INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Review Article

SOLUBILITY IMPROVEMENT USING SOLID DISPERSION; STRATEGY, MECHANISM AND CHARACTERIZATION: RESPONSIVENESS AND PROSPECT WAY OUTS

Sharma Dinesh Kumar[1,2]*, Gupta Vipin Bihari[2] and Purohit Suresh[1,3]
[1]Jodhpur National University, Jodhpur, India
[2]B.R.Nahata College of Pharmacy, Department of Pharmaceutics, Mhow-Neemuch Road, Mandsaur – 458001, M.P. India
[3]P.D.M.College of Pharmacy, Bahadurgarh, India

*Dinesh Kumar Sharma, Jodhpur National University, Jodhpur, India
E-mail: dineshsharma1973@rediffmail.com
Article Received on: 02/01/11 Revised on: 09/01/11 Approved for publication: 17/01/11

ABSTRACT
New chemicals entities, being synthesized by various techniques, successfully present superior pharmacological activities. However 35-40 % of these new chemicals entities suffer from poor aqueous solubility. The current review extensively highlights various approaches used to enhance solubility, mechanisms responsible for improvement of solubility and characterization. This review also presents attentiveness amongst investigators working on this area and proposes assured promising way outs to improve solubility to obtain stable and effective final products.

KEYWORDS: Solubility enhancement, dissolution enhancement, carriers, mechanisms, characterization

INTRODUCTION
For a drug to enter the systemic circulation to exert a therapeutic effect, it must be in solution. Relatively insoluble compounds often exhibit incomplete or erratic absorption. Recent technologies innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility[1-2].

TECHNIQUES/APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE WATER DRUG
The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes

Micronization
Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions[3-4].

Crystal habits of drug substances
Certain medicinal agents may be produced to exist in either a crystalline or an amorphous state. Since the amorphous form of a chemical is usually more soluble than crystalline form, different extents of drug absorption may result with consequent differences in the degree of pharmacological activity. Crystalline forms of drugs may be used because of greater stability than corresponding amorphous forms. The various polymorphic forms of the same chemical generally differ in many physical properties. Differences in drug action (pharmaceutically and therapeutically) can be expressed from polymorphs contained in solid dosage forms. The use of metastable forms generally results in higher solubility and dissolution rates than the respective stable crystal form of the same drug[1].

Solubilization and Complexation – use of surfactants and cyclodextrins

Solubilization has been used in pharmacy to bring into solution a wide range of materials indulging volatile oils, coal tar and resinous material, phenobartital, sulfonamide, vitamins, hormones, dyes and beta-arteether. Cyclodextrins have been widely studied as solubilizing and stabilizing agent in pharmaceutical dosage forms. Lach and associates used cyclodextrins to trap, stabilize and solubilize sulfonamide, tetracyclines, morphine, aspirin and benzocaines[5].

Salt formation

All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different form that of parent compound. However sodium and potassium salts of weak acids dissolve more rapidly than the free salts. Potential disadvantages of salt forms include high reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity. Even though use of co solvent and surfactants to improve dissolution rate pose problems such as patient compliance and commercilation[6]

Solid Dispersions

The solubility behaviour of drugs remains one of the most challenging aspects in formulation development with the advent of combinatorial chemistry and high through put screening, the number of poorly water-soluble compounds has dramatically increased. Solid dispersions have tremendous potential for improving drug solubility and the literature reviews of past four decades of research suggest that there is an increasing interest in using this approach[7].

SOLUBILITY ENHANCEMENT STRATEGIES FOR POORLY WATER-SOLUBLE DRUGS IN SOLID DISPERSIONS

Various strategies investigated by several investigators include fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology. These strategies have been discussed in elaborated in our review article 'solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: a review'[8].

MECHANISMS OF ENHANCED DISSOLUTION IN SOLID DISPERSIONS

Solid dispersions have attracted considerable interest as a mean of improving the dissolution rate, hence possibly bioavailability of a range of hydrophobic drugs. The increase in dissolution rate for solid dispersion can be attributed to a number of factors. These include the following –

Reduced Particle Size or Reduced Agglomeration

These may be usefully considered together as both are related to increases in the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area[9].

