CHAPTER-II

1.0. INTRODUCTION TO FREE FLOWING SOLID DISPERSIONS

Aqueous solubility of any therapeutically active substance is a key property, it governs dissolution, absorption and thus the in vivo efficacy **(Modi, P and Tayade, H. K, 2007).** The enhancement of the bioavailability of poorly water-soluble drugs is one of the greatest challenges of drug development **(Karavas, E., et al., 2007).** 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 **(Shah TJ., et al. 2007)**. Oral bioavailability of a poorly water-soluble drug was greatly enhanced by using its solid dispersion in a surface-active carrier **(Joshi, H., et al., 2004).** Solid dispersions have been explored as potential delivery systems for poorly water soluble drugs **(Khoo, S M., 2000).** Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs **(Dhirendra, K., 2009).** The use of solid dispersions to increase the dissolution rate and the bioavailability of poorly water-soluble drugs is now well established. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms **(Ozkan, Y., et al., 2000).** Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine and nimodipine **(Ganesh C, et al. 2008).** Improvement in its solubility and dissolution rate may lead to enhancement in bioavailability **(Dixit, R. P and Nagarsenker, M. S, (2007).**

Efavirenz is a novel non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1-infected individuals **(Veldkamp, A I., et al., 1999).** Efavirenz is a classII drug according to the

biopharmaceutical classification system. It often demonstrates poor gastrointestinal absorption due to inadequate drug solubility in GI fluids. Efavirenz is a hydrophobic drug with low density and high flow resistance **(**Sathigari, S K., et al., 2009). The concept of solid dispersions dates back to 1961 when Sekiguchi & Obi found that the administration of a fused mixture of the poorly water-soluble drug sulphathiazole and the water-soluble carrier urea produced an enhanced absorption of the drug in rabbit **(Sekiguchi, K., et al., 1961).** Subsequently, hundreds of papers have been published detailing the physico-chemical properties phase equilibrium and pharmacological activity of solid dispersion-based drug carrier systems **(Ford and Timmins, 1989).** However, only few drug products based on solid dispersions have reached the market, because of physico-chemical instability and scale-up problems **(Serajuddin, AT., 1999), (Craig, DQ., 2002).**

Solid dispersions are generally prepared by either a solvent method, whereby the drug and carrier are dissolved in a mutual solvent followed by solvent removal, or by a melting method, whereby drug-carrier mixtures are prepared by co-melting/cooling. The disadvantage of the solvent method is the use of organic solvents with issues of toxicity, safety hazards and solvent residuals and also the possible precipitation of the drug into various polymorphic forms, which have different solubilities and bioavailability. Therefore, melting is often the method of choice for the preparation of solid dispersions despite the potential problem of heat-induced degradation of drugs and carriers. In general, for solid dispersion formulations contains high amount of polymers and all polymers are very sticky in nature which creates problems like practical yield and flow problems during scale up. Polyvinyl pyrrolidone, hydroxy propyl cellulose and hydroxy propyl methyl cellulose are commonly used in solid dispersion formulations.

The amorphous presentation of the Efavirenz was preferred as the highly disordered form has a lower energy barrier to overcome for dissolution than the structured crystalline form. Accordingly, excessively high temperatures and high amount of solvents were not required to produce the solid dispersion using solvent heat method. Additionally, neusilin acts as anti sticking agent which reduces the processing problems like less practical yield and flow problems normally occur in solid dispersion formulations.

Drug absorption from solid oral dosage forms depends on the release of the drug substance from the delivery system, the dissolution of the drug under the physiological conditions and the drug permeability across the gastrointestinal tract **(Muhammad Tayyab Ansari., et al., 2012).** Poorly water-soluble drugs are expected to have dissolution-limited absorption. Increasing the drug solubility may substantially contribute to improved drug absorption, and consequently, drug bioavailability. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs **(Muhammad, J., et al. 2000).**

