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Review On: Solubility Enhancement Techniques for Poorly Water-soluble Drugs

Rachel Geevarghese[1], Yogesh Choudhari[2], Poonam Rathod[3*], Akanksha Chikhale[4*]
Department of Pharmaceutics, Dr. L. H. Hiranandani College of Pharmacy, CHM Campus, Opp. Railway Station, Ulhasnagar (W)-421003, Distt. Thane, Maharashtra

Corresponding Author
E,mail Id: rathod.poonam@dlhhcop.org

ABSTRACT
Solubility is important when a drug's capacity to diffuse uniformly in the liquid phase determines how effective it is. At the site of absorption, any medication that is to be absorbed has to be there in an aqueous solution. When it comes to liquid medicinal formulations, water is the preferred solvent. However, most of the active pharmaceutical ingredients are poorly soluble in water. However, the bulk of pharmacologically active compounds are poorly soluble in water. The solubility of the medications is one of the most critical elements in the formulation creation process. When developing novel drug entities, a formulation scientist's biggest obstacle is the drug's solubility behaviour. Most medications have limited water solubility and are mildly basic and acidic. Therefore, a variety of methods such as micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, etc. are employed to increase the solubility of weakly water-soluble pharmaceuticals. Enhancing solubility is a crucial factor to consider before formulating BCS class II medications into a dosage form. Enhancing the solubility, permeability, and bioavailability of poorly soluble substances is the goal of this review.

INTRODUCTION
The ability of a chemical substance, known as a solute, to dissolve in a solid, liquid, or gaseous solvent and create a homogenous solution in the solvent is known as solubility.[1]

The rate at which the drug molecule or dosage form dissolves into the solution is known as the drug solubility, and it is crucial when the dissolving time is limited. ''Solubility'' has been well–defined as the quantity of solute, which dissolves in a quantity of solvent. The term "quantity" describes the solute concentration in a saturated solution at a specific temperature. Promising elements for in vivo absorption are the permeability and solubility. Solubility improvement strategies can be used to improve them.[2]

When tablets and capsules are taken orally in solid dose forms, their dissolution in the gastrointestinal fluids determines the pace at which they will be absorbed. Notably, certain medications have a sluggish rate of dissolution, which may require inadequate absorption and result in limited bioavailability. Due to their limited solubility and slow dissolution rates, medicines with low water solubility have less of a concentration gradient between the blood arteries and the stomach, which restricts drug transport and, in turn, impacts oral absorption. Development of novel products, especially for the oral route of administration, has a significant risk of reduced and irregular bioavailability, which affects safety and efficacy due to the increasing prevalence of less dissolveable medicines. The dissolving rate of many poorly soluble medicines limits their bioavailability. Therefore, increasing the solubility and dissolution velocity is essential for medications that are not very soluble in water [3]. Many distinct technologies are used to increase solubility and give an existing product a new edge,

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including micronization, solid dispersion, co-solvency complication, hydrotrophy, sono-crystallization, reduction in particle size, micro emulsion, use of surfactant, nano suspensions, and other cryogenic techniques.[1]

Table 1: Definition of Solubility[4]

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

Importance of Solubility

Because oral ingestion is the most practical and extensively utilized drug delivery technique, it is also the most economical due to its low administration costs, high patient compliance, sterility constraints, and customizable dosage forms. When it comes to oral medications getting the necessary concentration in systemic circulation for a pharmacological response, solubility is the crucial rate-limiting factor. Poor solubility and permeability are the two most common causes of insufficient oral bioavailability. Conversely, one of the main challenges in the design of oral dose forms is their low bioavailability. The solubility issue is therefore a major concern for formulation experts.[5] Drug release from the dose form and stomach solubility are the rate-limiting steps for BCS class II and IV medicines. BCS Classification System with examples of different drug is discussed in Table-2.[4]

Table 2: BCS classification of drugs[4]

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol.
II	High	Low	Neteglinide.
III	Low	High	Cimetidin.
IV	Low	Low	Hydrochlorothiazide.

