Review Article [Modasiya *et al.*, 3(2): Feb., 2012]
ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Techniques to improve the solubility of poorly soluble drugs

Jinal N. Patel[1]*, Dharmendra M. Rathod[1], Nirav A. Patel[2] and Moin K. Modasiya[1]
1, APMC College of Pharmaceutical Education and Research, Himatnagar, (Gujarat) - India
2, Naratha Mandal College of Pharmacy, Belgaum, (Karnataka) - India

Abstract

A drug administered in solution form immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques such as Physical method, Chemical method. Co-crystallisation, co-solvency solubilizing agents, molecular encapsulation with cyclodextrins, nanotechnology approaches and hydrotropy.

Key-Words: Solubility, Dissolution and Bioavailability

Introduction

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability [1].

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature [2]. In the other words the solubility can also define as the ability of one substance to form a solution with another substance [3]. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water [4].

*** Corresponding Author**
E-Mail: m_chandni2004@yahoo.co.in

Process of solubilisation [3]

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. When Solubilisation process occur break down of solute bond occurs and holes can be seen as shown in Figure 1. When solubilisation process occur solid molecules break down because of breaking of inter molecular bonding shown in Figure 2.About freed solid molecule is integrated in the solvent shown in Figure 3.

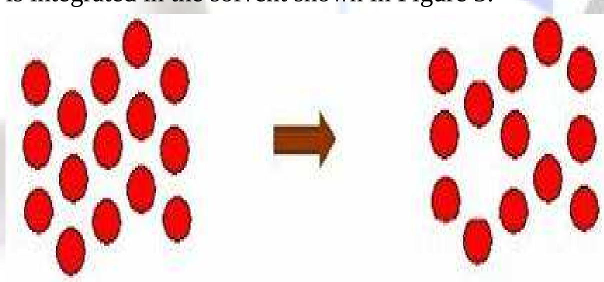

Fig. 1: Holes opens in the solvent

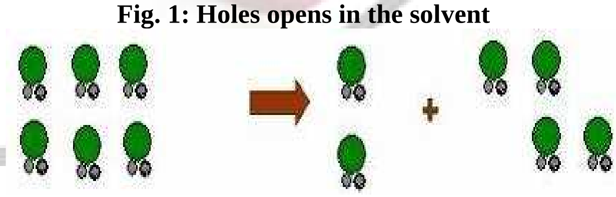

Fig. 2: Molecules of the solid breaks away from the bulk

ISSN: 0976-7126

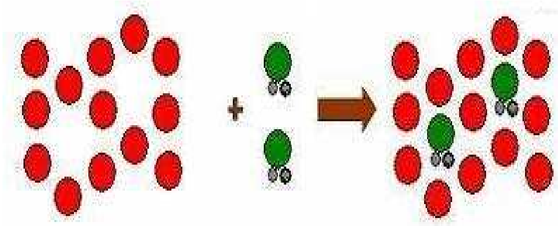

Fig. 3: The freed solid molecule is integrated into the hole in the solvent.

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 [6].

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. The effect of particle size on solubility can be explained as per the following equation. [3]

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

S is the solubility of infinitely large particles, **S** is the solubility of fine particles, **V** is molar volume , ***G*** is the surface tension of the solid, **R** is the radius of the fine particle

Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature [7]. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases [2].

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 [2].

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 solubilities of these two substances is the result of differences in their nature [2].

Molecular size

The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate 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 [7].

Polarity

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 [7].

Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell.The capacity for a substance to crystallize in more than one crystalline form is polymorphism [8].

Techniques of solubility enhancement

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are [9]:

Physical Modifications

Particle size reduction

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution [10-11].

Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants [12]. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald

ISSN: 0976-7126

ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. Techniques for the production of nanosuspensions [12]

Homogenization

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles. Three types of homogenizers are commonly used such as conventional homogenizers, sonicators, and high shear fluid processors [13].

Wet milling

Active drug in the presence of surfactant is defragmented by milling. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one [9,14]. Drying of nanosuspensions can be done by lyophilisation or spray drying.

