AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Solid Dispersion: A Promising Tool for Solubility Enhancement of Poorly Water Soluble Drugs

Devidas G. Bachhav*[1], Somashekhar. S. Khadabadi[2], Leena P.Deore[3]

1. *MGV'S SPH College of Pharmacy, LVH Marg, Malegaon Camp, Malegaon, Nashik-423105*
2. Government College of Pharmacy, Aurangabad.
3. K.B.H.S.S trust's Institute of Pharmacy, Malegaon, Nashik, Nashik-423105.

ABSTRACT

Poor water solubility has always been one of the most fundamental problem in drug delivery. It is estimated that around 40% of drugs in the pipeline cannot be delivered through the preferred route or in some cases, at all owing to poor water solubility. Different methods available to improve solubility and dissolution include salt formation, micronization, chemical modification, pH adjustment, solid dispersion, complexation, hydrotropy, micellar solubilisation. Among these, solid dispersions have proved to be a successful strategy for enhancing aqueous solubility of drugs. The present review focus on different solid dispersion techniques used for the improvement of solubility and dissolution rate of poorly water soluble drugs, carriers used, advantages and limitations of each technique.

Keywords: Solubility, dissolution, solid dispersion techniques, carriers.

*Corresponding Author Email: devidas015@yahoo.co.in

Received 04 February 2013, Accepted 19 February 2013

Please cite this article in press as: Bacchav DG. *et al.*, Solid Dispersion: A Promising Tool for Solubility Enhancement of Poorly Water Soluble Drugs. American Journal of PharmTech Research 2013.

INTRODUCTION

The proper design and formulation of dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and pharmaceutical ingredients to be used in fabrication the product. An important physiochemical property of a drug substance is solubility, especially aqueous solubility. Solubility is predetermined and rate limiting step for absorption. Drugs must have to enter in systemic circulation to exert a therapeutic effect[1].

Poor water solubility has always been one of the most fundamental problem in drug delivery. It is estimated that around 40% of drugs in the pipeline cannot be delivered through the preferred route or in some cases, at all owing to poor water solubility [2].

The simplest and easiest way of administering drugs is oral drug delivery [3,4]. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid dosage forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities under development these days are intended to be used as a solid dosage form that originate an effective reproducible in vivo plasma concentration after oral administration[5,6]. In fact, most new chemical entities are poorly soluble drugs, not well-absorbed after oral administration[7,8]. Which can distract from the drug's inherent efficacy[8-10].

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the in vitro dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms[11]It classifies drugs into four classes as shown in table 1.The key parameters on which BCS of a drug depends upon are solubility and permeability, solubility play an important role for the absorption of drugs[12] .

In general solubility is expressed in terms of the maximum mass or volume of solute that will dissolve in a given mass or volume of solvent at a particular temperature and at equilibrium for therapeutic efficacy. For a drug to enter the systemic circulation and exert therapeutic effect it must be in solution. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction[14].

It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized [18]. Therefore lots of efforts have been made to increase dissolution of drug. Methods available to improve dissolution include salt

formation, micronization, chemical modification, pH adjustment, solid dispersion, complexation, hydrotropy, micellar solubilisation [19]. Among these, solid dispersions have proved to be a successful strategy for enhancing aqueous solubility of drugs. It has been used by various researchers who have reported encouraging results with different drugs. This system provides the possibility of reducing the particle size of a drug to molecular level, to transform the drug from the crystalline to the amorphous state, and/or to locally increase the saturation solubility [20].The present review focus on various solid dispersion techniques used for solubility enhancement.