Increased Solubility or Dissolution Rate of the Drug

Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in vitro experiments the carriers often elicit minimal solubility increases. There appear to be two sets of observations with regard to the mechanism of drug release from solid dispersions. In the first instance, some systems appear to show carrier-controlled release whereby, at least at low drug loadings, the rate of release is controlled by that of the carrier and is independent of drug properties. Secondly some systems show release behaviour that is dependent on the properties of the drug rather the polymer, even at low drug loadings[9].

Transferring the Drug from Crystalline to (Partially) Amorphous State/ Formation of High Energy States

Amorphous drugs represent the higher energy states and can be considered as cooled liquids. They have greater aqueous solubility than crystalline forms because the energy required to transfer a molecule from crystal is greater than required for non crystalline (amorphous) solid, for example, the amorphous state of

novobiocin is 10 times more soluble than crystalline form. Chloramphenicol palmitate, cortisone acetate and Phenobarbital are other examples where the amorphous forms exhibit higher water solubility[10].

Wetting

When a strong affinity exists between a liquid and a solid , the liquid forms a film over the surface of the solid . When this affinity is non existent or weak , however , the liquid has difficulty displacing the air or other substances surrounding the solid, and there exists an angle of contact between the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions, specially, those acting at the interfaces between the liquid and the vapor phases, at the solid and liquid phases, and at the solid and vapor phases. The contact angle concept is important because it affords a method of considering degree of wetting and indicates that surface properties are important[11].

Soluble Complex Formation in Microenvironment

Organic compounds in solutions generally tend to associate with each other to some extent. Frequently, this association is too weak to be detected by standard techniques. In other cases, the intermolecular associations or complex can be readily observed and quantitated by one or more of numerous published techniques. One of more widely used methods, and one that is highly germane is the solubility analysis technique. Every substance has specific, reproducible equilibrium solubility in given solvent at a given temperature[12].

Saturation of Drug in Microenvironment

Another mechanism, creation of microenvironment, by hydrophilic carrier has also been reported as mean of solubility enhancement, where in a microenvironment is created where the solubility of the drug particles is increased due to high concentration of hydrophilic carrier in surrounding solution [13].

Solubilization of the Hydrophobic Drug in Presence of the Surfactant:

Solubilization is thought to occur by virtue of the soluble dissolving in or being adsorbed onto the micelle. Thus, the ability of surfactant solutions to dissolve or solubilize water-insoluble materials starts at the critical micelle concentration and increases with the concentration of the micelles. Cholesterol was markedly more soluble in aqueous soap solution than in pure water. Solubilization of prednisolone, methyl-prednisolone and flourometholone, nifedipine was reported as function of surfactant concentration. This resulted in enhanced solubility of hydrophobic drug[14].

SELECTION OF CARRIERS FOR SOLID DISPERSIONS

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suit for increasing the dissolution rate of a drug: be freely water-soluble with intrinsic rapid dissolution properties, be nontoxic and pharmacologically inert, be heat stable with a low melting point for the melt method, be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method, preferably increase the aqueous solubility of the drug and be chemically compatible with the drug and not form a strongly bonded complex with the drug. Following are the few examples of **c**ommonly used pharmaceutical carriers for solid dispersions PVP , Crospovidone ,Croscarmellose sodium, Low-substituted HPC , Sodium starch glycolate, Mannitol, Sorbitol,Dextrin,Lactose, PEG, Hydroxyproyl beta-cyclodextrin, Ethylcellulose, Cyclodextrin,Nicotinamide, Ethylurea, HPMC, HPMC phthalate, Gelucire, Labrasol, Poloxamer 407, Poloxamer 188, Pluronic F68, polyvinyl alcohol (PVA), Pullulan, Citric acid[15-30].