Other techniques for reduction of the particle size

Sonocrystallisation

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is sonocrystallisation [15-17].

Supercritical fluid process

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes [18]. A supercritical fluid (SF) can be defined as a dense noncondensable fluid [19]. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). The most widely employed methods of SCF processing for micronized particles are rapid expansion of supercritical solutions (RESS) and gas antisolvents recrystallisation (GAS), both of which are employed by the pharmaceutical industry using carbon dioxide (CO_2) as the SCF [18] due to its favourable processing characteristics like its low critical temperature (Tc = 31.1-C) and pressure (Pc = 73.8 bar) [20-22].

Spray drying

Spray drying is a commonly used method of drying a liquid feed through a hot gas. Typically, this hot gas is air but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used instead. The liquid feed varies depending on the material being dried and is not limited to food or pharmaceutical products and may be a solution, colloid or a suspension. This process of drying is a one step rapid process and eliminates additional processing [23]. Spray drying of the acid dispersed in acacia solutions resulted in as much as a 50% improvement in solubility of poorly water soluble salicylic acid [24].

Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties.

Drug dispersion in carriers

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961 [25].The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method [26]. Novel additional preparation techniques have included rapid precipitation by freeze drying [27] and using supercritical fluids [28] and spray drying [29], often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion [30].

The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone [31, 32], polyethylene glycols [33], Plasdone-S630 [34]. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used [34]. The solubility of etoposide [35], glyburide [36], itraconazole [37], ampelopsin [38], valdecoxib [39], celecoxib [40], and halofantrine [41] can be improved by solid dispersion using suitable hydrophilic carriers. The eutectic combination of chloramphenicol/urea [42] and sulphathiazole/ urea [25] served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

Hot melt method

Sekiguchi and Obi [25] used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can

ISSN: 0976-7126

be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process [43].

Solvent evaporation method

Tachibana and Nakumara [44] 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. This enabled them to produce a solid solution of the highly lipophilic β-carotene 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 [43]. The solvent can be removed by various methods like by spray-drying [45] or by freeze-drying [46].

Temperatures used for solvent evaporation generally lie in the range 23-65 C [47, 48]. The solid dispersion of the 5- lipoxygenase/cyclooxygenase inhibitor ER-34122 shown improved in vitro dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation [49]. These techniques have problems such as negative effects of the solvents on the environment and high cost of production due to extra facility for removal of solvents [50]. Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions [26, 51].

Hot-melt extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971[52]. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient [53]. The process has been useful in the preparation of solid dispersions in a single step.

(d) Melting –solvent method

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used. Carriers for solid dispersions as shown in table 2.

Table 2: Carriers for solid dispersions[26]

S/No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid
2	Sugars	Dextrose, Sucrose, Sorbitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000,Cellulose
4	Surfactants	Polyxyethylene Stearate, Tweens and Spans
5	Miscellaneous	Urea, Urethase

Complexation

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in below table 3.

Staching complexation

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation. Some compounds that are known to form staching complexes are as Nicotinamide[54-56], Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene etc.

Table 3: List of complexing agents[3]

S/No.	Types	Examples
1.	Inorganic	I_B^-
2.	Coordination	Hexamine cobalt(III) chloride
3.	Chelates	EDTA, EGTA
4.	Metal-Olefin	Ferrocene
5.	Inclusion	Cyclodextrins, Choleic acid
6.	Molecular Complexes	Polymers

Inclusion complexation

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced[57-65].

ISSN: 0976-7126

Solubilization by surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic [67]. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent [15].

Microemulsion

The term microemulsion was first used by Jack H. Shulman in 1959. A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter[69-71].

Chemical Modifications

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances [72-74].

Co-crystallisation

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystals, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex) [11]. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces [75]. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature [76-78].

Co-solvency

The solubilisation of drugs in co-solvents is a technique for improving the solubility of poorly soluble drug [79]. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs [80-81]. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, cosolvents reduce waters ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization [82]. Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone [83].

