Sudarshan Publication

Available online at S-epub.in

THE PHARMA RESEARCH
An International Journal of Pharmacy Research

APPROACHES FOR ENHANCEMENT OF SOLUBILITY TO IMPROVE THE ABSORPTION AND BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

Anuj Agarwal*, Bhuvnesh Kumar Singh, Neelanchal Trivedi, Keshari Kishore Jha

Teerthanker Mahaveer College of Pharmacy, Moradabad, Uttar Pradesh, India

ARTICLE INFO

Published on: 15-09-2014
ISSN: 0975-8216

Keywords:
Poorly solubility, low bioavailability, less absorption

ABSTRACT

The therapeutic response and effectiveness of a formulation depend largely on the availability of the concentration of the drug present at the site of action. The therapeutic effect, directly related to the amount of the drug absorbed, which determines ultimately the bioavailability of the drug. Most of the drugs are poorly water-soluble so formulation of such drugs in to a stable dosage form is a great task and involves specialized techniques. The improvement of solubility is not only beneficial for oral formulations but also useful for parenteral formulations to improve absorption and bioavailability of the drug. The current review describes the various approaches to improve the solubility of poorly soluble drugs.

INTRODUCTION

A large number of drugs are lipophilic in nature. Lipophilic drugs are the chemicals that have strong affinity and the ability to dissolve in fats, lipids and non-polar solvents such as hexane and toluene. These drugs have low or no water solubility; therefore, formulation of such drugs as water-soluble formulation is problematic and involves specific techniques.

* Corresponding Author:
Anuj Agarwal
Teerthanker Mahaveer College of Pharmacy, Moradabad, P.O Box: 244001, Uttar Pradesh, India

Nearly 40% or more of the drugs are lipophilic and are poorly water-soluble. Low solubility leads to low absorption and thus low bioavailability.

The solubility is defined as a maximum quantity of the solute that can be dissolved in a certain quantity of solvent or quantity of solution at a specified temperature *[1]*. When expressed quantitatively, solubility defined as the concentration of the solute in a saturated solution at a certain temperature and when expressed qualitatively, it may be defined as

the spontaneous interaction of two or more substances to form homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent *[2]*. Solubility of a drug can be a major factor that can decide the usefulness of the drug that will dissolve and will be available for absorption.

The solubility of poorly soluble lipophilic drugs depends on following two factors:

(1) Dissolution of the drug (in-vivo) to produce a solution

(2) Permeation or transportation of the dissolved drug across the gastro-intestinal membrane

If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate-limiting step in the absorption process *[3]*. If the permeation of the drug across the gastro-intestinal tract is slower than rate of dissolution of the drug, the permeation becomes the rate-limiting step in the absorption process.

In biopharmaceutical terms based on the solubility and permeability, the drugs classified into the four groups as follows:

Table 1: The Biopharmaceutical Classification System for Drugs:

CLASS	SOLUBILITY	PERMEABILITY	EXAMPLES
Class 1	High	High	Acetaminophen, Acyclovir, Antipyrine, Buspirone, Diazepam
Class 2	Low	High	Amiodarone, Carvedilol, Dapsone, Flurbiprofen, Glipizide, Indinavir
Class 3	High	Low	Amoxycillin, Cetrizine, Cloxacillin, Dicloxacillin, Famotidine
Class 4	Low	Low	Amphotericin B, Colistin, Furosamide, Mebendazole, Neomycin

Expression of solubility:

The Solubility is usually expressed by a number of concentration terms such as Quantity per quantity, Percentage, Parts, Molarity, Molality, Mole fraction, Milliequivalents and normal solutions. It can also be explained in term of parts of solvent required for 1 part of solute as explained in U. S pharmacopeia as follows:

Table 2: Examples of the drugs with their solubility as per USP *[5, 6, 7, 8]*

Terms	Parts of solvent required for 1 part of solute	Examples of drugs
Very soluble	Less than 1parts	Deltiazam, Metoprolol
Freely soluble	From 1-10 parts	Ipratropium bromide
Soluble	From 10-30 parts	Carmustine, Cyclophosphamide, Procainamide, Propananolol, Quinidine, Timolol
Sparingly soluble	From 30-100 parts	Fluorouracil, Labetolol, Quinidine Sulphate, Ramipril
Slightly soluble	From 100-1000 parts	Atenolol, Fludrabine, Valsartan
Very slightly soluble	From 1000-10,000 parts	Busulphan, Doxazocine, Flecainide, Lomustine,
Practically Insoluble	More than 10,000 parts	Candesartan, Chlorambucil, Irbesartan, Lidocaine, Melphlan, Nifedipine