CHARACTERIZATION OF SOLID DISPERSIONS

Many methods are available which provides an insight into the physical nature of a solid dispersion system and the nature of interaction between the components. Characterization requires pooling of data from several methods of study to finally arrive at conclusion regarding the nature of the solid dispersion

Thin layer chromatography

Drug-excipient interactions can be studied by thin layer chromatography. When excipients are present it is advisable to set a mixture of the excipients at the same conditions as the drug-excipient mixtures. This will give chromatograms of both systems. If any degradation products are present, the source may be determined more easily[31].

Spectroscopic methods

In the Ultra Violet studies the spectra of the pure and the dispersed drugs are scanned. Assay of the solid dispersion and calculation of molar extinction provides evidence of any decomposition of the drug.

Hypsochromic or bathochromic shift or increase or decrease in the absorptivity without change in λ_{max} has been considered as evidence for interaction between β–cyclodextrin and drug in the formation of complexes[31].

The Phase solubility Analysis

The solubility studies are performed according to a methods described by Higuchi and Connors[32]. An excess quantity of the drug is added to the simulated gastric fluid placed in glass vials, tightly closed and shaken at room temperature up to 24-72 hrs using rotary shaker. After attainment of equilibrium, the contents of each vial are filtered through a 0.45 μm filter and then assayed for the drug content at appropriable wavelength.

Microscopic methods

Particle size and morphology of solid dispersions can be observed by microscopy. Scanning electron microscopy can be used for this purpose, wherein, the samples are coated with gold and palladium using a vacuum evaporator and are examined at accelerating voltage with a suitable magnification. This method has been used to study the Naproxen-chitosan systems, Glibenclamide-polyglycolized Glycerides, Naproxen-PVP etc[33].

Thermal analysis

This technique is useful in investigation of solid-state interaction between two or more component systems. It is based on the principle of change of thermal energy as a function of temperature and may be carried out in any of the following ways

Cooling curve methods

The physical mixtures of various compositions are heated to produce a homogeneous melt. The temperature of each mixture during the cooling process is recorded as a function of time and from a series of temperature - time curves, the phase diagram is established. The method is time consuming, requires relatively large amount of sample and changes in slopes can be missed especially if cooling takes place rapidly. The method can not be applied to samples that decompose after melting.

Thaw melts methods

A sample of solid dispersion is heated gradually in a capillary tube and the thaw and melting points are noted by visual observation. The principal drawback of this method is that it depends on a subjective observation, and is, therefore, not highly reproducible.

Thermo microscopic methods

This is a simple method in which hot stage microscope is used to study the phase diagrams of binary systems. The physical mixture or dispersion (approx. 1 mg) on a slide is heated at the rate of 1-5 °C per minute. The thaw and melting points are then recorded by visual observation. This method requires only a small amount of sample but it is limited to thermally stable compounds only. This technique has been used to characterize diflunisal–PEG solid dispersion[30].

Differential thermal analysis (DTA) and differential scanning calorimetry

Differential scanning calorimetry (DSC) has become the most widely used thermal analysis technique. In this technique, the sample and reference materials are subjected to a precisely programmed change. When a thermal transition (a chemical or physical change that results in the emission or absorption of heat) occurs in the sample, thermal energy is added to either the sample or the reference containers in order to maintain both the sample and reference at the same temperature. Because the energy transferred is exactly equivalent in magnitude to the energy adsorbed or evolved in the transition, the balancing energy yields a direct calorimetric measurement of the transition energy.

In differential thermal analysis (DTA), the difference in temperature between the sample and a thermally inert reference material is measured as a function of temperature (usually the sample temperature). Any transition that the sample undergoes results in liberation or absorption of energy by the sample with a corresponding deviation of its temperature from that of the reference. A plot of the differential temperature versus the programmed temperature indicates the transition temperature and whether the transition temperature is exothermic or endothermic[34].