Molecular encapsulation with cyclodextrins

The beta- and gamma- cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility. These bucket shaped oligosaccharides produced from starch are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drug as guests; the outside of the host molecule is relatively hydrophilic. Thus the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. There are several examples of drugs with improved bioavailability due to such phenomenon- thiazide diuretics, barbiturates and a number of NSAIDs.[84].

Solubilizing agents

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide [85]. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine [86]. The aqueous solubility of the antimalarial agent halofantrine is increased by addition of caffeine and nicotinamide [87].

Nanotechnology approaches

Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less [88]. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution [89] and the next step taken was Nanonisation [90].

ISSN: 0976-7126

Nanocrystal

A nanocrystal is a crystalline material with dimensions measured in nanometers; a nanoparticle with structure that is mostly crystalline. The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 nanometers. Nanocrystallization is thought to be an universal method that can be applied to any drug [91]. There are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development[92]. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

Milling

Nanoscale particles can be produced by wet-milling process [93]. In ball mills, particle size reduction is achieved by using both impact and attrition forces. The most common models are a tumbling ball mill and a stirred media mill. One problem of this method is the degradation of mill surfaces and subsequent suspension contamination.

High pressure homogenization

In high pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity [94]. Homogenisation can be performed in water (DissoCubes) or alternatively in non-aqueous media or water-reduced media (Nanopure) [90]. The particles are disintegrated by cavitation and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles [95]. The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles.

Precipitation

In the precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good [96].The solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtering and then dried in air.

d) Cryo-vacuum method:

In the cryo-vacuum method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution [97]. The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 ºC). Rapid cooling causes a very fast rise in the degree of saturation based on the decrease of solubility and development of ice crystals when the temperature drops below 0 ºC. This leads to a fast nucleation of the dissolved substance at the edges of the ice crystals. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of the particles produced, so they will remain crystalline. The method yields very pure nanocrystals since there is no need to use surfactants or harmful reagents.

NanoMorph

The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Water redispersable dry powders can be obtained from the nanosized dispersion by conventional methods, e.g. spray-drying. Nanotechnology approaches to improve the solubility of hydrophobic drugs shown in table 4.

Table 4: Nanotechnology approaches to improve the solubility of hydrophobic drugs [98-99]

Company	Nanoparticulate Technologies	Description
Elan	Nano Crystal	Nano crystal drug particles (<1000 nm) produced by wet-milling and stabilised against agglomeration through surface adsorption of stabilizers applied to NMEs eg. Reformulation of existing drugs eg. sirolimus
BioSante	CAP	Calcium-phosphate based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin

Hydrotropy

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water soluble drugs [100-101]

