CHAPTER –III
LITERATURE ON SOLID DISPERSIONS
The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. In 1961, Sekiguchi and Obi\textsuperscript{1}, developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome.

**Principle and applications of solid dispersion**

This method, which was termed as solid dispersion\textsuperscript{2}, involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi\textsuperscript{1}, suggested that the drug was present in eutectic mixture in a microcrystalline state. Later, Goldberg et al\textsuperscript{3} demonstrated that the entire drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high. The advantage of solid dispersion, compared with conventional capsule and tablet formulations, is shown schematically in Figure 3.1. From conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case, an average particle size of 5 µm is usually the lower limit, although higher particle
sizes are preferred for ease of handling, formulation, and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size $^4$.

Eutectic systems are one example of solid dispersions. The solid phases constituting the eutectic, each contain only one component and the system may be regarded as an intimate crystalline mixture of one component in the other $^5$. These types of solid dispersions are prepared by rapid solidification of the melts of the drug and inert carrier that show complete liquid miscibility but negligible solid-solid solubility. Thermodynamically, such systems are intimately blended physical mixtures with its two crystalline components. Therefore, the X-ray diffraction pattern of such type of solid dispersion constitutes an additive composite of the two components $^6$. Chloramphenicol-urea $^7$, griseofulvin and tolbutamide in PEG 2000 $^8$, and paracetamol-urea $^3$, may be cited as examples of simple eutectic mixtures.
Figure 3.1. A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.4

The second major group of solid dispersions is solid solution. In this case each solid phase contains both components, that is, a solid solute is dissolved in a solid solvent to give a mixed crystal. These are also called mixed crystals as the two components crystallize together in a homogenous one-phase system. Since the particle size of the drug in this type of dispersion is reduced to a molecular size, the dissolution rate is faster in solid solution than in the corresponding simple eutectic mixtures.5

Hence solid dispersion in water-soluble carriers has attracted considerable interest as a means of improving the dissolution rate, and possible enlargement of bioavailability, of a range of hydrophobic drugs.7,9,10. But despite an active research interest, the commercial
application of solid dispersion in dosage form design has been very limited. Only two products, a Griseofulvin-in Poly (ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a Nabilone-in-Povidone solid dispersion (Cesamet, Lilly) were marketed during three decades following the initial work of Sekiguchi and Obi in 1961.

**Methods of preparation of solid dispersion**

**Melting method**

In the melting method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed, pulverized, and sieved. The main advantage of the melting method is its ease and lower cost. The disadvantages include drug degradation or decomposition at the melting temperature employed. Drugs that decompose on melting may be unsuitable. Also, volatile drugs may be lost due to volatization at the high temperatures employed. In a binary mixture consisting of a drug that melts with decomposition and a carrier, however, if the carrier has a lower melting point than the drug, then the melting point of the binary mixture is frequently lower than the decomposition melting point of the drug, and as such the melt method may still be used without drug degradation.

**Solvent evaporation method**

In this method the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid
dispersion. This method has been used to prepare various dispersions. The main advantage of this method is that thermal decomposition of drugs and carriers can be prevented because of the low temperatures required in the evaporation of the organic solvents. The disadvantages of the solvent evaporation method include the high cost of preparation, difficulty in completely removing the solvent and possible adverse effects of residual solvent on the chemical stability of the drug7.

**Melting-solvent evaporation method**

The melting-solvent evaporation method uses a drug in solution (solution amount must be less than 10% of the total solid carrier) that is incorporated into a molten mass of polyethylene glycol at a temperature below 70°C without removing the solvent7.

