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SOLID DISPERSION TECHNIQUE: A TOOL FOR ENHANCING BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Over the years, a variety of solubilization techniques have been studied and widely used, by many estimates up to 40 per cent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous.

Different methods are also been used for preparation of solid dispersions such as Melting method, Solvent method, Melting solvent method (melt evaporation), Melt extrusion method, Lyophilisation Technique, Melt Agglomeration Process, The Use Of Surfactant, Electro spinning and Super Critical Fluid (SCF) Technology.

KEY WORDS: solubility enhancement, solid dispersions, poorly soluble drugs.

1.INTRODUCTION

The progress in treatment of diseases has been evident within upsurge in development of new drugs. An estimated 40% of these drugs are poorly water soluble. Although most of the drugs have encouraging experimental data obtained *in vitro*, the *in vivo* results have been disappointing. The attributes include

1.Poor absorption, rapid degradation, and lamination (peptides and proteins) resulting in insufficient concentration,
2.Drug distribution to other tissues with high drug toxicities (anticancer drugs),
3.Poor solubility of drugs, and
4.Fluctuations in plasma levels owing to unpredictable bioavailability.

The enhancement of oral bioavailability of such drugs, whose solubility is poor, remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization
by cosolvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. In spite of these advantages, only a very few products have been marketed since the development of this technology 4 decades ago.

The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include

1.Laborious and expensive methods of preparation,
2.Reproducibility of physicochemical characteristics,
3.Difficulty in incorporating into formulation of dosage forms,
4.Scale-up of manufacturing process, and
5.Stability of the drug and vehicle.

Definition: The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particle based on their molecular arrangement.

There are many types of solid dispersions which includes Simple eutectic mixtures, solid solutions, glass solutions, amorphous precipitation in a crystalline carrier and according to the way in which the solvate molecules are distributed in the solvent.

For Example: Table 1:

S.No.	Carrier	Drug
1	Polyethylene glycol (PEG)	Griseofulvin
2	Polyvinyl pyrrolidone (PVP)	Flufenamic acid
3	Hydroxy propyl methyl cellulose (HPMC)	Albendazole, Benidipine
4	Sorbitol	Prednisolone
5	Urea	Ofloxacin

Ideal candidates for solid dispersion: Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption *in vivo* will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) Class II drugs are those with low aqueous solubility and high membrane permeability and therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances are classified in four groups as shown in Table 2 (FDA 2000). Table 3 represents some BCS Class II drugs on the WHO model list of Essential Medicines. The table is adopted from Lindenberg, 2004, only for the BCS Class II drugs.

Table 2 Biological classification system (BCS)

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Table 3 Some BCS class II drugs on the WHO model list of Essential Medicines

Drug	Used as
Carbamazepine	Antiepileptic
Dapsone	Antirheumatic/leprosy
Griseofulvin	Antifungal
Ibuprofen	Pain relief
Nifedipine	Ca-channel blocker
Nitrofurantoin	Antibacterial
Phenytoin	Antiepileptic
Sulfamethoxazole	Antibiotic
Trimethoprim	Antibiotic
Valproic acid	Antiepileptic

Categories of Solid Dispersions: a. Simple eutectic mixtures, b. Solid solution
According to their miscibility: 1.Continuous, 2.Discontinuous solid solutions
According to the way in which the solvate molecules are distributed in the solvent:
1.Substitutional crystalline solid solutions, 2.Interstitial crystalline solid solutions, 3.Amorphous solid solutions
c. Glass solutions
d. Amorphous precipitation in a crystalline carrier
Simple eutectic mixtures: When a mixture containing A and B (Figure.1) with composition 'E' is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out of the solution before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

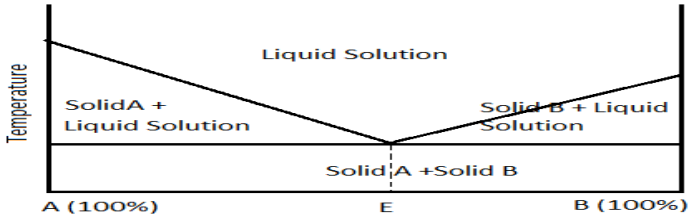

Fig.1. Phase diagram for a eutectic system

Solid solutions:

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

Discontinuous solid solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. One of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg (1964) that the term solid solution should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

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

Interstitial crystalline solid solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

Amorphous solid solutions: In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to bind the polymer, leading to a reduction in its glass transition temperature.