Table 1: The Biopharmaceutical Classification System for drugd.[13]

BCS Class	Solubility	Permeability	Examples
I	High	High	Acylovir,Daizepam,Acetoaminophen,Antipyrine
II	Low	High	Dapsone,Aceclofenac,Glipizide,Carvedilol
III	High	Low	Amoxycillin ,Citrizine,Dicloxacillin,Cloxacillin
IV	Low	Low	Mebendazole,Neomycin,Furosamide,Amphotericin B

Table 2: Examples of drug with their solubility [15,16,17]

Terms	Parts of solvent required for 1 part of solute	Examples of drugs
Very soluble	Less than 1parts	Metoprolol, Deltiazam
Freely soluble	From 1-10 parts	Ipratropium bromide
Soluble	From 10-30 parts	Quinidine, Propananolol, Timolol
Sparingly soluble	From 30-100 parts	Fluorouracil, Labetolol, Ramipril
Slightly soluble	From 100-1000 parts	Fludrabine, Atenolol, Valsartan
Very slightly soluble	From 1000-10,000 parts	Busulphan,Flecainide, Doxazocine

SOLID DISPERSION:

Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs[21,22]. Since 1961, many investigators have studied SDs of poorly water-soluble drugs with various pharmacologically inert carriers to increase the dissolution and oral absorption of poorly water-soluble drugs[23]. Chiou and Reigelman first by defined solid dispersion in 1971 as "dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method". Dispersions prepared by fusion process are often termed as melts, e.g., nimusulide- PEG 4000 and those obtained by the solvent method are frequently referred to as co precipitates or co evaporates, e.g., co precipitates of furosemide crosspovidone [24].

Classification:

Solid dispersions are classified as shown in figure 1

Mechanism [26]**:**

Mechanism of Increased Dissolution Rate by Solid dispersion

1. Reduction in particle size.

2.Solubilisation effect (use of carriers).

3. Increased wettability and dispersibility by carriers.

4. Formation of metastable dispersion with reduced lattice energy for faster dissolution.

Carriers used in solid dispersion:

The properties of carriers have influence on the dissolution characteristics of the dispersed drug . A carrier should have the following properties[27].

1. Freely water soluble with rapid dissolution properties.

2. Nontoxic and pharmacologically inert.

3.Heat stable with a low melting point for the melt method.

4. Soluble in a variety of solvents.

5. Preferably enhancing the aqueous solubility of the drug.

6. Chemically compatible with the drug.

7. Forming only weakly bounded complex with the drug.

Various types of carries and solvents used in preparation of solid dispersion are as shown in table 3 and 4:

Table 3:List of carriers used in solid dispersion [28]

Nature	Carrier
Acids	Citric acid, tartaric acid, Succinic acid, phosphoric acid
Sugars	Dextrose, Mannitol, Sorbitol, Sucrose, Maltose, Galactose, Xylitol , Lactose, Soluble starch, D- glucose (Chitosan), Galactose, Xylitol, Galactomannan, British gum, Amylodextrin
Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000,PVP, CMC, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, ß- CD, HPß-CD, Eudragit® L100 sodium salts\
Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Docusate sodium, Myrj-52, Pluronic-F68,SLS, Gelucire 44/14, Vitamin E
Hydrotropes	Sodium acetate, Sodium- o- hydroxy benzoate, Sodium- p- hydroxy benzoate, Sodium citrate, Resorcinol, Ascorbic acid
Dendrimers	polyamidoamine (PAMAM), Starburst

Table 4:List of solvents used in solid dispersion[29]

Solvent	Melting Point (°C)	Boiling Point(°C)
Water	0	100
Methanol	-93.9	65
Ethanol	-117	78.5
Acetic acid	17	118
1-propanol	-85	97.4
2-propanol	-127	82.4
Chloroform	-63	62
DMSO	19	189

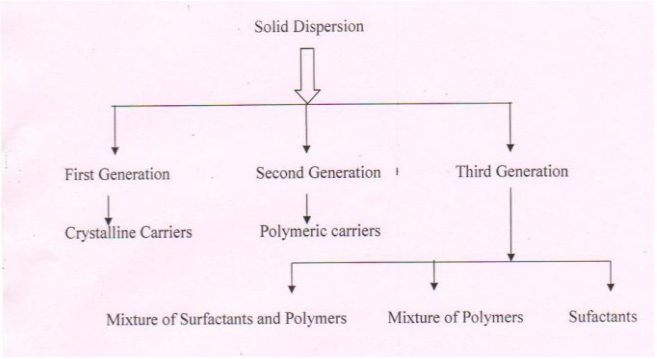

Figure 1: Classification of solid dispersions[25] .