References

1. Improving solubility & permeability in drug candidates. Conference: 23rd & 24th June, 2005, Pre-conference workshop: 22nd June 2005, Thistle Marble Arch, London, UK.
2. shttp://www.sciencebyjones.comm
3. http://www.cop.ufl.edu/safezone/prokai/pha5100/pha5110.htm
4. http://en.wikipedia.org/wiki/Solubility
5. Indian Pharmacopoeia, Ministry of Health and family welfare, Government of India, Published by the controller of publications, Delhi, 1996¡ 1-76.
6. James K., Solubility and related properties. 28: Marcel Dekker Inc., Newyork, 986, 127 – 395.
7. http://www.chem.lsu.edu/lucid/tutorials/tutorials.html
8. Singhal D, Curatolo W.Drug polymorphism anddosage form design a practical perspective, Adv. Drug. Deliv. Rev., 2004¡ 56, 335-347.
9. Pinnamaneni S., Das N.G., Das S.K.Formulation approaches for orally administered poorly soluble drugs. Pharmazie, 2002¡ 57:291 – 300.
10. Chaumeil J.C.Micronisation: a method of improving the bioavailability of poorly solubledrugs, Methods and Findings in Experimental and Clinical Pharmacology, 1998¡20:211-215.
11. Blagden N, Matas M, Gavan P.T, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Advanced Drug Delivery Reviews2007¡ 10 May.
12. Nanosuspension drug delivery Technology and application - Nanotech – Express Pharma Pulse.htm, http://www.expresspharmapulse.com
13. Medical Design Technology online at www.mdtmag.com or Microfluidics at http://www.microfluidicscorp.com
14. M.E.Aulton .Pharmaceutics, The science of dosage form design, 2nd edition, Churchill Livingstone, London, 2002¡113 – 252.
15. Michael Hite, Lead Research Associate, Stephen Turner, Oral Delivery of Poorly Soluble Drugs 400, Pharmaceutical Manufacturing and Packing Sourcer Summer ’03 issue. Samedan Ltd. 2003.
16. Banga Sheere, Chawala Garima , Bansal Arvind K .New Trends in the Crystallisation of Active Pharmaceutical Ingredients, Businessbriefing Pharmagenerics 2004¡70-74.
17. Crystallization process using ultrasound, United States Patent 2002¡003¡1577.
18. Kakumanu Vasukumar ,Bansal Arvind K .Supercritical Fluid Technology in Pharmaceutical Research Businessbriefing: Labtech, 2004¡71-73.
19. Irene Pasquali, Ruggero Bettini, Ferdinando Giordano. Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics, European journal of pharmaceutical sciences 2006¡27: 299–310.
20. Hamsaraj Karanth,1 Vikram Subraya Shenoy , Rayasa Ramachandra Murthy, Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report, AAPS PharmSciTech 2006¡7 (4) Article 87.
21. Perrut M, Jung J, Leboeuf F. Enhancement of dissolution rate of poorly soluble active ingredients by supercritical fluid processes Part II: Preparation of composite particles, International Journal of Pharmaceutics 2005¡ 288:11–16.
22. Prajapati Bhupendra G, Patel Rakesh P, Patel Ritesh B, Patel Girish, N, Patel Hitesh R, Dr. Madhabhai Patel, Novel Pharmaceutical Methods Improve one of the Principal Pharmacokinetic Properties of Lipophilic Drug, www.pharmaquality.com
23. Spray drying From Wikipedia, the free encyclopedia. Retrieved from http://en.wikipedia.org
24. Kawashima Y, Saito M, Takenaka H, Improvement of solubility and dissolution rate of poorly water-soluble salicylic acid by a spray-drying technique. J. Pharm. Pharmacol. 1975, 27:1-5.
25. Sekiguchi K,Obi N. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, Chem. Pharm. Bull., 1961¡9: 866-872.
26. Chiou W L, Riegelman S. Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 1971¡ 60: 1281-1302.