1.1. Historical background of Solid dispersions

Increasing oral absorption of a drug incorporated into a 'eutectic mixture' is very successful. Sulfathiazole in a 'eutectic mixture' with urea showed higher oral absorption and excretion than ordinary sulfathiazole. The term 'solid-in-solid solutions' indicates that many drugs could form 'solid-solid solutions' with mannitol. The sulfathiazole-urea fused mixtures, at specific concentrations, form 'solid solutions' or 'amorphous precipitations', in which the dissolution rate of sulfathiazole increases significantly. Furthermore, 'glassy solutions' were obtained after cooling the melts of 5 and 20% of griseofulvin in citric acid, and again, the dissolution rate of the drug was increased and thus classified them into categories under the term 'solid dispersions' **(Sekiguchi, K., et al. 1961).** One of the underlying principles of formulation of solid dispersion

is achievement of the amorphous state which is considered to be more soluble than the crystalline state. Amorphous state in the solid dispersion system has its own advantages as well as limitations. This can be explained by the fact that in the amorphous state, no energy is required to break the crystal lattice found in the crystalline phase **(Mooter GVD, et al., 1998; Habib MJ, 2000; Law D, et al., 2000).**

1.2 Definition of solid dispersions

A solid dispersion **(Chiou W.L., et al. 1969; Monica R, 2010; Chiou W.L., et al. 1971)** is "the dispersion of one or more active ingredients in an inert carrier at solid-state prepared by melting (fusion), solvent or the melting-solvent method". The carrier used has traditionally been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as urea, citric acid and mannitol. However, the proliferation of publications in the solid dispersions area has led to a broadening of these definitions to include water-insoluble matrices such as Gelucires **(Kanig, J.L., 1964), (Levy, G., 1963).**

Table 1: Different materials used as carriers for solid dispersions

Sugars	**Acids**	**Polymeric materials**	**Insoluble or enteric polymers**	**Surfactants**	**Miscellaneous**
Dextrose	Citric acid	Polyvinylpyrrolidone (PVP)	Hydroxy propyl methyl cellulose phthalate	Polyoxyethylene stearate	Pentaerythritol
Sucrose	Succinic acid	Polyethylene glycols (PEG)	Eudragit L-100	Poloxamer 188	Pentaerythrityltetracetate
Galactose		Hydroxypropyl-methylcellulose	Eudragit S-100	Deoxycholic acid	Urea
Sorbitol		Methylcellulose	Eudragit RL	Tweens	Urethane
Maltose		Hydroxyethylcellulose	Eudragit RS	Spans	Hydroxyalkylxanthins
Xylitol		Hydroxypropylcellulose			
Mannitol		Cyclodextrins			
Lactose		Pectin			
		Galactomannan			

1.3 Methods of preparing solid dispersions

1.3.1. Melting or fusion method

In this method, a physical mixture of the drug and the carrier is heated until it is melted. The melt is then cooled, and the resultant solid dispersion is pulverized and sieved. The question of whether the drug needs to be dissolved in the molten carrier or not has not been fully resolved **(Craig, DQ., 2002).** Indeed, a low temperature fusion meth **(Jani Rupal, et al. 2009), (Mushir Ali, et al., 2010)** to prepare solid dispersions. They added the drug to the molten carrier at a relatively low temperature. By using this method, the structure of the drug particles remains largely unchanged during the manufacturing process (**Mariko lwata, et al. 1996), (Shinde, S.S., et al., 2010).**

Nevertheless, the cooling rate used may significantly affect the aging behavior of the solid dispersions. It has been reported that the crystallinity of drug in solid dispersions is less affected by aging when a slow cooling rate is used because thermodynamically more stable systems are produced **(Hemant, N., et al 2004).** On the other hand, rapid cooling of molten mixtures is desirable because it leads to instantaneous solidification, resulting in the drug molecules being trapped in the carrier matrix for rapid cooling **(Geert Verreck, et al. 2003), (M. Franco, G., et al. 2001), (Madhuri Newa, et al 2008), (Kazunari Yamashita, et al 2003), (P. N. Murthy, et al 2009), (Riikka Laitinen, et al 2010), (Jani Rupal, et al. 2009)** used icebath with vigorous stirring and poured the fused mixture onto ferrite plate. On the other hand, stainless steel plates are cooled by flowing air or water on opposite side of the plate. However, a solid mass was formed after cooling the molten mixture, so it was necessary to pulverize the solidified mixture before it could be tested. To avoid the pulverization process which would change the physical structure of solid dispersions, spray congealing technique is used. By using this technique, solid

dispersions in pellet form were obtained (**Goldberg, A.H., et al. 1965), (Goldberg, A.H., et al. 1966a), (Goldberg, A.H., et al. 1966b)**