Solid dispersion preparation methods:

Various methods for solid dispersion preparation are:

1)Fusion Method:

The melting or fusion method is technically less difficult method of preparing dispersion provided the drug and carrier miscible in the molten state .This method is first proposed by Sekiguchi and Obi 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. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs 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 [30,31]. Chiou and Riegelman hardened the solid dispersion of griseofulvin-PEG 6000 by the use of cold air after spreading it on plate of stainless steel [32]. Shah et al. studies on dissolution enhancement revealed that solid dispersion of rofecoxib-poloxamer 188 prepared by melt method showed enhancement of rofecoxib dissolution due to the conversion of rofecoxib into a less crystalline and/or amorphous form[33].

The advantages of this method are technically it is easier method the drug and carrier are miscible in molten state[5]. Also its simplicity and economical. It precludes the use an organic solvent thereby circumventing the enigmas of its removal from the dispesrsion[34]. Also it have some limitations as thermal degradation or instability may result at the melting point[35]. Immiscibility between drug and carrier results in irregular crystallization that causes problem during formulation[36].

2)Hot Melt Extrusion:

Hot melt extrusion can be simply defined as the process of forming new material (the extrudate)

by forcing it through a orifice or die under controlled conditions such as temperature, mixing, feed-rate and pressure[37].Hot melt differs from simple extrusion that ,polymer, drug and excipient blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder. Simple extrusion process uses aqueous or organic solvents for wetting polymer blend for granulation[38]. Follonier et al. produced sustained release pellets of diltiazem hydrochloride with negligible drug degradation by using holt met extrusion[39]. This technique employs the use of extruder which consist of a conveying system and die system. Conveying system is useful in transportation of materials and mixing and the die system shapes the melt into required shape like pellets, granules, or powder. Currently it has received attention in preparation of solid dispersions, where co rotating twin screw-extruder is mostly used[40]. It involves introducing drug-polymer mixture into hopper by gravimetric feeder where transportation and mixing takes place. Mixture is then melted by the extruder and shaped by the die into granules, pellets or powders[41].

Advantages of hot melt extrusion are: Processing in the absence of solvents and water. Economical process with reduced production time, fewer processing steps, and a continuous operation. Sustained, modified and targeted release capabilities. Uniform dispersion of fine particles occurs. Good stability at varying pH and moisture levels. Although it has some disadvantages: Thermal process (Drug/Polymer), Limited number of polymers available. Requires high energy input. This technique cannot be applied to heat sensitive materials owing to the elevated temperatures involved. Flow properties of the polymer are essential to processing[37,42].

3) Solvent Evaporation:

Tachibana and Nakamura were the two researchers who firstly applied solvent evaporation method for the formation of solid dispersions. Drug(β- carotene) and carrier(PVP) were dissolved in a common solvent(chloroform) and the solvent was evaporated to form the solid mass[43]. In this method, the first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involves the removal of solvent resulting in the formation of solid dispersion. First, to dissolve both the drug and the carrier in a common solvent and secondly, to evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier polyvinylpyrrolidone. 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 various methods like by spray-drying or

by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65°C[44].Adavatages of this method are high melting carriers can also be utilized[45].Thermal decomposition of drug and carriers associated with the fusion method can be avoided as low temperature is required for the evaporation of the organic solvents. This method has several drawbacks as: high cost of preparation, difficulty in selecting a common solvent for both drug and carrier, difficulty of producing crystal forms, drug particle size affected by temperature and rate of evaporation [46].

4) Lyophilization Technique:

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[47]. An important advantage of Lyophilization is that the drug is subjected to minimal thermal stress during the formation of the solid dispersions. Also the risk of phase separation is minimized as soon as the solution is vertified[48].Drawback of this technique are: expensive manufacturing, not suitable for all products[50].