27. Emara L H, Badr R M, Elbary A A. Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers, Drug. Dev.Ind.Pharm., 2002, 28: 795-807.
28. Juppo A M, Boissier C, Khoo C. Evaluation of solid dispersion particles prepared by SEDS, Int. J. Pharm., 2003¡250, 385-401.
29. Kai T, Akiyama Y, Nomura S, Sato M. Oral absorption improvement of poorly soluble drug using solid dispersion technique, Chem. Pharm. Bull 1996, 44:568-571.
30. Forster A, Hempenstall J, Rades T.Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers, J. Pharm. Pharmacol., 2001, 53: 303-315.
31. Ambike AA, Mahadik KR, Paradkar A. Stabil ity study of amorphous valdecoxib. Int. J. Pharm. 2004, 282: 151-162.
32. Paradkar A, Ambike AA, Jadhav BK, Mahadi k KR. Characterization of curcumin PVP solid dispersion obtained by spray drying. Int J Pharm 2004, 271:281-286.
33. Doshi DH, Ravis WR, Betageri GV. Carbama zepine and polyethylene glycol solid dispersion preparation, invitro dissolution, and characterization. Drug Dev Ind Pharm., 1967, 23: 1167-1176.
34. Ghebremeskel Alazar N, Vemavarapu Chandra, Lodaya Mayur. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer–surfactant combinations using solubility parameters and testing the processabilit International Journal of Pharmaceutics2007, 328: 119–129.
35. Shah Jaymin C, Che Jivn R, Diana Chow, Preformulation study of etoposide: II. Increased solubility and dissolution rate by solid-solid dispersions, International Journal of Pharmaceutics 1995, 113:103-111.
36. Betageri G V, Makarla K R. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. International Journal of Pharmaceutics, 1995, 126: 155-160.
37. Jae-Young Jung, Sun Dong Yoo, Sang-Heon Lee, Kye-Hyun Kim, Doo-Sun Yoon, Kyu-Hyun Lee. Enhanced solubility and dissolution rate of itraconazole by a solid Dispersion technique. International Journal of Pharmaceutics, 1999, 187:209–218.
38. Li-Ping Ruan, Bo-Yang Yu, Guang-Miao Fu, Dan-ni Zh. Improving the solubility of ampelopsin by solid dispersions and inclusion complexes.Journal of Pharmaceutical and Biomedical Analysis 2005, 38: 457–464.
39. Aftab Modi and Pralhad Tayade, Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique, AAPS PharmSciTech 2006, 7 (3) Article 68.
40. Gupta Piyush , Kakumanu Vasu Kumar , Bansal Arvind K.Stability and Solubility of Celecoxib-PVP Amorphous Dispersions: A Molecular Perspective, Pharmaceutical Research 2004, 21:1762-1769.
41. Ahmad M. Abdul-Fattah, Hridaya N. Bhargava.Preparation and in vitro evaluation of solid dispersions of Halofantrine. International Journal of Pharmaceutics 2002, 235: 17–33.
42. Sekiguchi K, Obi N, Ueda Y. Studies on absorption of eutectic mixtures. II. Absorption of fused conglomerates of chloramphenicol and urea in rabbits, Chem. Pharm. Bull. 1964¡ 12: 134-144.
43. Christian Leuner, Jennifer Dressman. Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics, 2000, 50:47-60.
44. Tachibana T, Nakamura A. 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.
45. Lo W Y ,Law S L.Dissolution behavior of griseofulvin solid dispersions using polyethylene glycol, talc, and their combination as dispersion carriers, Drug Dev. Ind. Pharm. 1996, 22: 231-236.
46. Betageri G V, Makarla K R. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int. J. Pharm 1995, 126: 155-160.
47. Kearney A S, Gabriel D L, Mehta S C, Radebaugh G W. Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the antiin ammatory Ci-987. Int. J. Pharm 1994, 104: 169-174.
48. El-Zein H, Riad L, Elbary A A. Enhancement of Carbamazepine dissolution - in vitro and in

