Review Article [Sharma *et al.*, 4(7): July, 2013]
CODEN (USA): IJPLCP **ISSN: 0976-7126**

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

A review on: Solid dispersion

Rajni Sharma*, Rupa Mazumder, Archana Sharma and Praveen Verma
Department of Pharmaceutical Technology, Noida Institute of engineering and technology (NIET), Greater Noida - India

Abstract

Solid dispersion, defined as the dispersion of one or more active ingredient in a carrier or matrix at solid state, is an efficient strategy for improving dissolution of poorly water-soluble drugs for enhancement of their bioavailability. Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor water solubility. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs.

Key-Words: Solid dispersion, solubility, Poorly water soluble

Introduction

The work of Sekiguchi and Obi (1961) was the first to show the possibility of increasing oral absorption of a drug incorporated into a 'eutectic mixture'. Sulfathiazole in a 'eutectic mixture' with urea showed higher oral absorption and excretion than ordinary sulfathiazole. The term 'solid-in-solid solutions' was first used by Levy (1963) and Kanig (1964) who indicated that many drugs could form 'solid-solid solutions' with mannitol.

Solid dispersion, as implied in its name, refers to the solid state where one substance is dispersed into another material. The substances can be mixed completely or partially, containing several phase. Basically in this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. The drug in solid dispersion can be dispersed molecularly, in amorphous particles, or in crystalline particles. The matrix can also be in crystalline or amorphous state. The purpose of making hydrophobic drugs into solid dispersion formulation is to disperse the hydrophobic drug into the hydrophilic matrix so that the hydrophilic matrix can melt prior to the drug in the gastrointestinal fluid.

*** Corresponding Author**
E.mail: rockrj.sharma.1234@gmail.com

The drug dispersed in the matrix can then be saturated in the gastrointestinal fluid with rapid dissolution rate when the solid dispersion drug is taken orally. Drug saturation in GI fluid can help improve the efficiency of drug absorption through the GI membrane. Most of the solid dispersion systems initially focused on producing increased dissolution rates and sustained release of drugs with improved solubility and stability.

Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system:

Particle Size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent.

Temperature

Generally, an increase in the temperature of the solution increases the solubility of a solid solute.

Pressure

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

Nature of the solute and solvent:

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures.

Molecular size

The larger the molecule or the higher its molecular weight the less soluble the Substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules.

This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute Molecules.

Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

Rate of solution

The rate of solution is a measure of how fast substances dissolve in solvents.

Various factors affecting rate of solution

(a) Size of the particles

Breaking a solute into smaller pieces increases its surface area, when the total surface area of the solute particles is increased; the solute dissolves more rapidly because the action takes place only at the surface of each particle and hence increases its rate of solution.

(b) Temperature

For liquids and solid solutes, increasing the temperature not only increases the amount of solute that will dissolve but also increases the rate at which the solute will dissolve. For the gases reverse is true.

(c) Amount of solute already dissolved

When there is little solute already in solution, dissolution takes place relatively rapidly. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

(d) Stirring

With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution.

Biopharmaceutical classification

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

Table 1: Biopharmaceutical Classification

Class	Solubility	Permeability	Absorptionrate control step
Class I	High	High	Gastric emptying
Class II	High	Low	Dissolution
Class III	Low	High	Permeability
Class iv	low	Low	Case by case

a. Class I (Reddy B.Basanta Kumar., et al 2011)

The drugs of this class exhibit high absorption number and high dissolution number. The rate-limiting step is drug dissolution, and if dissolution is very rapid, then the gastric-emptying rate becomes the rate-determining step. These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate. Examples include metoprolol, diltiazem, verapamil, and Propranolol.

b. Class II The drugs of this class have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time. In vitro–in vivo correlation (IVIVC) is usually accepted for Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the in vivo bioavailability and the in vitro solvation can be found. Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine, ketoprofen, naproxen, carbamezapine and ketoconazole.

c. Class III

Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These

drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors.If the formulation does not change the permeability or gastrointestinal duration time, then Class I criteria can be applied. Examples include cimetidine, ranitidine, acyclovir, neomycin B, atenolol, and captopril.

d. Class IV

The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Fortunately, extreme examples of Class IV compounds are the exception rather than the rule, and these are rarely developed and marketed. Nevertheless, several Class IV drugs do exist. Examples include hydrochlorothiazide, taxol and furosemide.