1.3.2. Solvent method

This method includes dissolving the drug and the carrier in a common organic solvent, followed by evaporating the solvent at elevated temperature, under vacuum, or by freeze-drying or spray-drying the mixture **(Serajuddin, A.T.M., et al. 1988), (Serajuddin, A.T.M., et al. 1990), (Erika Broman, et al. 2001).**

1.3.3. Melting-solvent method

In this method, the drug is dissolved in a minimum amount of an organic solvent, and then it is added to the molten carrier. It is reported that in the preparation of spironolactone-polyethylene glycol 6000 solid dispersion without removing the solvent, 5-10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property **(Chiou, W.L., et al 1969).**

1.3.4. Hot-melt extrusion

In this technique, the blend of drug and carrier is processed with a twin-screw extruder of the same type used in the polymer industry. The blend is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. An important advantage of the hot melt extrusion method is that the drug-carrier mixture is only subjected to elevated temperatures for a few minutes, which enable both the drug and the carrier to remain thermally stable **(Goldberg, A.H., et al. 1966a).**

1.3.5. Supercritical fluid process

This process includes dissolving the drug and carrier in supercritical CO_2 under precise conditions of temperature and pressure, followed by rapid depressurization. Supercritical CO_2 is nontoxic and it has the potential as an alternative for organic solvents **(Serajuddin, A.T.M., et al. 1990).**

1.4 Classification of solid dispersions

1.4.1 Simple eutectic mixture

Simple eutectic mixture can be obtained from the rapid solidification of the fused liquid of two components that show complete liquid miscibility and negligible solid-solid solubility. **(Goldberg, A.H., et al. 1966b).**

1.4.2. Solid solution

In this class, the drug and the carrier crystallize together in a homogeneous one phase system, and the particle size of the drug is reduced to its molecular size. In other words, the dissolution of the drug in the carrier occurs in the solid state. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems. Examples include digitoxin, hydrocortisone acetate and prednisolone dispersions in polyethylene glycol 6000 (PEG 6000). In practice, the occurrence of solid solubility of less than 2% is considered insignificant **(Erika Broman, et al. 2001).**

1.4.3. Amorphous precipitation in a crystalline carrier

The active ingredient in some solid dispersion may precipitate out as an amorphous deposit in the crystalline carrier, such as the dispersion of sulfathiazole in urea **(Goldberg, A.H., et al. 1966b).** In amorphous materials, molecules are randomly arranged, in contrast to crystalline materials where the molecules are arranged in an ordered three-dimensional array.

1.4.4. Glassy solutions or suspensions

Amorphous polymers, such as polyvinylpyrrolidone (PVP), can form glassy systems in which the drug is dispersed either as molecules or as particles **(Ozkan, Y., 2000).**

1.4.5. Compound or complex formation

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. For example, it was reported that digoxin and hydroquinone formed a complex which exhibited a high dissolution rate.

1.5. Characterization of solid dispersions

Several methods have been used to characterize solid dispersions, such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), infrared spectroscopy (IR), hot stage and electron microscopy, and dissolution testing. Among these, thermal and spectral methods (i.e. DSC, XRD and IR) are of special interest. The main purpose of using these methods is to differentiate between crystalline and non-crystalline structure of solid dispersions.

1.5.1. Differential scanning calorimetry

When a material is heated or cooled, there is a change in its structure (e.g. melting or crystallization), or its composition (e.g. oxidation). These changes are connected with heat exchange. Some of these changes are endothermic (i.e. heat consuming process such as melting), and others are exothermic (i.e. heat producing process such as crystallization). Differential scanning calorimetry (DSC) is used for measuring the differences in heat flow between a sample and a reference during a controlled change of temperature. DSC analysis allows quantitative and qualitative information to be obtained about the physical and chemical changes that occur in the sample. DSC is used extensively in pharmaceutical industry to determine the melting points, purity, and glass transition temperatures of materials. In the solid dispersion area, DSC is a

powerful tool in evaluating the drug-carrier interactions, determining the solubility of a drug in a polymeric carrier, detecting polymorphic modifications and examining age-induced changes. The absence of the drug melting peak in the DSC thermal profile of a solid dispersion indicates that the drug is dispersed molecularly, or it exists in the amorphous form.