**Other methods of preparation**

The use of supercritical fluid process in the preparation of solid dispersion of carbamazepine in poly (vinylpyrrolidone) K30 were studied11. Additionally the use of mechanical mixing followed by heating to temperatures below the melting point in the preparation of solid dispersion of indomethacin with crospovidone12, spray drying13, spray freezing14, spray congealing15, and melt extrusion16, techniques are also reported. Co-grinding of the drug with the carrier has also shown an increase in dissolution rate in the study made on frusemide17.
Carriers used in solid dispersion

The carriers used in the preparation of solid dispersions should be freely water soluble with intrinsic rapid dissolution properties, being non-toxic, pharmacologically inert, chemically compatible and not form strongly bonded complexes with the drug that may reduce dissolution rates. In addition, if the carrier is intended to be used in fusion processes, it should be chemically, physically, and thermally stable with a low melting point to avoid the use of excessive heat during dispersion. On the other hand, those carriers used for solvent evapoartion processes should be soluble in a variety of organic solvents and be able to co-precipitate with the drug upon the removal of the solvent to retard the crystallization of the drug. Although several polymers have been applied to produce sustained release solid dispersions, PEGs and PVPs have dominated the field for improving the dissolution rate of poorly water soluble drugs. Due to their low melting points, PEG’s are economically suitable for preparing dispersions by the melt method. In addition, since they have high solubility in a wide range of organic solvent and since highly concerned PEG solutions are viscous and retard crystallization of drugs, they are also suitable for solvent method of preparation of solid dispersions. However, although rare, chemical instability of some drugs such as digitoxin and glutethimide have been reported with PEG’s. Moreover, certain drugs such as phenobarbitone may form complexes that are poorly soluble thereby further reducing the bioavailability of the drugs. PVP is freely
soluble in water and a variety of organic solvents. Since it melts only at temperatures above 275°C with decomposition it is only suitable for the solvent method of preparation of solid dispersions.

The conversion of drug to crystalline state is the primary stability issue with solid dispersions prepared by the solvent method. But PVP, which is used as a carrier in this project and commonly used in many other solid dispersions, is amorphous and does not convert to a crystalline state. However, certain other carriers may convert from their amorphous states to crystalline states in solid dispersions. This issue was extensively studied by Andronis et al.\textsuperscript{20} and observed that the crystallization of amorphous materials is facilitated by moisture. As a result it is recommended that a strict protection should be made against moisture during the preparation and storage of most solid dispersions.

Several surface active agents have been also used as carriers in solid dispersion technology because they have an additional advantage that the liberated particles will be wetted and solubilized. They act as emulsifying agents for the liberated drug, thus preventing water-insoluble layer formation. Thus, having a high surface area, enhanced dissolution of the drug can be achieved in the gastrointestinal fluid, especially in the presence of the bile salts, lecithin, and lipid digestion mixtures.\textsuperscript{4}

**Direct Compression in Dosage Form Development of Solid dispersions**

Prior to the late 1950s, the literature contained few references on the direct compression of pharmaceuticals. A great deal of attention has been
given to both product and process development in the recent years. The availability of new materials, new forms of old materials and the invention of new machinery has allowed the production of tablets by simplified and reliable methods. In early 1960’s, the introduction of spray-dried lactose (1960) and Avicel (1964) had changed the tablet manufacturing process and opened avenues of direct compression tableting.

Previously, the word “direct compression” was used to identify the compression of a single crystalline compound (i.e. sodium chloride, potassium chloride, potassium bromide, etc) into a compact form without the addition of other substances. Current usage of the term “direct compression” is used to define the process by which tablets are compressed directly from the powder blends of active ingredient/s and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible adjuvants may yield satisfactory tablets for such materials.

Development of solid dispersion into convenient dosage forms is unquestionable for further clinical use and successful commercialization. Solid dispersions produced by solvent evaporation method have to be pulverized after solvent removal and hardening. Some of the challenges in the dosage form development of such materials are difficulty of
pulverization and sifting of the dispersions, which are usually soft and tacky, poor flow and mixing properties of powders thus prepared, poor compressibility, drug-carrier incompatibility and poor stability of dosage forms. However, there are very few reports in the literature addressing these important issues\textsuperscript{18} Even the limited number of reports describing any dosage form developmental aspects of solid dispersions only confirm that the task of formulating solid dispersions into capsules or tablets may be a very complex and difficult\textsuperscript{4}.