APPROACHES TO IMPROVE THE SOLUBILITY:

There are various approaches to improve the solubility of poorly soluble drugs. Some of them are as follows *[9, 10]:*

1. Physical Modifications:

(A). Particle Size Reduction:

Supercritical Fluid Process: Supercritical fluids are the fluids containing more temperature and pressure than its critical temperature (Tc) and critical pressure (Tp) and have the properties of both a liquid and a gas. The critical point represents the highest temperature and pressure at which the substance can exist as a vapor and liquid in equilibrium. At near-critical temperatures, SCFs are high compressible and changes a little in pressure cause great changes in the density. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels*2*. By this processes nanoparticulate suspensions of particles 5-2,000 nm in diameter can be prepared *[11, 12]*.

In this technique, the active ingredient and the carrier dissolve in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution sprayed, the solvent rapidly extracted by the supercritical fluid, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel*13*.

The most commonly used supercritical fluids are supercritical fluid carbon dioxide (SC-CO2), nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane and ammonia etc. SC-CO2 is a popular solvent because of its safety, cheapness, readily availability and being an ideal substitute for many hazardous and toxic solvents.

By controlling the level of pressure and temperature SC-CO2 can dissolve a broad range of compounds, both polar and non-polar. There are various SCF process such as precipitation with compressed antisolvants process (PCA), solution enhanced dispersion by SCF (SEDS), and supercritical antisolvants processes (SAS), Rapid Expansion of Supercritical Solutions (RESS), Gas Anti Solvent Recrystallization (GAS) and aerosol supercritical extraction system (ASES) *[14]*.

Sonocrystallization: This technique utilizes ultrasound waves of frequency range of 20–100 kHz for inducing crystallization and size reduction. It is an effective mean of size reduction and controlling size distribution of the active pharmaceutical ingredients *[15]* (API). Recrystallization of poorly soluble materials using liquid solvents and anti-solvents has also been employed successfully to reduce particle size *[16]*. Most applications utilize ultrasound in the frequency range of 20 kHz-5 MHz.

Micronization: As the particle size is reduced, the drug will have higher surface area and

more dissolution. Milling and spray drying are the general methods of particle size reduction and these methods utilize mechanical energy to disaggregate the particles. The particle size is greatly co-related with the solubility of the drug. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills or fluid energy mill (by attrition method) and so micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug *[17]*. The size range of drug particles after this process is 1-10 microns.

Nanosuspension: Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants *[18]* and can be used for either oral and topical use or parenteral and pulmonary administration. Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs *[19]*. This technology is most suitable for the poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nano-suspensions is 200 to 600 nm *[20]*. Techniques for the production of nanosuspensions are as follows *[21]*:

a. Homogenization: The homogenizers are the instruments that are commonly used for particle size reduction in the pharmaceutical industries. A number of homogenizers are used in pharmaceutical industries. Eg: conventional homogenizers, sonicators, and high shear fluid processors *[22]*. The suspension is forced under pressure through a valve that has nanoparticle. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks and reduce the size of the particles.

b. Wet milling: In this technique a drug solution is sprayed in a volatile organic solvent involves into a heated aqueous solution. Rapid evaporation of the solvent occurs and it produces drug precipitation in the presence of surfactants. Tarazepide, Atovaquone, Amphotericin B, Paclitaxel and Bupravaquone etc are some examples of the drugs undergoing by this process for making nanosuspension.

(B). Modification of the crystal habit:

A solid can exist in either in a crystalline or amorphous form. When a substance exists in more than one crystalline forms, the different forms are designated as polymorphs and the phenomenon as polymorphism *[23]*. Different polymorphic forms are chemically identical but they differ from each other with respect to their physical properties such as solubility, density, hardness and compression characteristics. Out of the different polymorphic some forms are physically more stable representing lower energy state, higher melting points and least aqueous solubility. The remaining polymorphic forms represent higher energy state, lower melting points and higher aqueous solubility thus called metastable forms. Due to their more aqueous solubility metastable forms are preferred in formulations than the stable forms.

Some drugs can exist in amorphous form in which there is no definite crystal structure and such drugs represent highest

energy, lowest melting point and lowest aqueous solubility. Amorphous forms are preferred over crystalline forms because of their more aqueous solubility. The order for dissolution of different solid forms of drugs is amorphous > metastable > stable polymorph.

