Review Article

# STRATEGIES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS

**Satish K. Patil*, Kalpesh S. Wagh,Venkatesh B. Parik, Anup M. Akarte, Dheeraj T. Baviskar.**
Department of Pharmaceutics, KVPS Institute of Pharmaceutical Education, Boradi, At-post: Boradi Tal: shirpur, Dist: Dhule, India.
*Corresponding author's E-mail: satishpatil269@gmail.com

**Accepted on:** 08-03-2011; **Finalized on:** 28-05-2011.

**ABSTRACT**

The solubility of drugs molecules remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has increased solubility. A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation. So many times it becomes challenging to formulate poorly water soluble drugs. Therefore it is necessary to improve solubility of drug by some methods like co-solvency, salt formation, addition of solubilizing agent, Micronization, Complexation, solid dispersion. Although these techniques have commonly been used to increase dissolution rate of the drug, there are practical limitations with these techniques, the desired bioavailability enhancement may not always be achieved. In this review we concentrated on improvement of the solubility of poorly water soluble drugs by preparing various methods.

**Keywords:** Bioavailability, salt formation, co-solvency, solubilizing agent, micronization, solid dispersion.

## 1. INTRODUCTION

The solubility is defined as a maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature[1]. In the other words the solubility can also define as the ability of one substance to form a solution with another substance[2]. 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[3].

Almost More than 90% drugs are orally administered. Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on Solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble[4]. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain. The 130 orally administered drugs on the WHO list, 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). The rate and extent of absorption of class II and class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility.[5] Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility[6]. Solubility is the characteristic physical property referring to the ability of a given substance, the solute, to dissolve in a solvent.

**Solvent –** The component which forms major constituent of a solution and is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level.[7]

**Solute - A** substance that present in small quantity and dissolves in solven.[7] "The solubility of a solute is the maximum quantity of solute that can dissolve in temperature."

**Table No. 1**

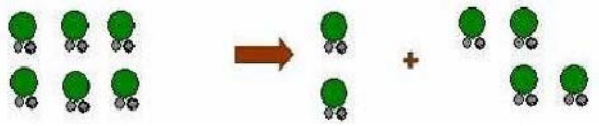
| Definition | Parts of solvent required for one part of solute |
|---|---|
| Very Soluble | < 1 |
| Freely soluble | 1 – 10 |
| Soluble | 10 – 30 |
| Sparingly soluble | 30 – 100 |
| Slightly | 100 – 1000 |
| Very slightly soluble | 1000 - 10,000 |
| Insoluble | > 10,000 |

## 2. PROCESS OF SOLUBILISATION

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute[8], 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[9].

Step 1: Holes opens in the solvent

Step 2: Molecules of the solid breaks away from the bulk



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

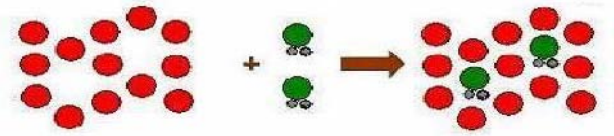


**Figure 1: Process of solubilisation**

## 3. FACTORS AFFECTING SOLUBILITY

**Molecular size:** Molecular size will affect the solubility of drug. 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].

**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 natures[2].

**Temperature:** Temperature will affect solubility. If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature[10]. 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].

**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 described by[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

**Polarity:** Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules[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. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities[3]. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy[8].

## 4. NEED OF SOLUBILITY ENHANCEMENT

According to recent estimates, nearly 40-50% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response

to be shown. Therapeutic effectiveness of a drug depends upon the bioavailability and solubility of drug molecules.

**Bioavailability** is rate and extent of therapeutically active drug that reaches systemic circulation and is available at the site of action. It is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non intravenous routes of administration[11].

**Poor aqueous solubility is caused by two main factors**

1) Strong intermolecular interactions which make the solubilisation of the solid energetically costly and

2) High lipophilicity.

## 5. TECHNIQUES TO OVERCOME POOR SOLUBILITY

The technology as **'solubility improve'** can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds. It is also important to be aware that water solubility also requires the specification of **temperature and pH**; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be met at the site of absorption[12]. This article focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference. The techniques that are used to overcome poor drug solubility are discussed under following major headings[9,13].