5)Spray Drying:

Manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920[46]. Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent[50]. Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications[51,52]. Spary drying usually yields drug in the amorphous state[53].Spary drying techniques has ability to work with temperature sensitive APIs. Tremendous formulation flexibility from the wide variety of solvents, polymers and adjuvants that can be employed. Enhancement in performance that can be obtained by mixing the API and polymer at the molecular level in solution and then freezing this morphology in place through rapid solvent removal. It has some limitations as: added costs associated with the use and consumption of the organic solvents. Requirement of unit operation for residual solvent removal[27].

6)Co-Griding Method:

In this method the weighed amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a sieve; the resultant granules were dispersed in petri dishes and dried at specific temperature under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies[54]. Boldyrev et al have termed this process as mechanical activation. Some drugs like griseofulvin lose their crystallinity when ground with microcrystalline cellulose in a vibrational ball mill with subsequent increase in dissolution rate and bioavailability[55].

7)Supercritical fluid technology:

This technology was introduced late in 1980s and early 1990s. Classification of SCFs based techniques can be proposed according to the role played by the SCFs in the process. Various SCF processes used in pharmaceutical processing [56,57] include i) Rapid expansion of supercritical solutions (RESS), (ii) Supercritical antisolvent (SAS) precipitation technique (iii) Particles from Gas Saturated Solutions (PGSS), (iv) Gas antisolvent system (SAS), (v) Precipitation using compressed antisolvent (PCA) , (vi) Aerosol solvent extraction system (ASES), (vii) Solution enhanced dispersion by supercritical fluids (SEDS), (viii) Supercritical antisolvent system with enhanced mass transfer (SAS-EM), (ix) Impregnation or infusion of polymers with bioactive materials. SCFT, although environmentally friendly and suitable for masproduction, requires specially designed equipment and is more expensive. Composite particle generation by SCF processes looks as a very promising solution to enhance the dissolution of poorly-soluble compounds and the most studies were conducted with hydrophilic polymers and cyclodextrins leading to size-controlled particles that rapidly release the active compound in the aqueous media [58]. A number of drying methods such as evaporation as a baseline, freeze drying, SCF, and a novel CO_2 sublimation are available. Based on drying time and production yields for all powders tested, SCF processing and CO_2 sublimation produce, by far, the most dispersible powder[59]. ASES process proved as a promising technique to reduce particle size and/or prepare amorphous solid dispersion of drugs in order to improve the solubility and bioavailability of poorly water-soluble drugs such as itraconazole [60]. Paclitaxel solid dispersion prepared by using the SCF process showed an improved solubility, thereby, being effectively used for the preparation of paclitaxel injection and oral preparation having a high bioavailability [61]. Dissolution studies of cefuroxime axetil solid dispersions with HPMC 2910/PVP K-30 prepared using SEDS indicated that the dissolution rates were remarkably increased in solid dispersions compared with those in the physical mixture and drug alone. Thus, an amorphous or non-crystalline solid dispersion

prepared using SEDS could be very useful for the formulation of solid dosage forms[62].Micronized solid dispersions containing hydrophilic carriers and a new chemical entity, YNS3107 prepared by PGSS process enhanced the rate of dissolution of YNS3107 in the solid dispersion microparticles [63].

8) Use of surfactants:

Surfactants are often used as solubilizers or emulsifying agents in amorphous solid dispersions. Their primary purpose is to increase the apparent aqueous solubility and bioavailability of the drug. The some common surfactants used in amorphous solid dispersions are polysorbates-80, polysorbates-20, polyoxyl-40 hydrogenated castor oil, polysorbitan monostearate-60/80. As with polymers, solubility in organic solvents is an important consideration when preparing amorphous solid dispersions from solvent. In the case of hot melt extrusion, surfactants can have a plasticizing effect, which allows processing at lower temperatures[64].The utility of surfactant systems in solubilization is well known. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension because of these unique property the attention of investigators for preparation of solid dispersions [65,66]. Few more examples of surfactants are glucire, poloxamer, pluronic F-68, SLS etc.

