691-697.
- [29] H. Karanth, V. S. Shenoy, and R. R. Murthy, "Industrially feasible alternative approaches in the manufacture of solid dispersions: A technical report," *AAPS PharmSciTech.*, vol. 7 issue 4, Article 87, 2006, pp. E31-38, doi: 10.1208/pt070487.
- [30] He X, "Integration of physical, chemical, mechanical, and biopharmaceutical properties in solid oral Dosage Form development," in *Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice*, 1st ed., Y. Qiu, Y. Chen, and G. G. Z. Zhang, Eds., Burlington, USA: Academic Press, 2009, pp. 409-441.
- [31] Remington: The Science and Practice of Pharmacy, 21st ed., D. B. Troy, Ed., Baltimore, Maryland, USA: Lippincott Williams & Wilkins.
- [32] K. Dua, K. Pabreja, and M. V. Ramana, "Preparation, characterization and in vitro evaluation of aceclofenac solid dispersions," *ARS Pharmaceutica*, vol. 51, no. 1, 2010, pp. 57-76.
- [33] A. Sayyad, and S. D. Sawant, "Techniques of solubility enhancement of poorly soluble drug with special emphasis on solid dispersion," *J. Pharm. Res.*, vol. 3, 2010, pp. 2494-2501.
- [34] S. Gahoi, G. K. Jain, M. Singhal, M. Anwar, F. J. Ahmad, and R. K. Khar, "Influence of novel dispersed fusion technique on dissolution and pharmacotechnical properties of pharmaceutical solid dispersion," *Int. J. Pharm. Sci. Rev. Res.*, vol. 8, issue 2, Article-028, May-June 2011, pp. 170-175.
- [35] T. Tachibana, and N. A. Nakamura, "A method for preparing an aqueous colloidal dispersion of beta-carotene by polyvinylpyrrolidone," *Colloid Polym. Sci.*, vol. 203, no.2, 1965, pp. 130-133, doi: 10.1007/BF01507758.
- [36] Y. Xie, G. Li, X. Yuan, Z. Cai, and R. Rong, "Preparation and in vitro evaluation of solid dispersions of total flavones of *hippophae Rhamnoides L.*," *AAPS Pharm Sci Tech.*, vol. 10, issue 2, 2009, pp. 631-640, doi: 10.1208/s12249-009-9246-x.
- [37] D. K. Sharma, and S. B. Joshi, "Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A review," *Asian J. Pharm.*, vol. 1, issue 1, 2007, pp.9-19.
- [38] M. M. Patel, and D. M. Patel, "Fast dissolving valdecoxib tablets containing solid dispersion of valdecoxib," *Indian J. Pharm. Sci.*, vol. 68, 2006, pp. 222-226, doi: 10.4103/0250-474X.25719.
- [39] S. Sethia, and E. Squillante, "Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods," *Int. J. Pharm.*, vol. 272, issues 1-2, 2004, pp. 1-10, doi:10.1016/j.ijpharm.2003.11.025.
- [40] S. Tasnim Jahan, M. S. Rahman Khan, M. Moniruzzaman, M. Rezowanur Rahman, S. M. Anowar Sadat, and R. Jalil, "Enhancement of dissolution profile for oral delivery of fexofenadine hydrochloride by solid dispersion (solvent evaporation) technique," *Am. J. Sci. Ind. Res.*, vol. 2, issue 1, 2011, pp.112-115, doi:10.5251/ajsir.2011.2.112.115.
- [41] V. Manimaran, N. Damodharan, M. Mothilal, K. Rajkumar, and R. M. Chalackal. "Enhancement of dissolution rate of glibenclamide by solid dispersion technology," *Int. J. Curr. Pharm. Res.*, vol. 2, issue 3, 2010, pp.14-17.
- [42] A. Paradkar, A. A. Ambike, B. K. Jadhav, and K. R. Mahadik, "Characterization of curcumin-PVP solid dispersion obtained by spray drying," *Int. J. Pharm.*, vol. 271, issues 1-2, 2004, pp. 281-286, doi:10.1016/j.ijpharm.2003.11.014.
- [43] I. Weuts, D. Kempen, G. Verreck, A. Decorte, and K. Heymans, "Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying," *Eur. J. Pharm. Biopharm.*, vol. 59, issue 1, 2005, pp.119-126, doi:10.1016/j.ejpb.2004.05.011.