**I. Physical Modifications**

A. Particle size reduction

- a. Micronization
- b. Nanosuspension

B. Modification of the crystal habit

- a. Polymorphs
- b. Pseudopolymorphs

C. Drug dispersion in carriers

- a. Eutectic mixtures
- b. Solid dispersions
- c. Solid solutions

D. Complexation

- a. Use of Complexing agents

E. Solubilization by surfactants:

- a. Microemulsions
- b. Self microemulsifying drug delivery systems

**II. Chemical Modifications**

1. Salt Formation
2. Co-crystallisation
3. Co-solvent
4. Hydrotropy

**I. Physical Modifications**

**A. Particle size reduction**

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

**1. 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 Micronization is used to increased surface area for dissolution[14]. Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility[15]. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

**2. Nanosuspension**

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants[16]. The advantages offered by Nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald 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]

**a. Homogenization:** The homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors[17]. 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 the particles.

**b. Wet milling:** Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage.

**Other techniques for reduction of the particle size**

1. 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.

Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients[18] (API). Most applications use ultrasound in the range 20 kHz - 5 MHz.

2. 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[19]. Spray drying of the acid dispersed in acacia solutions resulted in as much as a 50% improvement in the solubility of poorly water soluble salicylic acid[20].

**B. Modification of the crystal habit**

Polymorphism is the ability of an element or compound to crystallize in more than 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. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates. Thus, the order for dissolution of different solid forms of drug is **Amorphous >Metastable polymorph >Stable polymorph.** Melting followed by a rapid cooling or recrystallization from different solvents can be produce metastable forms of a drug.

**C. 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[21]. 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[22]. Novel additional preparation techniques have included rapid precipitation by freeze drying[23] and using supercritical fluids[24] and spray drying[25], often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion[26]. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone[27] polyethylene glycols[28], Plasdone-S630[29]. 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[30]. The solubility of etoposide[31], glyburide[32], itraconazole[33], ampelopsin[34], valdecoxib[35], can be improved by solid dispersion using suitable hydrophilic carriers. The eutectic combination of chloramphenicol/urea and sulphathiazole/ urea[21] served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

**1. Hot Melt method**

Sekiguchi and Obi[21] 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 be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process[36]. An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

**2. Solvent Evaporation Method**

Tachibana and Nakumara[37] 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[38]. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 C. 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. 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. Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions.

**3. Hot-melt Extrusion**

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. 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[39]. The process has been useful in the preparation of solid dispersions in a single step.

**4. 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

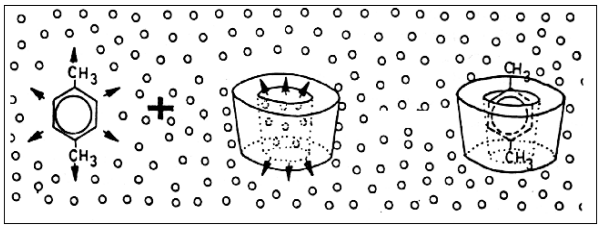
**D. Complexation:** Complexation is the association between two or more molecules to form a non bonded entity with a well defined stochiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are; chelates-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

Complexes are two categories :

1. **Stacking complexes** is driven by association of non polar area of drug and complexes agent this 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.

2. **Inclusion complexes** are formed due to the ability of a compound to enclose in another complex. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes.

Complex Formation by Cyclodextrin




Drug Cyclodextrin Drug/Cyclodextrincomplex

**E. 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. When small a polar molecule 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[18].

**II. CHEMICAL MODIFICATIONS**

**1. Salt Formation:** is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin**,** Theophylline, Barbiturates.

**2. Co-crystallisation:** new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A Co-crystals may be defined as crystalline material that consist of two or more molecular (& electrical neutral) species held together by non-covalent forces. 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.

**3. Co-solvent**: It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Solvent used to increase solubility known as cosolvent. It is also commonly referred to as solvent blending. 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. Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone.

**4. 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.

**5. Solubilising Agents:** The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. PEG 400 is improving the solubility of hydrochlorothiazide. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide.

**6. Nanotechnology Approaches:** Nanotechnology will be used to improve drugs that currently have poor solubility[7]. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronised product has very low effective surface area for dissolution and next step taken was nanonisation.

## FUTURE POTENTIAL AND CONCLUSION

A drug administered in solution form immediately available for absorption and efficiently absorbed than the same amount of drug administered in a solid dosage form such as tablet or capsule. 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 8-10% 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 as mentioned above.