Glass solutions and glass suspensions: Chiou and Riegelman (1969) first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The familiar term glass however, can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature. On heating, it softens progressively and continuously without a sharp melting point.

Methods of Preparation of Solid Dispersions: Different methods are also been used for preparation of solid dispersions such as Melting method, Solvent method, Melting solvent method (melt evaporation), Melt extrusion method, Lyophilisation Technique, Melt Agglomeration Process, The Use Of Surfactant, Electro spinning and Super Critical Fluid (SCF) Technology .

Melting method: The melting or fusion method, first proposed by Sekiguchi and Obi (1961) involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by blowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

Solvent method: In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main

advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

Some disadvantages are associated with this method such as

1.The higher cost of preparation.

2.The difficulty in completely removing liquid solvent.

3.The possible adverse effect of traces of the solvent on the chemical stability

4.The selection of a common volatile solvent.

5.The difficulty of reproducing crystal form.

6.In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties.

Melting solvent method (melt evaporation): It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5–10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

Melt extrusion method: The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

Solid dispersion by this method is composed of active ingredient and carrier, and prepared by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185 ^{0}C from feeder to the die cavity. The extrudates are collected after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm.

Lyophilisation Technique: Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Melt Agglomeration Process: This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration because these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates.

The use of surfactant: The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.

Advantages of solid dispersion:

Particles with reduced particle size: Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

Particles with improved wettability: A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any

surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with higher porosity: Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state: Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution; a unit is speculated that, if drugs precipitate, it is as a meta stable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Characterization of solid dispersion:

Detection of crystallinity in solid dispersions: Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are available which detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is mostly derived from the amount of crystalline material in the sample. It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed whether the drug is present as amorphous drug particles or as molecularly dispersed molecules.

Currently, the following techniques are available to detect (the degree of) crystallinity:

1.Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi-quantitative.

2.Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibration bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material. However in solid dispersions only qualitative detection was possible.

3.Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

4.Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg). However, this technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

5.Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

6.Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solid.

7.A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting-and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material. Possibly, the re-crystallization energy can be used to calculate the amount of amorphous material provided, that all amorphous material is transformed to the crystalline state. If during DSC-measurements, amorphous material crystallizes, information is obtained on the crystallization kinetics and on the physical stability of the amorphous sample. To quantify the amount of crystalline material, measurements should be completed before crystallization of amorphous material has started. In some cases, this can be established applying high scanning rates.

Detection of molecular structure in amorphous solid dispersions*:*

1.Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP. It was described that a standard deviation in drug content smaller than10% was indicative of homogeneous distribution. Because of the pixel size of 2µm, uncertainty remains about the presence of nano-sized amorphous drug particle.

2.Using IR or FTIR, the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements.

3.Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC. Therefore this technique can be used to assess the amount of molecularly dispersed drug, and from that the fraction of drug that is dispersed as separate molecules is calculated.

Alternative strategies in the manufacturing of solid dispersions:

Spraying on sugar beads using a fluidized bed coating system: The approach 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 has been applied for both controlled- and immediate-release solid dispersions. Itraconazole coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxyl propyl methyl cellulose (HPMC) in an organic solvent of dichloromethane and ethanol. A solid solution of drug in HPMC is produced upon coating (co solvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole. The supersaturated solutions of itraconazole are sufficiently stable to allow for absorption and distribution.

Direct capsule filling: Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatine capsules has been feasible in molten dispersions of Triamterene-PEG 500 using a capsule-filling machine. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (e.g.: polysorbate 80 with PEG, phosphatidylcholine with PEG). The temperature of the molten solution should not exceed70^0 C because it might compromise the hard-gelatin capsule shell.