Table 5:Marketed drugs are designed for improved solubility by solid dispersion[67-70]

Product/Substance	Dispersion Polymer or Carrier	Technology used	Company
Intelence (Etravirine)	HPMC	Spray drying	Tibotec
Certican (Everolimus)	HPMC	Melt or Spray drying	Novartis
LCP-Tacro (Tracrolimus)	HPMC	Melt-granulation	Life Cycle Pharma
Gris-PEG® (Griseofulvin)	Polyethylene glycol	Melt process; exact process unknown	Novartis
Sproramax capsules (Itraconazole)	Hydroxypropylmethylcellulose (HPMC)	Spray layering	Janseen pharmaceutica
Isoptin SRE-240 (Verapamil)	Various	Melt-extrusion	Soliqs
Intelence (Etravirine)	HPMC	Spray drying	Tibotec
Certican (Everolimus)	HPMC	Melt or Spray drying	Novartis
LCP-Tacro (Tracrolimus)	HPMC	Melt-granulation	Life Cycle Pharma
Afeditab (Nifedipine)	Poloxomer or PVP	Melt/absorb on carrier	Élan Corp.
Kaletra (lopinavir and ritonavir)	Polyvinylpyrolidone (PVP)/polyvinyl acetate	Melt-extrusion	AbbottLab.
Ibuprofen	Various	Melt-extrusion	Soliqs
Cesamet®(Nabilone)	Povidone	process unknown	Lilly

NOVELTY OF TOPIC:-

The pressing challenge pharmaceutical scientists have to face is the poor solubility of drug

candidates. Solubility is one of the important factors in formulation of pharmaceutical dosage forms. A good number of drugs, which are in market, have solubility problems. In case of new drug molecule, evaluation is carried out for number of its physical and chemical properties of which solubility has prime importance. The number of poorly soluble drugs is steadily increasing.

Recent technologies innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities. However 40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility. In the present era, 1/10 of marketed drugs have solubility problems, more than 1/3 of drugs in the pipeline are poorly soluble and nearly 2/3 of drugs coming directly from synthesis have low solubility. It is necessary to improve solubility & thus bioavailability of such drugs and can be formulated in to suitable dosage forms. The present review focus on various solubility enhancement techniques by solid dispersion.

CONCLUSION:

Solubility, especially aqueous solubility is an important physiochemical property of a drug substance. Different methods are available to improve solubility of poorly water soluble drugs. Solid dispersion is one of the technique is proven to be effective in improving dissolution properties of poorly water soluble drugs. There are various techniques of solid dispersion are available but all are not effective. In development of solid dispersion of any drug it is very important to understand the physiochemical properties of drug and carriers according to method used. So that it can leads to solubility enhancement of drug and stable formulation development.

REFERENCES:

1. Ansel HC, Allen LV, Popovich CG. Pharmaceutical dosage forms and drug delivery systems.8th ed., New Delhi: Lippincott Willams and Wilkins; 2005,93:100
2. Salata OV. Applications of nanoparticles in biology and medicine. J Nanobiotechnology. 2004; 2(1):3. Available at: www.jnanobiotechnology.com/content/2/1/3.
3. Wadke DA, Serajuddin ATM, Jacobson H, Lieberman, HA, Lachman L, Schwartz JB and Marcel D .Vol.1. New York :Preformulation testing In Pharmaceutical Dosage Form;1989, 1-73.
4. Sekiguchi K , Obi N. Studies on absorption of eutectic mixture, a comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull 1961; 9: 866-872.