Importance of Solubility Enhancement

Oral ingestion is the most practical and widely used method of drug delivery because it is simple to administer, has a high rate of patient compliance, is economical, has minimal sterility requirements, and allows for dosage form design flexibility. Many generic medicine manufacturers are therefore more likely to create oral drug formulations that are bioequivalent. In order to get the desired concentration of the medication in the systemic circulation and the necessary pharmacological reaction, solubility is one of the key criteria. In order to affect therapeutic plasma concentrations after delivery, hydrophobic medications

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usually need large dosages and high dosing regimens.[6]

The pharmaceutical industry has found that over 40% of NCEs (new chemical entities) are insoluble in water. The aqueous gastrointestinal fluids have low solubility and low dissolving rate, which results in insufficient bioavailability. Enhancing the drug's solubility and rate of dissolution in gastrointestinal fluids can increase bioavailability, which is mostly targeted at group II drugs that impart to the BCS. The release of the drug from the dosage form and stomach fluid solubility, not absorption, is the ratio-restrictive factor for class II BCS; so, improving the solubility will increase the bioavailability of BCS class II drug molecules.[2]

The primary issue with NCE development and manufacture, as well as generic medication development, is low water solubility. One of the critical rate-limiting factors for oral medications to achieve the appropriate concentration in full circulation for pharmacological response is solubility.[6]

Techniques for Solubility Enhancement:[1-8]

PHYSICAL METHODS	CHEMICAL METHODS	BIOTECHNOLOGICAL METHODS
Particle size reduction (Milling, Micronization, Nanonization)	Prodrug formation	Lipid based formulations (Micro emulsions, SMEDDS)
Drug dispersion by surfactant	Co-solvency	Nanotechnology approaches (Nanoparticles, Nanosuspensions)
Complexation	pH adjustment	Solid lipid nanoparticles
Cryogenic techniques	Hydrotropy	
	Salt formation	

The following methods have been employed in an effort to increase the solubility and dissolution rates of medications that are not very soluble in water:[3]

A. PHYSICAL METHODS

1) Micronization

There are number of formulation strategies employed to target the poor aqueous solubility of pharmaceutical compounds. Micronization is one of the widely explored strategies used for particle size reduction and thus providing improved dissolution rates of poorly water-soluble drugs by increasing their surface area. Micronization is performed by milling techniques and instruments which are used for milling are rotor stator colloid mills, jet mills etc. This technique has been used for griseofulvin, progesterone, fenofibrate, and spironolactone. Among micronization techniques, dry milling is the most popular. Micronization increased a drug's absorption while also enhancing its bioavailability and therapeutic efficacy. In biorelevant medium, micronized fenofibrate increased its dissolution rate by more than ten times (1.3–20%) in under thirty minutes. In addition to labor-intensive processes like crushing, milling, grinding, freeze drying, and spray drying, recrystallization of the solute particles from the solutions, which employ liquid antisolvents, can also reduce the size of the

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drug particle. On the other hand, certain medications may break down due to heat or mechanical stress, and solvents naturally contain toxins. [1]

2) Addition of surfactants

Surfactants are the surface-active chemicals that are frequently employed to improve formulation wetting and stability, thereby making poorly water-soluble medications more soluble. Micelle production is facilitated by the self-association of surfactant molecules in an aqueous media. By means of their hydrophobic micelle core, contact with the head group during inclusion into the water micelle interface, and head group interaction, these micelles improve the aqueous solubility of lipophilic weakly water-soluble medicines.[6]

Molecules known as surfactants have separate polar and nonpolar sections. Anionic, cationic, zwitterionic, or nonionic might be the polar group. The hydrophobic center of the micelles might get crowded with tiny polar molecules when they are introduced. Both natural and industrial processes depend heavily on this solubilization process. Surfactants have the potential to lower surface tension and improve a drug's solubility in organic solvents. It is feasible to utilize surfactants to enhance the dissolve capabilities of medicinal formulations that are not very soluble. Drug suspensions are stabilized with the application of surfactants. Micelle production, which traps the pharmaceuticals inside the micelles, happens when the concentration of surfactants exceeds their critical micelle concentration (CMC), which is typically in the range of 0.05–0.10%. This process, called micellization, often makes poorly soluble drugs more soluble.[3]