(C). Drug Dispersions in Carriers:

Eutectic Mixtures: Eutectic mixture is a mixture of the constituents in such a proportions that the melting point is lowest than that of each of the constituent of the mixture. Eutectic mixtures have higher aqueous solubility than the individual component of the mixture.

Solid Dispersions: 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 *[24}*. Other techniques for preparation solid dispersions are rapid precipitation by freeze drying and using supercritical fluids and spray drying, generally in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. Polyvinylpyrrolidone, polyethylene glycols, plasdone-S63029 etc. are the most commonly used hydrophilic carriers of solid dispersion. Some surfactants may also be used for preparation of solid dispersions. eg: tween-80, docusate sodium, myrj-52, pluronic-F68 and sodium lauryl sulphate. The eutectic combination of chloramphenicol/urea and sulphathiazole/ urea are used to prepare the solid dispersion in a highly water soluble carrier.

Solid Solution: A solid solution is a solid-state solution of one or more solutes in a solvent. Such a mixture is considered a solution rather than a compound when the crystal structure of the solvent remains unchanged by addition of the solutes, and when the mixture remains in a single homogeneous phase *[25]*.

Examples of solid solutions include crystallized salts from their liquid mixture, metal alloys, moist solids. In the case of metal alloys intermetallic compounds occur frequently.

(D). Complexation:

Complexation is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. Complexation is based on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes and cyclodextrins. Complexes are two categories:

(a). Stacking complexes: These are formed by the association of non-polar area of drug and complexing agent which results in exclusion of the non-polar area from contact with water, thereby reducing total energy of the system. Stacking can be homogeneous or mixed, but results in clear solution.

(b). Inclusion Complexes: Inclusion complexes are formed when a compound has an ability to enclose in another compound. No force and bond is involved

for such a complexes and so they are also called as no-bond complexes.

Inclusion complexes are formed by the encapsulation 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 guest molecule should be properly fit into the cavity of host molecule for making an inclusion complex. There are three naturally occurring Cyclodextrins are

i. α-Cyclodextrin,

ii. β-Cyclodextrin

iii. γ- Cyclodextrin.

The main aim of complexation with cyclodextrins is to increase solubility *[26]*. In cyclodextrin inclusion, complex one guest molecule interacts with the cavity of a cyclodextrins molecule to become entrapped and form a stable association. The internal surface of cavity of the cyclodextrin molecule is hydrophobic and external is hydrophilic. Complex formation of cyclosporine A *[30]* melarsoprol *[31]*, Clofibrate *[32]*, Rofecoxib *[33]*, taxol *[34]* celecoxib *[35]*, etc. with cyclodextrins improves the solubility of particular drugs. It was found that cyclodextrins increased the paclitaxel solubility by 950 fold *[27]*. Cyclodextrins enhance aqueous solubility of drugs through inclusion complexation.

(E). Solubilization by surfactants:

Surfactants are the chemicals having both polar and non-polar group within the same molecule. The polar group can be anionic, cationic, and zwitterionic or nonionic *[28]*. They are preferentially absorbed on the interface and reduce the surface tension between the phases. So they can play a major role for improving the solubility and bioavailability of poorly soluble hydrophobic drugs.

Microemulsion: Micro emulsions are widely used to increase the solubility of many drugs that are practically insoluble in water. Many drugs and substances including proteins for oral, parenteral and transdermal use can be administered in the form of microemulsions. The Hong-Mei Piao et.al increased the solubility of fexofenadine through microemulsion *[29]*. The solubility of fenofibrate can be increased by formulating its intranasal microemulsion *[30]*. The droplet diameter of microemulsions is 10 – 100 nm. Micro emulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light.

2. Chemical Modifications:

Salt Formation: It is the most common, effective, simple and useful method of increasing solubility of acidic and basic drugs. Acidic or basic drugs, when converted into salt form, have more solubility than their respective drug. Eg: Aspirin**,** Barbiturates, Theophylline.

Change in pH of the solution: Change in pH of a system is the simple and most effective method for increasing the aqueous solubility of poorly water-soluble drugs. There is an increase in the solubility of ionizable drug by changing the pH of solution. The drug, that efficiently solubilized, should be a weak base with a high pKa value or weak acid with a low pKa value.

Co-crystallization: A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces *[31]*. Co-crystals are also called 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 *[32]*. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt & slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds.