5. Chiou WL , Riegelman S. Pharmaceutical applications of solid dispersion system. J Pharm Sci 1971; 60: 1281-1302.
6. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of eutectic mixture: urea-acetaminophen system. J Pharm Sci 1966; 55: 482-487.
7. Goldberg AH, Gibaldi M ,Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III. Experimental evaluation of griseofulvin-succinic acid solution. J Pharm Sci 1966; 55: 487-492.
8. Serajuddin ATM. Bioavailability enhancement of poorly water-soluble drugs by solid dispersion in surface active and self-emulsifying vehicles. Bull Technique Gattefosse 1997; 90: 43-50.
9. Ford JL. The current status of solid dispersions. Pharm Acta Helv 1986; 61: 69-88.
10. Goldberg AH, Gibaldi M, Kanig JL, Mayersohn, M. Increasing dissolution rates and gastrointestinal absorption of drugs via solid dispersion in eutectic mixtures IV. Chloramphenicol-urea system. J Pharm Sci 1969; 58: 1505-1509.
11. Yu LX, et al. A Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions. Pharm res 2002; 19: 921-925.
12. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics – A Treatise. 2nd ed. New Delhi. Vallabh Prakashan: 1995; 345-346.
13. Wu CY, Benet LS. Predicting drug disposition via application of BCS: Transport /Absorption elimination interplay & development of a biopharmaceutical drug disposition classification system. Pharm Res 2005;22(1):23-27.
14. Aulton ME. Dissolution & Solubility In, Pharmaceutics: The Science of Dosage Form and Design . 3rd ed.; 2007:22-23.
15. Goel A, Sharma M, Sharma S, Haffez A, Arora J. Pharmacokinetic data and solubility profile of antihypertensive drugs. Int J Pharma Prof Res 2010; 1: 61-77.
16. Goel A, Saini S, Chowdhry V, Haider SA, Singh RK. Pharmacokinetic solubility and dissolution profile of anticancer drugs.Int J Pharma Prof Res 2011; 2(4): 502-539.
17. Goel A, Aggarwal S, Partap S, Saurabh A, Choudhary V. Pharmacokinetic solubility and dissolution profile of antiarrythmic drugs. Int J Pharma Prof Res 2012;3(1) :592-601.
18. .A. Arunachalam, M. Karthikeyan, K. Konam, Prasad PH, S. Sethuraman, and S. Ashutoshkumar .Solid dispersions: A review. Curr. Pharm October- December 2010;1(1): 82-90.

19. Luhadiya A, Agrawal S, Jain P, Dubey P K.. A review on solid dispersion. IJARPB, 2012; 1 (2): 281-291
20. Lakhvir kaur, Sandeep Kumar. Solid Dispersions: A Promising Approach for Improving Dissolution Characteristics of poorly soluble drug. IJPRR 2011; 3(1):1-7
21. Janssens Sandrien, Roberts, Clive, Smith, Emily F,Guy. Physical study of ternary solid dispersions of itraconazol in polyethyleneglycol6000 hydroxy propyl methyl cellulose 2910 E5 blends. International Journal of Pharmaceutics 2008;355: 100–107.
22. Patel RP, Patel MM.Physicochemical Characterisation and Dissolution Study of Solid Dispersions of Lovastatin with Polyethylene Glycol 4000 and Polyvinylpyrrolidone K30.Pharmaceutical Development and Technology 2007 ;12:21–33.
23. yh-Nam P ,Jing-Huey C, Russel RC, Enhancement of and bioavailability of piroxicam in solid dispersions system. Drug Dev. Ind. Pharm. 2000; *26*:989–994.
24. Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion. J Pharm Sci. 1971; 60:1281-1302.
25. Aggarwal Shikha, Gupta GD, Sandeep Chaudhary Solid dispersion as an eminent strategic approach in solubility enhancemet of poorly water soluble drugs. Int J Pharm Sci Res 2 010; 1, Issue 8 (Suppl.):1-13.
26. Purwa J, Achhrish G. Solubility enhancement techniques with special emphasis on hydrotrophy. Int J Pharma Professional's Res 2010; 1(1):34-45
27. Kapoor Bhawana, Kaur Ramandeep ,Kour Sukhdeep,Bhel Hemani. Solid Dispersion: An Evolutionary Approach for Solubility Enhancement of Poorly Water Soluble Drugs. Int J Recent Adv Pharm Res 2012; 2(2):1-16
28. Galia E, Nicolaides E, Hoerter D, Loebenberg R, Reppas C, Dressman JB. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm Res 1998; 15: 698-705.
29. Kushwaha Anjali .Solid dispersion- A promising novel approach for improving solubility of poorly water soluble drug. IJPSR 2011; 2(8): 2021-2030.
30. Sekiguchi K and Obi N. Studies on Absorption of Eutectic Mixture II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem. Pharm. Bull. (Tokyo);12: 134-144.
31. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. II. Experimental evaluation of eutectic mixture: urea-acetaminophen system. J Pharm Sci1966; 55:482-487.

32. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci 1969; 58: 1505–1510.
33. Shah TJ, Amin AF, Parikh JR, Parikh RH. Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug. AAPS Pharm Sci Tech 2007; 8(2):E1-E7.
34. Vasconcelos T, Sarmanto B, Costa P. Solid dispersion as strategy to improve oral bioavailability of poorly water soluble drugs. J Pharm Sci. 2007; 12:1068-1075.
35. Kanig JL. Properties of fused mannitol in compressed tablets. J Pharm Sci. 1964; 53:188-192.
36. Walker SE, Gangley JA, Bedford K, Eaves T. The filling of molten and thyrotrophic formulations into hard gelatin capsule. J Pharm Pharmacol 1980; 32:389-393.
37. Singhal S, Lohar VK, Arora V. Hot melt extrusion technique. Webmed Central Pharmaceutical Sciences 2011;2(1):1459.
38. Khatry Sadhana.,Abbulu K.Melt Extrusion –An overview. IJPT,2011;3(1):685-703.
39. Follonier N, Doelker E, Cole ET. Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs, Drug Dev Ind Pharm 1994; 20: 1323–1339.
40. Nakamichi K, Yasuura H, Kukui H, Oka M, Izumi S, Andou T, Shimizu N, Ushimaru K. New preparation method of solid dispersion by twin screw extruder. Pharm Tech J 1996; 12:715-729.
41. Sethia S.Solid dispersions-Revival with greater possibilities and applications in oral drug delivery. Critical Review Tm in Therapeutic Drug carrier systems 2003; 20(2&3): 215-247.
42. Jones DS ,Andrews GP ,Williams M,Tian Y . Hot-melt extrusion technology: Optimizing drug delivery. European Industrial Pharmacy, 2010;7:7-10.
43. Tachibana T, Nakamura N. A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of beta-carotene by polyvinylpyrrolidone, Kolloid-Z .Polym 1965; 203: 130-133.
44. Serajuddin A.Ssolid dispersion technique . J Pharm Sci 1999; 88(10):891-900.
45. Vadnere MK. Coprecipitates and melts. In: Swarbrick J, Boylan, JC.Encyclopaedia of pharmaceutical technology 2nd ed. New York (USA) Marcel Dekker, Inc.; 2002; 641-647.
46. Sharma DK and Joshi SB .Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A review. Asian J Pharm 2007;1(1):9-19.