3) Complexation

Drugs have been complexed with cyclodextrins to improve medication stability and water solubility. The complex is the result of the interaction of two or more molecules that form an entity apart from a specific balancing. [7] London forces, hydrogen bonds, and hydrophobic interactions are examples of relatively weak forces that are necessary for this. More specifically than any other solubility enhancement strategy, inclusion complex formation has been used to increase the aqueous solubility, dissolution rate, and bioavailability of medicines that are poorly soluble in water. Inclusion complexes are created when a non-polar molecule or a non-polar portion of a molecule (referred to as the guest) inserts itself into the cavity of a different molecule or collection of molecules (referred to as the host). Cyclodextrin is the most often utilized host molecule. [2,6]

4) Cryogenic Techniques

By producing highly porous, nanostructured, amorphous drug particles at extremely low temperatures, cryogenic procedures have been developed to increase the rate at which pharmaceuticals dissolve. The classification of cryogenic innovations can be based on the kind of injection device (rotary, pneumatic, capillary, and ultrasonic nozzles), the placement of the nozzle (above or below the liquid level), and the cryogenic liquid composition (organic solvents, N2, Ar, O2, and hydrofluoroalkanes). Dry powder can be created via lyophilization, vacuum freeze drying, spray freeze drying, and atmospheric and atmospheric freeze drying, among other drying techniques, after cryogenic processing.

a) Spray freezing onto cryogenic fluids: It was created by Briggs and Maxvell.Using this method, a boiling, agitated fluorocarbo refrigerant was exposed to a mixture of the medication and the carrier (mannitol, maltose, lactose, inositol, or dextran) that had been

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dissolved in water. The aqueous solution's dispersion can be improved by submerging a sonication probe in the agitated refrigerant.

b) Spray Freezing to Cryogenic Liquids (SFL): Drug powder aggregates with a large surface area and good wettability have been created using the SFL particle engineering method. These aggregates are amorphous nanostructured. In order to achieve strong atomization into microdroplets and thus much quicker freezing rates, it integrates direct liquid-liquid impingement between the cryogenic liquid and the automated feed solution. The lyophilization of the frozen particles yields dry, freely-flowing micronized powders.

c) (SFV/L) Spray Freezing into Vapor over Liquid: It is possible to generate tiny drug particles with good wettability by freezing drug solutions in cryogenic fluid vapours and then removing the frozen solvent. Prior to coming into contact with the cryogenic liquid during SFV/L, the atomized droplets usually begin to freeze in the vapor phase. Drug nucleation and growth may occur in the atomized droplet due to the drug's supersaturation in the unfrozen areas caused by the solvent freezing.

d) Ultra-Rapid Freezing: Ultra-rapid freezing is a new cryogenic technique that uses solid cryogenic materials to produce nanostructured drug particles with a significantly increased surface area and desired surface topology. Drug solutions applied to cryogenic substrates' solid surfaces instantly freeze, and when the solvent is removed by lyophilization, the result is finely powdered, more soluble drug particles. The pharmaceutical components become closely mixed, amorphous drug-carrier solid dispersions, and solid solutions when ultra-fast freezing prevents phase separation and crystallization.[7]

B. CHEMICAL METHODS

1) Pro-Drug Approach

Prodrugs are synthetic derivatives of drug molecules, such as amides and esters, that may have intrinsic pharmacological activity but typically require some sort of in-vivo transformation to release the active drug molecule. Salt information is restricted to molecules with ionisable groups, but prodrugs can be formed with any organic molecule having a chemically reactive functional group. Several side chains or functional groups can be added to a molecule to enhance its biological or pharmacological capabilities through the development of a pro drug . Amidon proposed in 1980 that the enzymes found in the intestinal brush border would use certain amino acids as substrates to generate water soluble pro-drugs. A possible increase in absorption rate was discovered in vivo utilizing perfused rat intestines and the lysine ester prodrug of estrone.[6]