Drugs classified in BCS on the basis of:

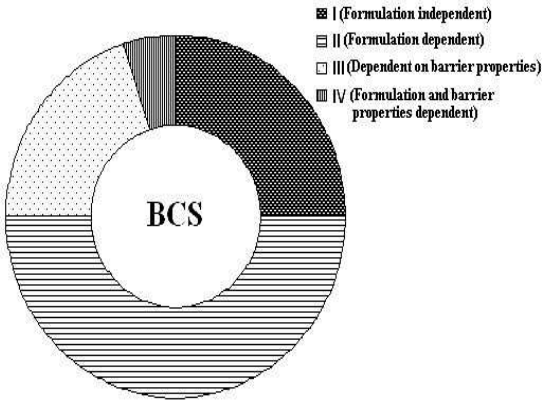
1.Solubility
2.Permeability
3.Dissolution

The class boundaries for these parameters are:

Solubility class boundaries- It is based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250ml or less of aqueous media over the ph range of 1 to 7.5. The volume estimate of 250ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

Permeability class boundaries- It is based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of prediction the drug absorption systems capable of predicting the drug absorption in humans can be used (such as in-vitro culture methods). A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of the administered dose based on a mass-balance determination or in comparsion to and intravenous dose.

Dissolution class boundaries- An immediate release products is considered rapidly dissolving when no less than 85% of the labelled amount of the drug substance dissolve within 15 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900ml or less in following media,) 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid.



Solid dispersion

First generation solid dispersions

The solid dispersions, which could be designed as first generation solid dispersions, were prepared using crystalline carriers. Crystalline carriers include urea and sugars which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second generation solid dispersions

In the late sixties it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers. Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates .Natural product based polymers are mainly composed by Cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins. Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both. In amorphous solid

solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them. In these systems, the drug and carrier interaction energy is extremely high, resulting in a really true solution. The use of polymers in the preparation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved.

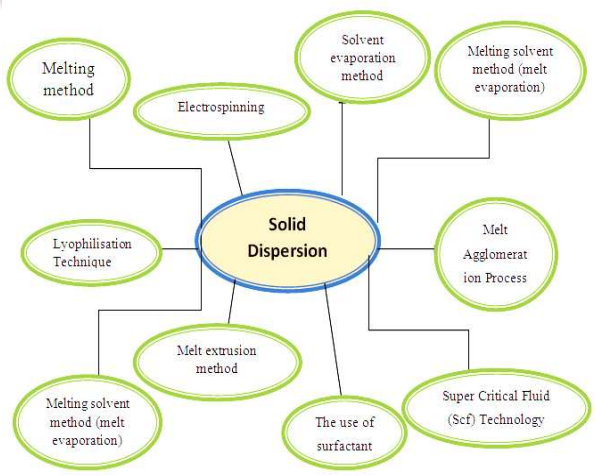
Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as insulin, inutec SP compritol 888 ATO gelucire 44/14and poloxamer-407as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.

Suitable properties of a carrier for solid dispersions

- High water solubility – improves wettability and enhances dissolution
- High glass transition point – improve stability
- Minimal water uptake (reduces Tg)
- Soluble in common solvent with drug – solvent evaporation
- Relatively low melting point –melting process
- Capable of forming a solid solution with the drug-similar solubility parameters

Methods of preparation of solid dispersions



Melting Technique

The melt method is sometimes referred to as the fusion method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix, which was melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I. Poly (ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly (vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its *Tg* (glass transition temperature). The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained. The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle. Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants. Secondly, a problem can 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, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method

Hot Melt extrusion

Melt extrusion is essentially the same as the fusion method except that the extruder induces intense mixing of the components. The hot melt method has enjoyed a renaissance in the form of hot melt extrusion When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excipients by adding the molten carrier to a heated mixture of drug and excipients or by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier.