Electrostatic spinning method: This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology in this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameters are formed. As the solvent evaporates, the formed fibres can be collected on a screen to give a nonwoven fabric, or they can be collected on as pinning mandrill. The fibre diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. Water soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and non-biodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared using this technique.

2.CONCLUSION

Extensive research has been done in the field of solid dispersions to enhance bioavailability of the poorly soluble drugs. The researchers have used different types of polymers to enhance the solubility of a variety of drugs. Some of the drugs and the polymers used to enhance solubility and bioavailability of the drugs is given the Table 4. Still there is a lot of scope for research on this subject, because so far the researchers have concentrated on the lab scale manufacturing and evaluation of solid dispersions, except a few articles, discussion on scaleup studies and methods for commercial manufacturing were not mentioned.

Table 4 List of drugs and polymers used to enhance bioavailability of the poorly soluble drugs

S.No	Drug	Polymer/ Excipient	Reference
1	Glipizide, Rofecoxib, Piroxicam and Carvedilol	Cyclodextrin	Anuj Kumar, Review On Solubility Enhancement Techniques For Hydrophobic Drugs, Available online at www.pharmacie-globale.infoPharmacie Globale© (IJCP), 2(3).
2	Efavirenz	Starch phosphate	K.P.R.Chowdary, Enhancement of Dissolution Rate and Formulation Development of Efaverenz Tablets Employing Starch Phosphate a New Modified Starch ,IJPSDR April-June, 2011, 3(2), 80-83.
3	Meloxicam	Polyvinyl Pyrrolidone (PVP) and PEG 6000	Mohammed Jafar **,** Enhancement of Dissolution and Anti-inflammatory Effect of Meloxicam Using Solid Dispersions, International Journal of Applied Pharmaceutics, 2(1), 2010.
4	Rofecoxib	Polyethylene glycol 6000	Rakesh Kumar Sharma, Preformulation studies a view to develop fast release solid dosage, International Journal of Drug Delivery, 2, 2010, 32-36.
5	Gliclazide	(PEG)4000, PEG6000 and PVPK 30	Averineni Ranjith Kumar, Enhanced dissolution and bioavailability of Gliclazide using solid dispersion techniques, International Journal of Drug Delivery, 2, 2010, 49-57.
6	Ritonavir	Starch Phosphate	K.P.R.Chowdary and Veeraiah Enturi, Enhancement of Dissolution Rate and Formulation Development of Ritonavir Tablets Employing Starch Phosphate-A New Modified Starch, IJPSR, 2(7), 2011, 1730-1735.
7	Valsartan	Polyvinyl pyrrolidone, Hydroxypropyl β-cyclodextrin, Hydroxypropyl methylcellulose	Amit R. Tapas, Spherically agglomerated solid dispersions of valsartan to improve solubility, dissolution rate and micromeritic properties, International Journal of Drug Delivery, 2010, 304-313.
8	Etoricoxib	Starch Citrate	Chowdary. K.P.R**,** Formulation Development of Etoricoxib Tablets by Wet Granulation and Direct Compression Methods Employing Starch Citrate, July – September 2011 RJPBCS, 2(3), 983.
9	Allopurinol	Gelucire 50/13	Jagdale S. C, Preparation and in vitro evaluation of Allopurinol-Gelucire 50/13 solid dispersions, International Journal of Advances in Pharmaceutical Sciences,1,2010, 60-67.
10	Aceclofenac	PVPk30, HPMC E-5 (BASF), Aerosil 200 (Degussa).	Shinde S.S, An approach for solubility enhancement: solid dispersion, International Journal of Advances in Pharmaceutical Sciences 1, 2010, 299-308.
11	Naproxen, Nifedipine and Carbamazepine (CBZ).	Hypromellose USP Type 2208 (METHOCELK 3LVPremium) Hypromellose USP Type2910 (METHOCEL E3LV Premium and E5LV Premium)	Shawna Mitchell, Tinap Dasbach, And Thomas D. Reynolds, Development of a compaction process to enhance dissolution of poorly water-soluble drugs utilizing hypromellose ,The Dow Chemical Company, Midland, MI 48674, USA
12	Progesterone	Cyclodextrine	Rajkumar S Moon, Methods For Enhancing Bioavailability Of Drug, IJPT, March-2011, 3(1), 912-926.
13	Atorvatstatin	PEG 4000, PVP-K30 and Mannitol	K.R.Bobe, Formulation And Evaluation of solid dispersion of Atorvatstatin with various carriers, Pharmacie Globale© (IJCP), 2(2).
14	Celecoxib	PVP-K30 and SLS	Muralidhar S, To Enhance Studies dissolution properties of Celecoxib, Pharmacie Globale© (IJCP), 2(1).
15	Rosiglitazone	PGS, SSG	K. Punitha *,ex vivo* permeability experiments in excised goat intestinal tissue and *in vitro* solubility enhancement of Rosiglitazone by solid dispersion technique, Journal of Pharmacy Research Vol.4.Issue 1, January 2011, K.Punitha et al. / Journal of Pharmacy Research 2011,4(1),80-82.