Direct compression is more suitable for moisture and heat sensitive active pharmaceutical ingredients, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects. This is also important in the case of solid dispersions where moisture can play a role in recrystallization of the amorphous drug. In developing a tablet formulation of the indomethacin-PEG6000 solid dispersion, Ford and Rubinstein\textsuperscript{24} reported that the solid dispersion was not amenable to wet granulation because water could disrupt its physical structure. In addition, the dispersion was soft and tacky. Additionally changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations\textsuperscript{22}. This is extremely important because the official compendium now requires dissolution specifications for most solid dosage forms\textsuperscript{25}. 

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Microcrystalline cellulose (MCC) is the material of choice in this work as a directly compressible diluent. It is a purified partially depolymerized cellulose, prepared by treating a cellulose with mineral acids. It is a white, crystalline powder composed of agglomerated porous micro fibers. After purification by filtration and spray-drying, porous microcrystals are obtained. Microcrystalline cellulose occurs as a white odourless, tasteless crystalline powder composed of porous particles of an agglomerated product. Apart from its use in direct compression, microcrystalline cellulose is used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. In the pharmaceutical market, microcrystalline cellulose is available under the brand names Avicel, Emcocel, Vivacel etc.

The flow properties of microcrystalline cellulose are generally good, and the direct compression characteristics are excellent. This is a somewhat unique diluent in that while producing cohesive compacts, the material also acts as a disintegrating agent. Avicel PH100 is the Avicel grade that is most widely used in direct compression tableting. Lahdenpaa et al demonstrated that the tablets containing higher percentage of Avicel PH101 exhibited higher crushing strength and lower disintegration time, while the tablets containing Avicel PH102 and PH200 showed lower crushing strength, shorter disintegration time.
Enhancement of dissolution of Fenofibrate by Solid dispersion Technique was done by Tejas Patel et al. Fenofibrate is a lipid lowering drug used in the treatment of hyperlipidemia, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate solid dispersions and Lyophilization of dispersion is designed and evaluated. Solid dispersions of Fenofibrate were prepared using PEG 6000, Poloxamer 407 and a mixture of PEG 6000 and Poloxamer 407(1:1 mixture). The effect of melt and solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. Dissolution studies indicated a significant increase in dissolution of Fenofibrate when dispersed in PEG6000 and Poloxamer 407. Physical mixtures containing PEG and Poloxamer 407 also showed improved dissolution of Fenofibrate as compared with that of pure drug, indicating the solubilizing effect of PEG6000 and Poloxamer 407. Solid dispersions containing Fenofibrate/Poloxamer 407, 1: 8, showed a 14-fold increase in dissolution after 60 min (D60) and another dispersion containing Fenofibrate /PEG 6000, 1:10, showed an 8-fold increase in the 0.1 N HCl systems. The dispersion containing six parts of the PEG 6000: Poloxamer 407 mixture (PEG 4000/PEG 6000, 1:1 mixture) showed a 12-fold increase in D60 as compared with pure drug. When multi-carrier solid dispersion containing six parts of mixture was prepared by the solvent method, the D60 value was about 2-fold that of the same dispersion prepared by the melt method. The
dissolution of lyophilized solid dispersions further increased the dissolution of Fenofibrate significantly.

Effect of Physical State and Particle Size Distribution on Dissolution Enhancement of Nimodipine/PEG Solid Dispersions Prepared by Melt Mixing and Solvent Evaporation was studied by George Z. Papageorgiou et al\textsuperscript{27}. The physical structure and polymorphism of nimodipine were studied by means of micro-Raman, WAXD, DSC, and SEM for cases of the pure drug and its solid dispersions in PEG 4000, prepared by both the hot-melt and solvent evaporation methods. The dissolution rates of nimodipine/PEG 4000 solid dispersions were also measured and discussed in terms of their physicochemical characteristics. Micro-Raman and WAXD revealed a significant amorphous portion of the drug in the samples prepared by the hot-melt method, and that saturation resulted in local crystallization of nimodipine forming, almost exclusively, modification I crystals (racemic compound). On the other hand, mainly modification II crystals (conglomerate) were observed in the solid dispersions prepared by the solvent evaporation method. However, in general, both drug forms may appear in the solid dispersions. SEM and HSM microscopy studies indicated that the drug particle size increased with drug content. The dissolution rates were substantially improved for nimodipine from its solid dispersions compared with the pure drug or physical mixtures. Among solid dispersions, those resulting from solvent coevaporation exhibited a little faster drug release at drug concentrations lower than 20 wt%. Drug
amorphization is the main reason for this behavior. At higher drug content the dissolution rates became lower compared with the samples from melt, due to the drug crystallization in modification II, which results in higher crystallinity and increased particle size. Overall, the best results were found for low drug content, for which lower drug crystallinity and smaller particle size were observed.