1.5.2. X-ray diffraction

Diffraction of X-rays is the basic technique for obtaining information on the atomic structure of crystalline solids. The phenomenon of X-ray diffraction by crystals results from a scattering process in which X-rays are scattered by the electrons of the atoms without change in wavelength. The crystallinity in a sample is reflected by a characteristic fingerprint region in the diffraction pattern. In a solid dispersion, the crystallinity in the drug can be separately identified from crystallinity in the carrier by using the X-ray diffraction. Therefore, it is possible to differentiate between solid dispersions in which the drug is molecularly dispersed, and solid dispersions in which the drug is present in the crystalline form. However, crystallinities of under 5-10% cannot generally be detected with X-ray diffraction.

1.5.3. Fourier transformed infrared spectroscopy

Fourier transformed spectroscopy is widely used because of its rapid providing of high resolution spectra with samples in the nanogram range. Structural changes and lack of crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not.

1.6. Advantages of solid dispersions

1.6.1. Increased dissolution rate

The fact that more than 40% of newly discovered drugs have little or negligible water solubility presents a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry. **(Sathigari, S K., et al., 2009).**

Factors influencing drug dissolution rate in aqueous solution are described in

Noyes-Whitney equation

dC/dT= AD(Cs-C) /h

dC/dT is the rate of dissolution, A is the surface area available for dissolution,

D is the diffusion coefficient of the drug, Cs is the solubility of the drug in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving drug.

According to this equation, dissolution rate can be increased by increasing the surface area, and this can be achieved through reducing the particle size. Different methods have been used to reduce the particle size, such as micronisation, recrystallization, freeze drying and spray drying.

1.6.2. Enhanced oral bioavailability

Drug dissolution is a prerequisite to drug absorption and *in vivo* effectiveness for almost all drugs given orally. This can be explained by **Fick's** first law which describes the diffusion of a substance through a membrane:

$$\boldsymbol{Dm/dt = -DAdc/dx}$$

dm/dt is the diffusion rate, D is the diffusion constant, A is the membrane, surface area,

dc is the change in concentration, and dx is the membrane thickness.

From this law, it can be inferred that the drug flux through the intestinal wall, during the diffusion process, is directly proportional to the concentration gradient between drug in the gut and drug in the blood. This may explain why poorly soluble drugs are represented very often by low absorption and poor bioavailability. Many studies indicated that increased dissolution rate of poorly soluble drugs, from their solid dispersions, led to an improvement in the oral bioavailability of those drugs. Examples include, but not limited to, phenytoin dispersions in polyethylene glycol 4000 (PEG 4000),nitrofurantoin dispersions in polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone (PVP) and mannitol,digitoxin dispersions in deoxycholic acid,tolbutamide dispersions in polyvinylpyrrolidone (PVP), sulfamethoxazole dispersions in polyvinylpyrrolidone (PVP) and dicumarol dispersions in polyvinylpyrrolidone (PVP) **(Erika Broman, et al. 2001).**

1.7. Limitations of solid dispersions

Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, griseofulvin in polyethylene glycol and nabilone in polyvinylpyrrolidone solid dispersions, were marketed. Main problems limiting the commercial application of solid dispersion involve

(a) The physical and chemical stability of drugs and vehicles,

(b) Method of preparation,

(c) Reproducibility of its physicochemical properties,

(d) Its formulation into dosage forms, and

(e) The scale-up of manufacturing processes.

1.7.1. Stability

Physical instability of solid dispersions such as phase separation and subsequent crystallization may reduce the dissolution rate of the active ingredients **(Serajuddin, A.T.M., 1999).** The moisture might facilitate the crystallization of amorphous drugs, and for this reason solid dispersions should be protected from moisture. Various studies reported reduced dissolution rates of drugs, incorporated into solid dispersions, upon ageing. Solid dispersion systems such as chlorpropamide-urea, Indomethacin-polyethylene glycol 6000, and phenylbutazone-polyethylene glycol 6000 showed reduced dissolution rates of active ingredients on storage **(Serajuddin, A.T.M., et al. 1988), (Serajuddin, A.T.M., et al. 1990).**

1.7.2. Method of preparation

When fusion method is used, high melting temperature may chemically decompose drugs and/or carriers. On the other hand, total removal of toxic organic solvents used in the preparation of the dispersions is the main problem associated with the solvent method. Hence, the extrusion method provides a good alternative to the fusion and solvent methods.