16	Clonazepam	PEG 4000	Swati C. Jagdale ,Solid State Characterization of Clonazepam in Solid Dispersion and Formulation of Fast Dissolving Tablet, Journal of Pharmacy Research Vol.4.Issue 2. February 2011, Journal of Pharmacy Research 2011,4(2),480-487.
17	Piroxicam	PEG-6000; Eudragit RL-100	Itishree Jogamaya Das, Enhancement of Dissolution Rate of Piroxicam Using Solid Dispersions With PEG-6000 and Eudragit RL-100, Journal of Pharmacy Research Vol.4.Issue 5. May, Journal of Pharmacy Research 2011, 4(5), 1473-1479.
18	Atorvatstatin	HPMC	Riazuddin, Water solubility enhancement of Atorvatatain by solid dispersion method, S.J.Pharm.Sci., 3(2), 43-46.
19	Daidzein	PEG, Tween-80	Jingyu Zhang, Effects of Tween-80 on the Dissolution Properties of Daidzein Solid Dispersion in Vitro, International Journal of Chemistry, 3(1), 2011.
20	Itraconazole	Poloxamer188	Siling Wanga, Increasing solubility and dissolution rate of drugs via eutectic mixtures: Itraconazole–poloxamer188, Asian Journal of Pharmaceutical Sciences, 2006, 1(3-4), 213-221.
21	Terbinafine Hydrochloride	PEG 6000 and polyvinyl pyrrolidone K 30	K. Arun Prasad, Preparation and evaluation of solid dispersion of Terbinafine hydrochloride, 3(1), Article 027.
22	Nimesulide, Ketoprofen, Tenoxicam, Nifedipine, Nimodipine, Ursodeoxy cholic acid, Carbamazepine, Celecoxib and Albendazole	Polyethylene glycol, polyvinyl pyrrolidone, hydroxypropyl cellulose, HPMC, gums, sugar, mannitol, urea, gelucires, eudragit and chitosan	Renu Kalyanwat, Solid Dispersion: A Method For Enhancing Drug Dissolution , International Journal of Drug Formulation & Research ,Nov-Dec. 2010, Vol. 1 (iii) 1-14.
23	Etilevodopa, Caepecitabine, Oseltamivir, Docarpamine and Simvastatin	Cyclodextrins	Yellela S R C Krishnaiah, Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs, 2(2), 2010, 028-036.
24	Glipizide	PEG 6000 and mannitol	Dehghan, Comparative Dissolution Study of Glipizide by Solid Dispersion Technique, Journal of Pharmaceutical Science and Technology, 2(9), 2010, 293-297.
25	Nevirapine	Polyvinyl pyrrolidone K 30	Ahire B. R, Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Techniques, International Journal of PharmTech Research, 2(3), 2010, 2007-2015.
26	Itraconazole and Carbamazapine	Hydroxy propyl methyl cellulose PEG 4000	Hamsaraj Karanth, Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report, AAPS PharmSciTech.,7(4),2006,Article 87.
27	Nevirapine	Dextran	Lokamatha K. M, Enhancement Of Solubility And Dissolution Rate Of Nevirapine By Solid Dispersion Technique Using Dextran: Preparation And *In Vitro* Evaluation, Publication, 2(12), 2001.
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