## 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. Lindenberg M, Kopp S, Dressman J, Classification of orally administered drugs on the WHOmodel list of essential medicines according to biopharmaceutical classification system; EuropeanJournal Of Pharmaceutics &Biopharmaceutics, 58 , 2004,265-278,
3. Dr. Ali MD, Dictionary Of Pharmacy, 2005-06, 357-363.
4. Indian Pharmacopoeia, Ministry of Health and family welfare, Government of India, Publishedby the controcller of publications, Delhi,1996,17.
5. Shinde A, Solublization of poorly water soluble drugs, Pharminfo.net, 5, 2007
6. Solubilityof Solute and Aqueous Solutions. http://www.chem.lsu.edu/lucid/tutorials/tutorials.html
7. Swarbrick J, Encyclopedia of Pharmaceutical Technology, 3, 2006, 3314-3328.
8. Ghosh TK, Jasti BR, Theory & Practice Of Contemporary Pharmaceutics, 2005, 70.
9. Chaumeil J.C., Micronisation: a method of improving the bioavailability of poorly solubledrugs, Methods and Findings in Experimental and Clinical Pharmacology, 20, 1998, 211-215.
10. Blagden N, Matas M,Gavan P.T., P. York, Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Advanced Drug Delivery Reviews 2007.
11. Nanosuspension drug delivery Technology and application - Nanotech - Express Pharma Pulse.htm, http://www.expresspharmapulse.com/
12. Medical Design Technology online at http://www.mdtmag.com/ or Microfluidics at http://www.microfluidicscorp.com/
13. 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.
14. Spray drying From Wikipedia, the free encyclopedia. Retrieved from http://en.wikipedia.org/
15. 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.
16. 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.
17. Chiou W.L., S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 60, 1971, 1281-1302.
18. 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.
19. Juppo A.M., C. Boissier, C. Khoo, Evaluation of solid dispersion particles prepared by SEDS, Int. J. Pharm., 2003, 250/ 385-401.
20. Kai T, Y. Akiyama, S. Nomura, M. Sato, Oral absorption improvement of poorly soluble drug using solid dispersion technique,Chem. Pharm. Bull., 44, 1996, 568-571.
21. Forster, J. Hempenstall, T. Rades, Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers, J. Pharm. Pharmacol.,53, 2001, 303-315.
22. Ambike AA, Mahadik KR, Paradkar A. Stability study of amorphous valdecoxib. Int J Pharm. 2004, 282, 151-162.
23. Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. Characte rization of curcumin— PVP solid dispersion obtained by spray drying. Int J Pharm, 2004, 271, 281-286.
24. Doshi DH, Ravis WR, Betageri GV. Carbamazepine and polyethylene glycol solid dispersion preparation, invitro dissolution, and characterization. Drug DevInd Pharm., 23, 1967, 1167-1176.

25. Alazar N. Ghebremeskel , Chandra Vemavarapu, MayurLodaya, Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer–surfactant combinations using solubility parameters and testing the processability, International Journal of Pharmaceutics, 2007, 328, 119–129.

26. Jaymin C. Shah, Jivn R. Chen, Diana Chow, Preformulation study of etoposide: II. Increased solubility and dissolution rate by solid-solid dispersions, International Journal of Pharmaceutics, 1995, 113, 103-111.

27. Betageri G.V., K.R. Makarla, Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques, International Journal of Pharmaceutics, 1995, 126, 155-160.

28. 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.

29. Li-Ping Ruan, Bo-Yang Yu ,Guang-Miao Fu, Dan-niZh, Improving the solubility of ampelopsin by solid dispersions and inclusion complexes, Journal of Pharmaceutical and Biomedical Analysis, 38, 2005, 457–464.

30. AftabModi and PralhadTayade, Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique, AAPSPharmSciTech 2006; 7 (3) Article 68.

31. Christian Leuner, Jennifer Dressman, Improving drug solubility for oral delivery using solid dispersions, European Journal of Pharmaceutics and Biopharmaceutics, 50, 2000, 47-60.

32. Tachibana T, A. Nakamura, 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.

33. W.Y. Lo, S.L. Law, Dissolution behavior of griseofulvin solid dispersions using polyethylene glycol, talc, and their combination as dispersion carriers, Drug Dev. Ind. Pharm., 22, 1996, 231-236.

34. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm., 54, 2002, 107-117.

35. Rawat S, Jain SK, Solubility enhancement of celecoxib using ß-cyclodextrin inclusion complexes, European Journal of Pharmaceutics and Biopharmaceutics, 57, 2004, 263– 267,

36. Swarbrick J., Boylan J.C., Encyclopedia Of Pharmaceutical Technology; 2, 2002, 2458-2479.

37. Sinko PJ, Martin's physical Pharmacy &Pharmaceuitical Sciences, 5, Chapter 9, 2006, 232-234-235-244.

38. Chaudhari P, Sharma P,Bharate N, Kulkarni P, Solubility enhancement of hydrophobic drugs.pharmainfo.net,4 issue3, 2006.

39. Patil V, Nanosuspension : A Novel approach In Drug Delivery, Pharminfo.net article, 6, 2008,227.


**********