- [44] B. Chauhan, S. Shimpi, and A. Paradkar, "Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique," *AAPS PharmSciTech.*, vol. 6, issue 3, 2005, pp. E405-E412, doi:10.1208/pt060350.
- [45] B. Chauhan, S. Shimpi, and A. Paradkar, "Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique," *Eur. J. Pharm. Sci.*, vol. 26, issue 2, 2005, pp. 219-230, doi:10.1016/j.ejps.2005.06.005.
- [46] H. Al-Obaidi, S. Brocchini, and G. Buckton, "Anomalous properties of spray dried solid dispersions," *J. Pharm. Sci.*, vol. 98, issue 12, 2009, pp. 4724-4737, doi: 10.1002/jps.21782.
- [47] K. Dhirendra, S. Lewis, N. Udupa, and K. Atin, "Solid dispersion: A review," *Pak. J. Pharm. Sci.*, vol. 22, issue 2, 2009, pp. 234-246.
- [48] S. K. Singh, K. K. Srinivasan, K. Gowthamarajan, D. Prakash, and N. B. Gaikwad, "Investigation of preparation parameters of solid dispersion and lyophilization technique in order to enhance the dissolution of poorly soluble glyburide," *J. Pharm. Res.*, vol. 4, issue 8, 2011, pp. 2718-2723.
- [49] K. M. Lokamatha, S. M. Shanta Kumar, and N. Rama Rao, "Enhancement of solubility and dissolution rate of nevirapine by solid dispersion technique using dextran: preparation and in vitro evaluation," *Int. J. Pharm. Res. Dev.*, vol. 2, issue 12, Article 01, February 2011, pp. 1-8.
- [50] M. Williams, Y. Tian, D. S. Jones, and G. P. Andrews, "Hot-melt extrusion technology: optimizing drug delivery," *Eur. Ind. Pharm.*, issue 7, October 2010, pp. 7-10.
- [51] K. Nakamichi, H. Yasuura, H. Kukui, M. Oka, S. Izumi, T. Andou, N. Shimizu, and K. Ushimaru, "New preparation method of solid dispersion by twin screw extruder," *Pharm. Tech. Jpn.*, vol. 12, 1996, pp. 715-729.
- [52] S. Hülsmann, T. Backensfeld, S. Keitel, and R. Bodmeier, "Melt extrusion-an alternative method for enhancing the dissolution rate of 17 β -estradiol hemihydrate," *Eur. J. Pharm. Biopharm.*, vol. 49, issue 3, 2000, pp. 237-242, doi:10.1016/S0939-6411(00)00077-1.
- [53] M. Langer, M. Höltje, N. A. Urbanetz, B. Brandt, H. D. Höltje, and B. C. Lippold, "Investigations on the predictability of the formation of glassy solid solutions of drugs in sugar alcohols," *Int. J. Pharm.*, vol. 252, issues 1-2, 2003, pp. 167-179, doi:10.1016/S0378-5173(02)00647-6.
- [54] A. Forster, J. Hempenstall, and T. Rades, "Characterization of glass solutions of poorly water soluble drugs produced by melt extrusion with hydrophilic amorphous polymers," *J. Pharm. Pharmacol.*, vol. 53, issue 3, 2001, pp. 303-315, doi: 10.1211/0022357011775532.
- [55] K. R. Bobe, C. R. Subrahmanya, S. Suresh, D. T. Gaikwad, M. D. Patil, T. S. Khade, B. B. Gavitre, V. S. VKulkarni, and U. T. Gaikwad, "Formulation and evaluation of solid dispersion of atorvastatin with various carriers," *Pharmacie Globale (IJCP)*, vol. 1, issue 02, 2011, pp.1-6.
- [56] A. Bornat, "Electrostatic spinning of tubular products," US Patent 4323525, April 6, 1982.
- [57] S. Sethia, and E. Squillante, "Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional solvent evaporation method," *J. Pharm. Sci.*, vol. 91, issue 9, 2002, pp. 1948-1957, doi: 10.1002/jps.10186.
- [58] G. Verreck, I. Chun, J. Peeters, J. Rosenblatt, and M. E. Brewster, "Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning," *Pharm. Res.*, vol. 20, no. 5, 2003, pp. 810-817, doi: 10.1023/A:1023450006281.
- [59] G. Verreck, I. Chun, J. Rosenblatt, J. Peeters, A. Van Dijck, J. Mensch, M. Noppe, and M. E. Brewster, "Incorporation of drugs in an amorphous state into electrospun nanofibers composed of a water-insoluble, nonbiodegradable polymer," *J. Control. Release*, vol. 92, issue 3, 2003, pp. 349-360, doi:10.1016/S0168-3659(03)00342-0.
- [60] P. Gilis, V. De Conde, and R. Vandecruys, "Beads having a core coated with an antifungal and a polymer," US patent 5633015, May 27, 1997.
- [61] F. V. T. Thakkar, T. G. Soni, M. C. Gohel, and T. R. Gandhi, "Supercritical fluid technology: A promising approach to enhance the drug solubility," *J. Pharm. Sci. Res.*, vol. 1, issue 4, 2009, pp. 1-14.
- [62] B. S. Sekhon, "Supercritical fluid technology: An overview of pharmaceutical applications," *Int. J. PharmTech Res.*, vol. 2, issue 1, 2010, pp. 810-826.
- [63] J. Fages, H. Lochard, J. J. Letourneau, M. Sauceau, and E. Rodier, "Particle generation for