vivo evaluation. Int. J. Pharm 1998, 168: 209-220.
49. Kushida I, Ichikawa M, Asakawa N.Improvement of dissolution and oral absorption of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenas inhibitor with anti-inflammatory activity by preparing solid dispersion, J. Pharm. Sci.2002, 9: 258-266.
50. Serajuddin, A.T.M. Solid dispersion of poorly watersoluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 1999, 88: 1058-1066.
51. Vadnere M. K. Coprecipitates and melts in Encyclopedia of pharmaceutical technology. 2nd edition, Marcel Dekker Inc. Newyork, 2002, 1: 641 -648.
52. el-Egakey MA, Soliva M, Speise P. Hot extruded dosage forms. Pharm Acta Helv. 1971, 46: 31-52.
53. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm 2002, 54:107-117.
54. Sanghvi Ritesh, Daniel Evans, Samuel H. Yalkowsky, Stacking complexation by nicotinamide: A useful way of enhancing drug solubility. International Journal of Pharmaceutics, 2007, 336: 35–41.
55. Higuchi T., Kristiansen H. Binding specificities between small organic solutes in aqueous solutions: classification of some solutes into two groups according to binding tendencies. J. Pharm. Sci. 1970, 59:1601–1608.
56. Rajewski R A, Stella V J. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. J. Pharm. Sci. 1996, 85: 1142-1169.
57. Joon Woo Park, Kinetics and Mechanism of Cyclodextrin Inclusion Complexation Incorporating Bidirectional Inclusion and Formation of Orientational Isomers, J. Phys. Chem. B, ASAP Article, www.aaps.org
58. Kaneto Uekama, Fumitoshi Hirayama, and Tetsumi Irie. Cyclodextrin Drug Carrier Systems, Chem. Rev. 1998, 98: 2045 -2076.
59. Singala Anil K , Garg Alka, Aggarwal Deepika. Paclitaxel and its formulations.International Journal of Pharmaceutics 2002, 235: 179–192.
60. Rawat S, Jain S K. Rofecoxib-β-cyclodextrin inclusion complex for solubility enhancement, Pharmazie. 2003, 58: 639-641.
61. Rawat Swati, Jain Sanjay K. Solubility enhancement of celecoxib using β-cyclodextrin inclusion complexes. European Journal of Pharmaceutics and Biopharmaceutics 2004, 57:263–267.
62. Anguiano-Igea S, Otero-Espinar F J,Vila-Jato J L,Blanco-M6ndez J. Improvement of clofibrate dissolution by complexation with cyclodextrin. International Journal of Pharmaceutics 1996, 135: 161-166.
63. St´ephaneGibaud, Siham Ben Zirar, Pierre Mutzenhardt, Melarsoprol–cyclodextrins inclusion complexes. International Journal of Pharmaceutics 2005, 306: 107–121.
64. Dordunoo Stephen K, Burt Helen M. Solubility and stability of taxol: effects of buffers and Cyclodextrins. International Journal of Pharmaceutics 1996, 133:191-201.
65. Ran Y, Zhao L, Xu Q, Yalkowsky SH. Solubilization of Cyclosporin A. AAPS PharmSciTech. 2001, 2(1): article 2.
66. Mosher G., Thompson D.O. Complexation and cyclodextrins, in Encyclopedia of pharmaceutical technology 2nd edition, Marcel Dekker Inc., Newyork, 2002, 1:531 – 558.
67. Swarbrick J., Boylan J.C. Encyclopedia of Pharmaceutical Technology; 2nd edn, 2002, 3:2458-2479.
68. Lawrence M.J., Rees G.D. Microemulsions based media as novel drug delivery systems. Adv. Drug. Del. Rev. 2000, 45: 89 – 121.
69. Tenjarla SN. Microemulsions: An overview and pharmaceutical applications. Critical Reviews ™ in Therapeutic Drug Carrier Systems, 1999, 16:461-521.
70. Lieberman HA, Rieger MM, and Banker GS. Pharmaceutical Dosage Forms: Disperse Systems, 2nd edn, New York, Marcel Decker, 1996, 1: 211–281, 315–370.
71. Kovarik JM, Muller EA, Van Bree JB, Tetzloff W, and Kathz K.Reduced inter- and intra- individual variability in cyclosporine pharmacokinetics from a microemulsion formulation. J Pharm Sci, 1994, 83: 444.
72. Solutions and Solubility. Adam M. Persky and Jeffrey A. Hughes, University of Florida, College of Pharmacy, Gainesville, FL 32610, USA
73. Agharkar S, Lindenbaum S , Higuchi T.Enhancement of solubility of drug salts by hydrophilic counter-ions: properties of organic