Co-solvency: The use of co-solvent is an effective way to improve the solubility of poorly soluble drugs. Co-solvents are the mixtures of miscible solvents often used to water, which can dramatically change the solubility of poorly aqueous soluble drugs *[33]*. Weakly electrolytes and non-polar molecules often have poor water solubility. Their solubility usually can be increased by the addition of water miscible solvent in which the drug has good solubility. This process is known as Co-solvency and the solvents used to improve solubility are called as co-solvents. Co-solvents reduce the interfacial tension between the aqueous solution and hydrophobic solute. Most co-solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility. It is also assumed that co-solvents make polar water environment more non-polar like the solute and thus facilitate solubilization. 20% of 2-Pyrrolidone is an important co-solvent which enhances solubility as high as 500-fold.

Hydrotropy: It designate to increase in solubility in water due to presence of large amount of additives. It improves solubility by Complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) & solute. Ex. Sublimation of Theophylline with Sodium acetate & Sodium alginate.

3. Other Methods:

Nanotechnology: Nanotechnology is the important technique to improve the solubility of drugs that have poor solubility. For many new chemical molecules micronization technique is not sufficient for improving solubility and bioavailability because micronized product has very low effective surface area. Nanotechnology refers broadly to the study and use of materials and structures at the nano scale level of approximately 100 nanometers (nm) or less *[34]*.

Conclusion: Solubility is an essential factor for the drug to be absorbed, showing better bioavailability and elicit desired therapeutic response. Dissolution of the drug is rate determining step particularly for the poorly soluble drugs so solubility is primary requirement for formulation of such drugs. Currently there are a few number of the drugs having good solubility. By using various

techniques and methods alone or in combination, as mentioned above it is possible to increase the solubility of poorly soluble drugs.

Table 3: Nanotechnology to improve solubility of hydrophobic drug*2*:

Nanoparticulate Technologies	Description
CAP(Calcium Phosphate-based Nanoparticles)	For improved oral bioavailability of hormones proteins such as insulin; also as vaccine adjuvant.
IDD (Insoluble Drug Delivery)	Micro-nm particulate/droplet water-insoluble drug core stabilized by phospholipids; formulations are produced by high shear, cavitation's or impaction.
NAB (Nanoparticle Albumin-Bound technology)	Injectable suspension of biocompatible protein with Drug improves solubility/removes need for toxic solvents; e.g. paclitaxel-albumin nanoparticles, injectable suspension of biocompatible protein with drug improves.
Nanocrystal	Nanocrystal drug particles (<1,000 nm) produced by wet-milling and stabilized against agglomeration through surface adsorption of stabilizers; applied to NMEs e.g. aprepitant/reformulation of existing drugs e.g. Sirolimus.
Nanoedge	Nanoedge technology: drug particle size reduction to Nano range by platforms including direct homogenization, micro precipitation, lipid emulsions and other dispersed-phase technology.

Use of soluble prodrugs: A prodrug is a chemically modified inert drug precursor which upon biotransformation liberates the pharmacologically active parent compound. In this method the polar or ionizable moiety is incorporated to the parent drug. A number of poorly soluble drugs can be converted into water soluble prodrugs as follows:

Table 4 : Hydrophilic prodrug of poorly aqueous soluble drugs:

Parent Drug	Prodrug with Enhanced Hydrophilicity
Chloramphenicol	Sodium succinate ester
Corticosteroid	21- sodium succinate, 21- phosphate esters
Diazepam	L-lysine ester
Menthol	β-Glucoside
Metronidazole	Amino acid esters
Sulfanilamide	Glucosyl sulfanilamide
Testesterone	Phosphate ester
Tocopherols	Sodium succinate ester

REFERENCES:

1. Stella V, Borchardt R, Hageman M, Oliyai R, Maag H and Tilley J, Biotechnology : Pharmaceuitical Auspects, 5(part 2), 2007, Publisher-Springer New York, 157-215.
2. Hameed M.A., Nazim S., Khan T., Usman M.R.M, "A Recent trends in Enhancement of Solubility and dissolution rate of poorly soluble

hydrophobic drugs by using physical and chemical modifications", Journal of Drug Discovery and Therapeutics 1 (5) 2013, 13-24, 13-24.