- pharmaceutical applications using supercritical fluid technology,” Powder Technol., vol. 141, 2004, pp. 219-226, doi:10.1016/j.powtec.2004.02.007.
- [64] S. Sethuraman, A. Arunachalam, M. Karthikeyan, Kishore Konam, Pottabathula Hari Prasad, and R. Senthilraj, “Formation and Characterization of solid dispersion of Piroxicam,” Int. J. Preclin. Pharm. Res., vol. 2, issue 1, Jan-Jun 2011, pp. 1-6.
- [65] S. W. Jun, M. S. Kim, G. H. Jo, S. Lee, J. S. Woo, J. S. Park, and S. J. Hwang, “Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids,” J. Pharm. Pharmacol., vol. 57, issue 12, December 2005, pp. 1529-1537, doi: 10.1211/jpp.57.12.0003.
- [66] H. Liu, L. L. Zhou, L. L. Wei, H. Guo, S. F. Nie, X. G. Yang, R. Tang, and W. S. Pan, “Preparation of budesonide-poly (ethylene oxide) solid dispersions using supercritical fluid technology,” Drug Dev. Ind. Pharm., vol. 33, no. 9, 2007, pp. 959-966.

Table I : Several marketed and late stage drugs are designed for improved solubility by solid dispersion [1, 17-19].

Product/Substance	Dispersion Polymer or Carrier	Technology used	Company
Gris-PEG[®] (Griseofulvin)	Polyethylene glycol	Melt process; exact process unknown	Novartis
Sporamax capsules (Itraconazole)	Hydroxypropylmethylcellulose (HPMC)	Spray layering	Janseen pharmaceutical
Cesamet[®] (Nabilone)	Providone	process unknown	Lilly
Kaletra (lopinavir and ritonavir)	Polyvinylpyrrolidone (PVP)/polyvinyl acetate	Melt-extrusion	Abbott Laboratories
Torcetrapib^a	HPMC acetate succinate	Spray drying	Pfizer
Ibuprofen	Various	Melt-extrusion	Soliqs
Isoptin SRE-240 (Verapamil)	Various	Melt-extrusion	Soliqs
Rezulin^b (Troglitazone)	PVP	Melt-extrusion	Pfizer
LCP-Tacro (Tracrolimus)	HPMC	Melt-granulation	Life Cycle Pharma
Intelence (Etravirine)	HPMC	Spray drying	Tibotec
Certican (Everolimus)	HPMC	Melt or Spray drying	Novartis
Afeditab (Nifedipine)	Poloxomer or PVP	Melt/absorb on carrier	Élan Corp.

^a Halted in phase III; ^b Withdrawn from market.