salts of an anti-malarial drug, J. Pharm.Sci. 1976, 65:747-749.
74. Abu T.M. Serajuddin, Salt formation to improve drug solubility, Advanced Drug Delivery Reviews 2007.
75. Aakeröy C B. Crystal engineering: Strategies andArchitectures, Acta Cryst. 1997, B53:569-586.
76. Almarsson O, Zaworotko M J. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? Chem. Commun., 2004, 1889-1896.
77. Trask A V, Motherwell W D S, Jones W. Solvent-drop grinding: green polymorph control of co-crystallisation Chem. Comm. 2004, 890-891.
78. Zaworotko M. Polymorphism in Co-Crystals and Pharmacuetical Co-Crystals, Congress of the International Union of Crystallography, Florence, 2005.
79. Amin K, Dannenfelser R M, Zielinski J, Wang B. Lyophilization of polyethylene glycol mixtures. J. Pharm. Sci. 2004, 93:2244-2249.
80. Yalkowsky S H., Roseman T J. Solubilization of drugs by cosolvents. In: Yalkowsky, S.H. (Ed.), Techniques of Soluhilization of Drugs. Dekker, New York 1981.
81. Rubino Joseph T. Cosolvents and Cosolvency. 2002, 1: 658-670, http://www.dekker.com
82. Millard Jeffrey W, Alvarez-Nu´n˜ez F A, Yalkowsky S H. Solubilization by cosolvents Establishing useful constants for the log /linear model. International Journal of Pharmaceutics, 2002, 245: 153-166.
83. Jain Parijat, Yalkowsky Samuel H. Solubilization of poorly soluble compounds using 2-pyrrolidone.International Journal of Pharmaceutics 2007.
84. Rao M.G. et al. Preparation and evaluation of solid dispersion of naproxen. Indian J. Pharm. Sci., 2005, 67: 26-29.
85. Vervaet C, Remon JP. Bioavailability of hydrochlorothiazide from pellets, made by extrusion/spheronisation, containing polyethylene glycol 400 as a dissolution enhancer, Pharm Res. 1997, 14:1644-1646.
86. G.V. Murali Mohan Babu, Ch. D.S. Prasad, K.V. Ramana Murthy. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine., International Journal of Pharmaceutics 2002, 234: 1–17.
87. Lee-Yong Lim, Mei-Lin Go, Caffeine and nicotinamide enhances the aqueous solubility of the antimalarial agent halofantrine. European Journal of Pharmaceutical Sciences, 2000, 10: 17–28.
88. Lynn L Bergeson and Michael F Cole, NanoBioConvergence – Emerging Diagnostic and Therapeutic Applications, www.touchbriefings.com, bioprocessing & biopartnering 2006, 1-4.
89. Valizadeh H, Nokhodchi A, Qarakhani N, et al. Physicochemical characterization of solid dispersions of indomethacin PEG 6000, Myrj 52, lactose, sorbitol, dextrin and Eudragit E100. Drug Dev Ind Pharm. 2004, 30: 303-317.
90. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm. 2006, 62: 3-16.
91. Radtke M.Pure dug nanoparticles for formulation of poorly soluble drugs. New Drugs, 2001, 3: 62-68.
92. Mazzola L. Commercializing nanotechnology. Nat Biotechnol, 2003, 10:1137-1143.
93. Kondo N, Iwao T, Masuda H, Yamanouchi K, Ishihara Y, Yamada N, Haga T, Ogawa Y, Yokoyama K. Improved oral absorption of a poorly water-soluble drug, HO-221, by wet-bead milling producing particles in submicron region. Chem Pharm Bull, 1993, 41:737-740.
94. RH, Becker R, Kruss B, Peters K.Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution, 1999, US Patent 5858410.
95. Hecq J, Deleers M, Fanara D, and Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm, 2005, 299: 167-177.
96. Chung H-R, Kwon E, Oikawa H, Kasai H, Nakanishi H.Effect of solvent on organic nanocrystal growth using the reprecipitation method. J Cryst Growth, 2006, 2:459- 463.
97. Salvadori B, Capitani GC, Mellini M, Dei L. A novel method to prepare inorganic water-soluble nanocrystals. J Colloid Interface Sci, 2006, 1:487-490.
98. NanoMorph technology for Amorphous Nanoparticles, www.soliqs.com

99. Roghieh Saffie-Siebert, Dr Jill Ogden and Dr Mark Parry-Billings. Nanotechnology approaches to solving the problems of poorly water-soluble drugs, Drug Discovery World Summer, 2005, 71-76.
100. Maheshwari R.K. A novel application of hydroscopic solubilization in Spectrometric estimation of Frusemide in tablets Pharma Rev. 2006, 4:148.
101. Rasool A.A. et al, Solubility enhancement of some water-insoluble drugs in the presence of Nicotinamide and related compounds.Journal of Pharmaceutical Sciences, 2006, 80: 4;387-393.