Preparation and evaluation of solid dispersion of Terbinafine hydrochloride was done by K. Arun Prasad et al. The study was aimed to formulate solid dispersion tablet of Terbinafine Hydrochloride by using carriers polyethylene glycol 6000 (by melting method) and polyvinyl pyrrolidone K 30 (by solvent method) in the drug carrier ratio of 1:1, 1:2 and 1:3. The prepared solid dispersions were characterized for their drug content, thermal studies, infrared spectral studies, differential scanning calorimetric studies, aqueous solubility studies and in-vitro release studies. From the results, it was clear that solid dispersion formulation showed improved dissolution rate than pure drug and physical mixture. The solid dispersion showing better release profile was chosen to formulate into a tablet dosage form of weight 600 mg. The tablets compressed were evaluated for its physical parameters like thickness, hardness, weight variation, friability, drug content and disintegration tests. The dissolution profile of formulated tablet was compared with the marketed product and the formulated tablet showed better release profile than the marketed product.
Studies on improving dissolution of meloxicam using solid dispersions was done by Mohamed Hassan G. Dehghan et al. Meloxicam is a poorly water soluble non steroidal anti-inflammatory drug and antipyretic agent. The aim of the present work was to investigate the effect of different types of carriers on in vitro dissolution of meloxicam. Meloxicam solid dispersions were prepared by physical mixing, co-grinding and solvent evaporation methods with polyethylene glycol (PEG) 6000. The effect of solubilization by sodium lauryl sulphate (SLS) was also studied. The dissolution was determined by USP XXVII Apparatus I, using phosphate buffer with a pH of 7.4 as the dissolution medium. The maximum in vitro dissolution of meloxicam, i.e. 97.45% in 60 min, was observed for solid dispersions containing meloxicam (150 mg), PEG 6000 (350 mg) and SLS (75 mg) prepared by solvent evaporation method containing a sum of 3 g of Lactose and MCC (4:1) as additives. The general trend indicated that there was an increase in dissolution rate for solid dispersions containing the solubilizer SLS. The best-fit model indicating the mechanism of dissolution from the formulation showing the highest release for was found to be Higuchi matrix release (r=0.9774, b=13.042, a=2.4798). Infra red spectroscopy (IR) indicated that meloxicam in solid dispersions showed physical entrapment. The increased in dissolution rate of meloxicam by solid dispersion technique may be due to increase wettability and hydrophilic nature of carrier.
Dissolution Improvement of High Drug-loaded Solid Dispersion was
done by Siriporn Okonogi et al. This study focused on an investigation of
a high drugloaded solid dispersion system consisting of drug, carrier, and
surfactant. Solid dispersions of a water-insoluble ofloxacin (OFX) with
polyethylene glycol (PEG) of different molecular weights, namely binary
solid dispersion systems, were prepared at drug to carrier not less than 5:5.
Polysorbate 80, a nonionic surfactant, was incorporated into the binary solid
dispersion systems as the third component to obtain the ternary solid
dispersion systems. The powder x-ray diffraction and differential scanning
calorimetric studies indicated that crystalline OFX existed in the solid
dispersions with high drug loading. However, a decreased crystallinity of
the solid dispersions obtained revealed that a portion of OFX was in an
amorphous state. The results indicated a remarkably improved dissolution
of drug from the ternary solid dispersion systems when compared with the
binary solid dispersion systems. This was because of polysorbate 80, which
improved wettability and solubilized the non–molecularly dispersed or
crystalline fraction of OFX.
References