3. Habib, M.J., Pharmaceutical solid dispersion Technology, Technomic Publishing Company, Inc. Lancaster, Pennsylvania (U.S.A.). 2001, pp. 1-36.
4. 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.
5. Martin A. Micromeritics in physical pharmacy. 2nd ed. Phikadelphia PA.1988. p.273.
6. 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.
7. 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.
8. 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.
9. P. S Mohanachandran1, P. G Sindhumol1 and T. S Kiran; Enhancement of Solubility and Dissolution Rate: An Overview Pharmacie Globale (Ijcp), Vol. 01, Issue 04
10. 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.
11. Sunkara G, Kompella U B; Drug Delivery Applications of Supercritical Fluid Technology. Drug. Del. Technol. 2002; 2: 44-50.
12. Manna L, Banchero M, Solta D, Ferri A, Ronchetii S, Sicrdi S; Impregnation Of Pvp Microparticles With Ketoprofen In The Presence Of Supercritical Co2. J. Supercritical Fluids. 2006; 78: 67-69.
13. T. Vasconcelos, B. Sarmento, and P. Costa, "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs," Drug Discov. Today. 2007, vol. 12 issues 23-24, pp. 1068-1075.
14. Anuj Kumar, Sangram Keshri Sahoo, Kumud Padhee, Prithi Pal Singh Kochar, Ajit Satapathy And Naveen Pathak ; Review On Solubility Enhancement Techniques For Hydrophobic Drugs Pharmacie Globale© (Ijcp), Vol. 02, Issue 03.
15. Emara L.H.,R.M. Badr, A.A. Elbary, Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers, Drug. Dev."Ind.Pharm.,28, 2002, 795-807.

16. Sharma D K, Joshi S B; Solubility Enhancement Strategies for Poorly Water-Soluble Drugs in Solid Dispersions: A Review. Asian J Pharmaceutics 2007; 1 (1):9-19.
17. (17). Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews*. 2007; 59 (7):617–630. [PubMed]
18. Sekiguchi K., N. Obi, 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. 9, 1961, 866-872.
19. Nash R A; Suspensions. In: J Swarbrick, Jc Boylan (Ed). Encyclopedia of Pharmaceutical Technology. Second Edition Vol. 3. New York, Marcel Dekker, 2002; 2045-3032.
20. Aulton M E; Pharmaceutics, The Science of Dosage Form Design, 2nd Edition, Churchill Livingstone, London, 2002; Pp.113 – 138, 234 – 252.
21. Medical Design Technology online at http://www.mdtmag.com/ or Microfluidics at http://www.microfluidicscorp.com/.
22. Chiou W.L., S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 60, 1971, 1281- 1302.
23. Brahmankar D.M., Jaiswal S.B., Biopharmaceutics and Pharmacokinetics, A Treatise, Vallabh Prakashan, 2005, Pp. 27-28.
24. Ambike AA, Mahadik KR, Paradkar A. Stability study of amorphous valdecoxib. Int J Pharm. 2004, 282, 151-162.
25. http://en.wikipedia.org/wiki/Solid_solution
26. Park J Woo; Kinetics And Mechanism Of Cyclodextrin Inclusion Complexation Incorporating Bidirectional Inclusion And Formation Of Orientational Isomers, J. Phys. Chem. B, ASAP Article, 2005; 32:124-127.
27. Uekama K, Hirayama F and Irie T; Cyclodextrin Drug Carrier Systems, Chem. Rev., 1998; 98: 2045-2076.
28. Swarbrick J, Boylan J C; Encyclopedia of Pharmaceutical Technology; 2nd Edn, 2002, 2458-2479.
29. Gershanik T., Benita S. Positively Charged Self- Emulsifying Oil Formulation For Improving Oral Bioavailability Of Progesterone. Pharm. Dev. Technol. 1996; 1(2): 147-157.
30. Mueller E.A., Kovarik J.M., Van Bree J.B., Tetzloff W., Grevel J., Kutz K. Improved Dose Linearity Of Cyclosporine Pharmacokinetics From A Micro emulsion Formulation. Pharm Res. 1994; 11(2): 301-304.
31. 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.

32. (32). Aakeroy C B; Crystal Engineering: Strategies And Architectures, Acta Cryst., 1997;45: 569-586.
33. S. H. Yalkowsky And T. J. Roseman, "Solubilization Of Drugs By Cosolvents," In Techniques of Soluhilization Of Drugs, S. H. Yalkowsky, Ed., P. 91, Dekker, New York, Ny, Usa, 1981.
34. Keck C M, Muller R H; Drug Nanocrystals of Poorly Soluble Drugs Produced By High Pressure Homogenisation. Eur J Pharm Bio pharm., 2006; 62: 3-16.