Zone melting method

In this method, a molten zone affected by a heater, traverses a cylindrical ingot or solidified melt at a rate of about 0.5 - 0.001 cm per hour. A mechanical stirring device is also required for the mixing of the liquid in the

molten zone. After zone melting is completed, the bar is sectioned and analysed for its chemical composition. A phase diagram is then constructed from the chemical compositions and freezing temperatures of the corresponding sections. The method is limited to compounds with high thermal stability and low volatility

Dissolution studies

The dissolution rate method was proposed by Alien and Kwan to study the degree of crystallinity in solid – solid equilibria. The method involves comparing the in vitro dissolution rates of the solute component from a constant surface tablet prepared from a solid dispersion, with a physical mixture of the same chemical composition. The method has been shown to be applicable to Indomethacin - PEG 6000 and sulphathiazole-urea systems[34].

Vibrational method

X-Ray diffraction

The diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. The intensity of the X-ray diffraction from a sample is measured as a function of diffraction angles. In a simple eutectic system, diffraction peaks of each crystalline component can be found in the diffraction spectra. While a gradual shift in the positions of diffraction lines with changes in composition, which reflects the resulting change in the lattice parameter, is accepted as sufficient evidence for the existence of solid solutions. The diffraction method is also particularly valuable in detecting compound or complex formation[35]. This method has been employed to characterize felodipine-HPMC, rofecoxib-PVP K 30 naproxen-chitosan systems and many more.

REFERENCES

1. Ansel HC, Allen LV and Popovich CG Eds. Pharmaceutical dosage forms and drug delivery systems, 7th Edn, Lippincott Williams and Wilkins 2000; 60-61(66): 108-110
2. Ohara T, Kitamura S, Kitagawa T and Terada K. Dissolution mechanism of poorly water-soluble drug from extended solid dispersion system with ethyl cellulose and hydroxypropyl methylcellulose. Int. J. Pharm 2005; 302: 95-102
3. Takano, Niichiro, Kawashima, Hiroyuki, Shinoda, Yasuo, Inagi and Toshio. Solid dispersion compositions. United States Patent No. 6753330, 2004
4. Yiyun C, Tongwen X and Rongqiang F. Polyamidoamine dendrimers used as solubility enhances of ketoprofen. Eur. J. Med. Chem 2005; 40: 1390-1393
5. Martin A Ed. In; Physical Pharmacy, 4th Edn. Lippincott Williams and Wilkins, Baltimore, Maryland 2001; 412: 206
6. Mohan Babu GVM, Prasad DS, and Ramana Murthy KV. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug Nimodipine. Int. J. Pharm 2002; 234: 1-17
7. Leuner C and Dressman. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm Biopharm., 2000; 50(1): 47-60
8. Sharma DK and Joshi SB. solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: a review. Asian Journal of Pharmaceutics 2007;1(1):9-19
9. Duncan QMC. The mechanism of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm 2002; 231: 131-144
10. Brahmankar DM and Jaiswal SB Eds.. Biopharmaceutics and pharmacokinetics A treatise. Vallabh Prakashan, Delhi, 2002; 29
11. Patel NK, Kennon L and Levinson. Pharmaceutical suspensions. In; Leon Lachman, Herbert A Lieberman and Joseph L Kanig eds. 3rd edition. The Theory and practice of industrial pharmacy. Varghese Publishing House hind Rajasthan Building Dadar Mombay 1987; 480
12. Boylan JC. Liquids In; Leon Lachman, Herbert A Lieberman and Joseph L Kanig Eds. The Theory and practice of industrial pharmacy. Varghese Publishing House hind Rajasthan Building Dadar Mombay 1987; 464-465
13. Weuts I, Kempen D, Verreck G, Decorte A, Heymans K, Peeters J, Brewster M and Mooter GV den. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG 6000 prepared by spray drying. Eur. J. Pharm. Biopharm 2005; 59: 119-126