47. Tsinontides SC, Rajniak P, Pham D, Hunke WA, Placek J, Reynolds SD. Freeze drying-principles and practice for successful scale-up to manufacturing. Int J Pharm 2004; 280:1-16.
48. Dhirendra K, Lewis S, Udupa N, Atin K.Solid dispersion: A review. Pak. J. Pharm. Sci 2009;22 (2) :234-246.
49. Takayama K, Nambu N, Nakai T. Factor affecting the dissolution of ketoprofen from solid disoersion in various water soluble polymers. Chem Pharm Bull. 1982; 30:673- 677.
50. Vasconcelos T, Sarmento B, Costa P.Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12(23-24):1068-75.
51. Chronakisa IS, Triantafyllou AO. Solid state characteristics and redispersible properties of powders formed by spray-drying and freeze-drying cereal dispersions of varying (1 3, 1 4)-β -glucan content. J cereal science 2005;40:183-193.
52. Patrice TT, Stephanie B, Hatem F. Preparation of redispersible dry nanocapsules by means of spray drying: Development and characterization. Eur J Pharm Sci 2007;30:124.
53. Ambike AA, Mahadik KR, Paradkar A. Spray dried amorphous solid dispersions of simvastatin, a low Tg drug: In vitro and in vivo evaluations. Pharm Res 2005; 22:990-98.
54. Mohamad HG. Jafar MH. , Dehghan M, Shareef A. Improving Dissolution of Meloxicam Using Solid Dispersions. Iranian Journal of Pharmaceutical Research 2006; 4: 231-238.
55. Yamamoto K, Nakamo M, Arita T, Nakai Y. Preparation and thermal characterization of poly (ethyl oxide)/ griseofulvin solid dispersions for biomedical application. J Pharmaco Biopharm. 1974; 2:487-495.
56. Mollan MJ, Needhamb TE. Vemavarapu C, Lodaya M. Design and process aspects of laboratory scale SCF particle formation systems. Int J Pharm 2005; 292: 1–16.
57. Gupta RD, Chatap VK, Gupta VB, Sharma K, Parial SD. A review: Supercritical fluid extraction technology. Pharm Rev. 2008 ; 6(2) Pharmainfo.net.
58. Perrut M, Jung J, Leboeuf F. Is it possible to enhance the dissolution rate of poorly-soluble active ingredients by supercritical fluid processes? Proceedings of the 9th Meeting on Supercritical Fluids, Trieste (Italy), Kikic I., Perrut M. edtitors, 2004.
59. Tedeschi S, Stevens N, Cepeda D, Lee YY, Powers K, Ranade M, El-Shalll H. Novel supercritical fluid processing techniques for the production of an aerosol. Powder Technol 2009; 191: 188-193.
60. Kim MS, Jun SW, Park JS, Woo JS, Hwang SJ, Lee S, Nam K. Preparation and Characterization of Solid Dispersions of Itraconazole by using Aerosol Solvent

Extraction System for Improvement in Drug Solubility and Bioavailability. Arch Pharm Res 2005; 28: 866-874.

61. Woo JS, Kim HJ, Kim YH. Method for the preparation of paclitaxel solid dispersion by using the supercritical fluid process and paclitaxel solid dispersion prepared thereby. USPTO Application #: 20060078619. 04/13/2006.
62. Jun SW, Kim MS, Jo GH, Lee S, Woo JS, Park JS, Hwang SJ. Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids. J Pharm Pharmacol 2005; 57:1529-1537.
63. Michael B, Severine J, Leonardo P, Geraldine P, Brigitte E. The supercritical micronization of solid dispersions by particles from gas saturated solutions using experimental design. J Supercrit Fluids 2009; 51: 50-56.
64. Brain EP, Jonathan MM ,Timothy Robbins , Philip DZ ,Leena Prasad ,Julie K. Spence ,Justin LaFountaine , Amorphous Solid Dispersions as Enabling Formulations for Discovery and Early Development, American pharmaceutical review, Saturday, January 01, 2011 (Retrieved from http://www.americanpharmaceuticalreview.com/Featured-Articles/37035-Amorphous-Solid-Dispersions-as-Enabling-Formulations-for-Discovery-and-Early-Development/)
65. Takeuchi H, Nagira S, Yamamoto H. And Kawashima Y. Solid dispersion particles of tolbutamide prepared with fine sillca particles by spray drying method. Powder technology2004;141:187-195.
66. Ghebremeskel AN, Vemavarapu C, Lodaya M. 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. Int J Pharm 2007; 328:119-129.
67. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull. 1961; 9:866-872.
68. Craig DQM. The mechanisms of drug release from solid dispersions in water soluble polymers. Int. J. Pharm. 2002;231(2) : 131-144.
69. Sethia S. Solid dispersions-revival with greater possibilities and applications in oral drug delivery. Crit. Rev. Ther. Drug Carrier Syst.2003; 20(2-3): 215-247.
70. Thayer AM. Custom manufacturer take on drug solubility issues to help pharmaceutical firms move products through development. Finding Solutions; 2010, 88(22): 13-18.