1.7.3. Reproducibility of physicochemical properties

Manufacturing conditions may greatly influence the physicochemical properties of solid dispersions. Various investigators observed that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate and method of pulverization might affect the properties of solid dispersions prepared by the melting method including the particle size distribution

1.7.4. Dosage form development

Pulverizing, sieving, mixing and compressing of solid dispersions, which are usually soft and tacky, are difficult. This may reduce the chance of developing suitable solid dosage forms of drugs dispersed in solid dispersions.

1.7.5. Scale-up of manufacturing processes

The physicochemical properties and stability of solid dispersions may be affected by scale-up processes because heating and cooling rates of solid dispersion prepared in a large scale may differ from that of a small scale. It is also expensive and not practical to evaporate hundreds and even thousands of liters of organic solvents to prepare solid dispersions for kilogram quantities of drugs **(Dhirendra, K., 2009).**

2.0. LITERATURE SURVEY FOR SOLID DISPERSIONS

Janssens et al ., (2008) Influence of the polyethylene glycol chain length on the miscibility of the PEG/HPMC2910E5 Polymer blends, the influence of polymer blends, the influence of polymer compatibility on the degree of molecular dispersion of Itraconazole , and in-vitro dissolution.PEG2000,6000,10,000 & 20,000 were included in the study. The polymer miscibility increased with decreasing chain length due to decrease in the Gibbs free energy of mixing. Finally Janssens concluded that shorter chain length PEG types (2000 & 6000) better than over the longer chain length PEG Types (10,000 & 20,000) (Janssens, S., et al 2008)

Bley et al., (2010) Explain Characterization and stability of solid dispersions (carbamazepine, nifedipine) based on PEG/polymer blends >80% drug released from all solid dispersions within 20 min. The dissolution rate is PEG1500>PEG1500 / Eudragit>PEG1500 / PVPK-30>PEG1500 / PVPVA>PEG 1500 / PVPK-12[76] **(**Bley, H., et al. 2010).

Dahlberg., (2010) Explains the Polymer-Drug interactions and wetting property of Solid dispersions. The Hydrophobic drug incorporated in hydrophilic polymer matrices, made of either Hydroxypropylmethylcellulose (HPMC) or Polyvinyl pyrrolidone (PVP). The physical mixtures of all combinations of drug and polymer presented surface hydrophobicites, as measured by the equilibrium advancing contact angle of water. The wetting behaviour is explained like that Pure drug<physical mixture<solid dispersions. The mechanism is formation of inter molecular hydrogen bonds, water ingress and swelling explained by water contact angle and NMR study[77] (Bley, H., et al. 2010).

Mohammad et al., (2007) Ibuprofen solid dispersions were prepared by the solvent and fusion-solvent methods using polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), eudragit RS PO, eudragit RL PO and hydroxypropylmethylcellulose (HPMC) as carriers to improve physicochemical characteristics of ibuprofen. The prepared solid dispersions were evaluated for the flowability, solubility characteristics and dissolution behavior **(Mohammad Fahim Kadir, et al. 2007).**

Evangelos et al., (2006) Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersion in hydrophilic carriers based on physical state of drug , particle size distribution and drug-polymer interactions **(Evangelos Karavas, et al. 2005)**

Ilse et al., (2005) Physical stability of the amorphous state of Loperamide and two fragment molecules in solid dispersions with the polymers PVP-K30 and PVP-VA64 (**Ilse et al., 2005)**.

Verheyen et al., (2002). The aim of the present study was to fill up the three above mentioned gaps in solid dispersion literature. Therefore, physical mixtures and solid dispersions were prepared and in order to unravel the relationship between their physico-chemical properties and dissolution characteristics, pure drugs (diazepam, temazepam), polymer (PEG6000), solid dispersions and physical mixtures were characterized by DSC, X-ray powder diffraction (Guinier and Bragg-Brentano method), FT-IR spectroscopy, dissolution and solubility experiments and the particle size of the drug in the dispersion particles was estimated using a newly developed method. Addition of PEG6000 improves the dissolution rate of both drugs. Mechanisms involved are solubilisation and improved wetting of the drug in the polyethylene glycol rich micro-environment formed at the surface

of drug crystals after dissolution of the polymer. Formulation of solid dispersions did not further improve the dissolution rate compared with physical mixtures.

Ali et al., (2010). This study probes the molecular interactions between model drugs and poloxamers that facilitate dissolution rate improvements using solid dispersions. Ibuprofen and ketoprofen solid dispersions were prepared at different mole ratios using poloxamers 407 and 188.