14. Chauhan B, Shimpi S and Paradkar A. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. Eur. J. Pharm. Sci 2005; 26: 219-230
15. Vadnere MK. Coprecipitates and Melts. In; James Swarbrick and James C. Boylan Eds, Encyclopedia of Pharmaceutical Technology, 2002; Vol. 1, Pg. 642-644
16. Nijlen Van T, Brennan K, Van den Mooter G, Blaton N, Kinget R and Augustijns P. Improvement of the dissolution rate of artemisinin by means of supercritical fluid technology and solid dispersions. Int. J. Pharm 2003 ; 254(2): 173-181
17. Hirasawa N. Application of nilvadipine solid dispersion to tablet formulation and manufacturing using crospovidone and methylcellulose as dispersion carriers. Chem Pharm Bull (Tokyo) 2004;52(2): 244-247
18. Mallick S, Sahu A and Pal K. Dissolution behaviour of nalidixic acid solid dispersions using water soluble dispersion carriers. Acta Pol Pharm 2004; 61(1): 21-30
19. Valizadeh H, Nokhodchi A, Qarakhani N, Zakeri-Milani P, Azarmi S, Hassanzadeh D and Lobenberg R . Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin, and Eudragit E100. Drug Dev. Ind. Pharm 2004; 30(3): 303-317
20. Suzuki H. Comparison of nicotinamide, ethylurea and polyethylene glycol as carriers for nifedipine solid dispersion systems.Chem Pharm Bull (Tokyo) 1997;45(10):1688-1693
21. Nagarsenker MS, Garad SD and Ramprakash G. Design, optimization and evaluation of domperidone coevaporates. J Control Release 2000; 63(1-2): 31-39
22. Lee S, Nam K, Kim MS, Jun SW, Park JS, Woo JS and Hwang SJ. 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(7): 866-874
23. Karatas A, Yuksel N and T Baykara. Improved solubility and dissolution rate of piroxicam using Gelucire 44/14 and Labrasol. Il Farmaco 2005; 60: 777-782
24. Chutimaworapan S. Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions. Drug Dev Ind Pharm 2000; 26(11): 1141-50
25. Sharma DK, Gupta VB and Purohit S. Industry feasible method to improve solubility of Piroxicam with Crospovidone: Preparation, Characterization and tableting Consideration. Der Pharmacia Lettre 2010; 2(3): 123-135
26. Six K, Daems T, de Hoon J, Van Hecken A, Depre M, Bouche MP, Prinsen P, Verreck G, Peeters J, Brewster ME and Van den Mooter G. Clinical study of solid dispersions of itraconazole prepared by hot-stage extrusion. Eur J Pharm Sci 2005; 24(2-3): 179-186
27. Jung JY, Yoo SD, Lee SH, Kim KH, Yoon DS and Lee KH. Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. Int. J. Pharm 1999; 187(2): 209-218
28. Suzuki H and Sunada H. Influence of water-soluble polymers on the dissolution of nifedipine solid dispersions with combined carriers. Chem Pharm Bull (Tokyo) 1998; 46(3): 482-487
29. Lu Q and Zografi G. Phase behavior of binary and ternary amorphous mixtures containing indomethacin, citric acid, and PVP. Pharm Res 1998;15(8): 1202-1206
30. Najib NM and Suleiman MS. Characterization of a diflunisal polyethylene glycol solid dispersion system Int. J. Pharm 1989; 51: 225
31. Ravin LJ and Radebaugh GW. Preformulation. In; Gennaro A R, Ed. Remington's Pharmaceutical Sciences. 18th edition. Mack Publishing Company. Easton, Pennsylvania 1990; 1448:1443
32. Higuchi T and Connors KA. Phase-solubility techniques. Adv Anal chem. Instrum 1995;4: 117-210
33. Wong DH, Kim MS, Lee S, Jeong SP and Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int. J. Pharm 2005;301: 199-208
34. Willard HH, Merritt LL and Dean FAS Jr Eds.. Instrumental methods of analysis. CBS publishers and distributors. 7th edition. New Delhi, 1986
35. Fiese EF and Hagen TA. In; Lachman L, Liebermann H A and Kanig J L Eds. The Theory and Practice of Industrial Pharmacy, 3rd Edn., Varghese Publishing House, New Delhi, 1987; 180