Solvent Evaporation

Solvent evaporation method is a simple way to produce solid dispersions where the drug and carrier is solubilized in a volatile solvent. The solvent is later evaporated. This

enable to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier. Tachibani and Nakumara (1965) were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. Mayersohn and Gibaldi (1966) then took up the method by dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent, they were able to achieve a solid dispersion. With the discovery of the solvent method, many of the problems associated with the melting method were solved and for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions (Nadia S etal., 2011).

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. Temperatures used for solvent evaporation usually lie in the range 23±65^{o}C. The solvent can also be removed by freeze-drying or by spray-drying. It must be remembered that when an organic solvent is to be removed, small variations in the conditions used can lead to quite large changes in product performance. Another point to consider is the importance of thoroughly removing all of the solvent, since most of the organic solvents used have toxicity issues. With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermolabile substances.

Lyophilization Technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization 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 solid dispersion wherein the binder acts as a carrier. In addition, solid dispersion 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. 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 solid dispersion by melt agglomeration. It has been found that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

The use of surfactant

The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant on solid

surface can modify their hydrophobicity, 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.

Electrospinning

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Super Critical Fluid (Scf) Technology

The supercritical fluid antisolvent techniques, carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid antisolvent, gas anti-solvent, solution enhanced dispersion by supercritical fluids, and supercritical antisolvent.

The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).

Characterization of solid dispersion

Drug -carrier miscibility

Hot stage microscopy

- Differential scanning calorimetry
- Powder X-ray diffraction
- NMR 1H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure

- Scanning electron microscopy
- Surface area analysis
- Surface properties
- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- Powder X-ray diffraction

Stability

- Humidity studies
- Isothermal Calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

Applications of solid dispersion

- To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailabilty.
- To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.
- To reduce side effect of certain drugs.
- Masking of unpleasant taste and smell of drugs. Improvement of drug release from ointment creams and gels.
- To avoid undesirable incompatibilities.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.

Ideal candidates for solid dispersion

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. So, the rate of absorption in vivo will be concurrently accelerated with an increase in the rate of drug dissolution

In the Biopharmaceutical Classification System Class II drugs are those with low aqueous solubility and high membrane permeability therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

References

1. Gill, Bhawandeep Kaur, Tejvir.Kumar Sandeep, Gupta GD., 2010. Formulation and evaluation of glimipride solid dispersion. *Asian Journal of Pharmaceutics*, 4, 3, 212-218.
2. Tiwari, Ruchi. Tiwari, Gaurav. Srivastava, Birendra and Rai, Awani K., Dec 2009.An Overview to Modify Bioavailability of Poorly Water Soluble Drugs. *International Journal of PharmTech Research*, 1, 4, 1338-1349.
3. Kim, K.T, Lee, J.Y, Lee, Song C.K, Choi,J andKim D.D., 2011. Solid Dispersions as a Drug Delivery System. *Journal of Pharmaceutical Investigation*, 41, 3, 125-142.
4. Mohd, Yasir.Mohd, Asif. Kumar, Ashwani.Aggarval,Abhinav.Biopharmaceutical Classification System: An Account., July-Sept 2010. *International Journal of PharmTech Research*, Vol.2, No.3, pp 1681-1690.
5. Mauludin, Rachmat .Pamudji, Jessie.S.Rayanti, Darra., 2011. Dissoluation improvement of ketofen tablets by solid dispersion technique. *Asian journal of Pharmaceutics and Clinical Research*, vol.4, 1ssue 4.
6. D.Kumar Praveen, 2012. Solid dispersion: A Review article. *Journal of pharmaceutical and scientific innovation*, pp27-34.
7. Sharma Pritika, Kapoor Anupriya,Bhargava Shilpi., march 2012 . Fast dissolving drug delivery system. Research Journal of Pharmaceutical, Biological and Chemical Sciences, Volume 3, Issue1, Page No. 847.
8. Anupama1, Setia. Surinder, Goyal.Birendra, Shrivastva. Goyal, N., December 2011. Formulation and optimization of solid dispersion tablets of albendazole using response surface methodology. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, Volume 2, Issue 4, and Page No. 740.
9. Ahmad, Z. Maurya, N. Mishra, S.K. Khan, I., 2011. Solubility enhancement of poorly water soluble drugs: A Review. *International Journal of Pharmacy &Technology*, Vol. 3, Issue.1, pp. 807-23.
10. Anonymous, 2005. *United States Pharmacopoeia* 27, *National Formulary* 22, Asian Edition, *United States Pharmacopeial Convention*, Rockville, MD.
11. Anupama, Setia. Surinder, Goyal.Birendra, Shrivastva. Goyal, N., December 2011. Formulation and optimization of solid dispersion tablets of albendazole using response surface methodology. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, Volume 2, Issue 4, and Page No. 740.
12. Anonymous, 2010. *Indian Pharmacopoeia*, Government of India, Ministry of health and Family welfare, The Indian pharmacopoeia commission, Ghaziabad, pp. 143.
13. Aulton, M.E., 2002. *Pharmaceutics- The Science of Dosage Form Design*. New York, Churchil Livingstone.
14. Brahmankar, D.M. Jaiswal, S.B., 2009. Biopharmaceutics And Pharmacokinetics - A Treatise. *Vallabh Prakashan*, chapter.2, pp. 38.

15. Buhler, V., 1998. Kollidon: Polyvinylpyrrolidone for the Pharmaceutical Industry, BASF, Ludwigshafen, pp. 106- 15.
16. Chauhan, B. Shimpi, S. Paradkar, A., 2005. Preparation and evaluation of glibenclamide polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *European Journal of Pharmaceutical Sciences*, Vol. 26, Issue 2, pp. 219–30.
17. Chiou, W.L. Riegelman, S., 1969. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *Journal of Pharmaceutical Science*s, Vol. 58, Issue 12, pp. 1505-10.
18. Chiou, W.L. & Niazi, S., 1976. Pharmaceutical application of solid dispersion systems: Dissolution of griseofulvin- succinic acid eutectic mixture. *Journal of Pharmaceutical Sciences*, Vol. 65, Issue 8, pp. 1212- 14.
19. Chiou, W.L., 1977. Pharmaceutical applications of solid dispersion systems: X-ray diffraction and aqueous solubility studies on griseofulvin-polyethylene glycol 6000 systems. *Journal of Pharmaceutical Sciences*, Vol. 66, Issue 7, pp. 989–91.
20. Choudhary, A. Aggarwal, G. Zakir, F. Kumar, V., 2011. Mini review: journey of solid dispersion technique from bench to scale. *International Research Journal of Pharmacy*, Vol. 2, Issue. 8, pp. 46-51.
21. Craig, D.Q.M., 2002. The mechanism of drug release from solid dispersion in water- soluble polymer. *International Journal of Pharmaceutics*, Vol. 231, Issue 2, pp. 131- 44.
22. Dhirendra, K. Lewis, S. Udupa, N. Atin, K.**,** 2009. Solid dispersions: A Review. *Pak. J. Pharm. Sci*, Vol. 22, Issue 2, pp. 234-46.
23. Drooge, D.J.V. Hinrichs, W.L.J. Visser, M.R. Frijlink, H.W., 2006. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *International Journal of Pharmaceutics,* Vol. 310, Issue. 1-2, pp. 220–29.
24. D.Kumar Praveen et al, 2012. Solid dispersion: A Review article. Journal of pharmaceutical and scientific innovation, 24 june, pp27-34.
25. El- Banna, H.M. Eshra, A.G. Hammouda, Y., 1977. The application of solid dispersion technique in the preparation of therapeutic tablets. Part 1: Paracetamol, amylobarbitone, and caffeine tablets. *Pharmazie*, Vol. 32, Issue 8-9, pp 511-15.
26. Elkordy, A.A. Essa, E.A., 2010. Dissolution of Ibuprofen from Spray Dried and Spray chilled Particles. *Pakistan Journal of Pharmaceutical Sciences*, Vol. 23, Issue 3, pp.284-90.
27. Flynn, G.L. Yalkowsky, S.H. Roseman, T.J., 1974. Mass transport phenomena and models: theoretical concepts. *Journal of Pharmaceutical Sciences,* Vol.63, Issue 4, pp. 479-510.
28. Gershanik, T. and Benita, S., 2000. Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. *European Journal of Pharmaceutics & Biopharmaceutics*, Vol. 50, Issue 3, pp. 179-88.
29. Ghebremeskel, A.N. Vemavarapu, C. Lodaya, M., 2007. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer-surfactant combinations using solubility parameters and testing the processability. *International Journal of Pharmaceutics*, Vol. 328, Issue. 2, pp.119–129.
30. Gill, Bhawandeep. Kaur, Tejvir.Kumar Sandeep, Gupta GD., 2010. Formulation and evaluation of glimipride solid dispersion. *Asian journal of Pharmaceutics* vol. 4, issue 3, pp212-218.
31. Jain, P. Goel, A. Sharma, S. Parmar, M., 2010 Solubility enhancement techniques with special emphasis on hydrotrophy. *International Journal of Pharma Professional's Research*, Vol. 1, Issue 1, pp. 34-45.
32. Kamble, V.A. Jagdale, D.M. Kadam, V.J., 2010. Nanosuspension- A novel drug delivery system. *International Journal of Pharma and Bio Sciences*, Vol. 1, Issue 4, pp. 352-60.
33. Kanig, J.L., 1964. Properties of fused mannitol in compressed tablets. *Journal of Pharmaceutical Sciences*, Vol. 53, Issue 2, pp. 188–92.
34. Karavas, E. Georgarakis, E. Bikiaris, D., 2006. Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. *Europian Journal of Pharmaceutics & Biopharmaceutics*, Vol. 64, Issue. 1, pp. 115–26.
35. Kobayashi, P. Ito, S. Itai, S. Yamamoto, K., 2000. Physicochemical properties and bioavailability of carbamazepine polymorphs

and dehydrate. *International Journal of Pharmaceutics*, Vol. 19, Issue. 3, pp. 137-46.

36. Kim, K.T, Lee, J.Y, Lee, Song C.K, Choi,J andKim D.D., March 29, 2011. Solid Dispersions as a Drug Delivery System. *Journal of Pharmaceutical Investigation*,Vol. 41, No. 3, 125-142.
37. Lachman, L. Liberman, H.A. Kanig, J.L., 1987. The Theory and practice of industrial pharmacy, *Verghese Publishing*, Indian edition, 3rd edn, pp. 460-61.
38. Leuner, C. Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. *Europian Journal of Pharmaceutics & Biopharmaceutics*, Vol. 50, Issue 1, pp. 47–60.
39. Mohanchandran, P.S. Sindhumol, P.G. Kiran, T.S., 2010. Enhancement of solubility and dissolution rate: an overview. *International Journal of Comprehensive Pharmacy*, Vol. 4, Issue 11, pp. 1-10.
40. Mukherjee, Sumantra. Dr. Patel, Piyush. Patel, Akshay. Patel, Harnish. Patel, Priyanka., 27 feb 2012. A Review on Solubility Enhancement Techniques. *International Journal Of Pharmaceutical Research And Bio –Science, Volume1 (1)*, pp34.
41. Mrs. Singh, Meera C. Sayyad, A. B. Dr. Sawant S. D., *October 2010* .Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion, *Journal of Pharmacy Research, Vol.3.Issue 10.*
42. Mohd, Yasir.Mohd, Asif. Kumar, Ashwani.Aggarval Abhinav.Biopharmaceutical Classification System: An Account., July-Sept 2010. *International Journal of PharmTech Research*, Vol.2, No.3, pp 1681-1690.

Classification of Solid Dispersion