2) Co-Solvency

Drugs that are not very soluble in water can become more soluble by being combined with a water-miscible solvent that the drug dissolves well in. Cosolvency is the term for this procedure, and cosolvent refers to the combined solvent employed in it. The way the co-solvent system functions is by lowering the tension at the interface between the hydrophobic solute and the aqueous solution. Solvent blending is another name for it that is frequently used. When an organic co-solvent is added to water, the solubility of the medicines is drastically altered. The cosolvents possess donor or acceptor groups of hydrogen that have a tiny hydrocarbon region. Hydrophilic hydrogen bonds guarantee water solubility, but

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hydrophobic hydrocarbon regions typically disrupt the hydrogen bonding network of water, reducing the intermolecular attraction of water.[8]

The drug's water solubility sharply drops as the structural complexity of newly created entities increases. A mixture of solvents is used to achieve high solubility when a compound's water solubility is significantly lower than its therapeutic dosage. By offering many nonpolar groups, co-solvents are utilized to increase a drug's solubility in water, or aqueous solution. Co-solvents are essential for pharmaceutical formulations, since they may be needed to improve the solubility of the medication.[2]

3) pH Adjustment

This is essential to the solubility of drugs. It may affect the medications' water solubility by adjusting the pH of the solution so that a specific molecule has no net electric charge. The charge state of the drug molecules can be changed by changing the pH of the solution. If the solute often exhibits low solubility and separates from the solution. The isoelectric point, commonly known as IEP, is the pH at which a certain molecule bears no net electric charge and the net charge is neutral. [2]

If the pH of the medicine is changed, a poor water soluble drug may dissolve in water. It is crucial to take into account the buffer capacity and the tolerance of the chosen pH in order to determine the solubility of this technique. Drug solubility is increased by soluble excipients that raise the pH of the surrounding environment inside the dosage form to a range higher than the pKa of weakly acidic pharmaceuticals; excipients that function as alkalizing agents may also improve the solubility of weakly basic drugs.[8]

4) Hydrotropy

A solubility process known as hydrotrophy occurs when a substantial amount of a second solute is added, increasing the solute's aqueous solubility. Many weakly water-soluble medications have been shown to become more soluble in water when they are dissolved in concentrated aqueous hydrotropic solutions including sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate.[8]

This solubility sensation allows the excess addition of a second solute to increase the solute's water solubility. In previous investigations, the word "hydrotrophy" was used to characterize organic compounds that are either solid or liquid and do not form micelles, or that are effective at increasing the solubility of insoluble molecules.[2]

5) Salt Formation

As compared to the original drug, salts offer better solubility and dissolving properties. The pKa difference of the group and its counter ions must differ by at least three units in order for stable salt to develop. Penicillin's alkali metal salt and atropine's strong acid salt are both more stable than their parent drugs .[6]

Drugs that are basic or acidic are less soluble in water than their salts. The most preferred approach for the advancement of parenteral administration is solubility augmentation by salt production. [2]

C. BIOTECHNOLOGICAL METHODS

1) Nanosuspension

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A colloidal dispersion of submicron drug components stabilized by a surfactant is a well-defined definition of nanosuspension. Wet milling and homogenization are utilized to create a nanosuspension. In the presence of a surfactant, milling breaks down the active component.

Benefits of nanosuspension:

- Enhanced drug solubility and bioavailability
- Increased drug loading
- Suitable for hydrophobic pharmaceuticals
- Passive drug targeting
- Dosage reduction
- Enhanced physical and chemical stability of the drug

Poorly soluble medications that are insoluble in both water and oils are treated using this method. Pharmaceutical nanosuspensions are biphasic systems for parenteral and pulmonary delivery or oral and topical usage that are composed of nanoscale drug particles stabilized by surfactants. There are several techniques used to create nanosuspensions, such as the precipitation technique, media milling, high-pressure homogenization in non-aqueous medium, high-pressure homogenization in water, and the combination of precipitation and high-pressure homogenization.

a) Precipitation Technique: To precipitate the crystals, a drug is dissolved in a solvent and then added to an anti-solvent mixture. Precipitation approach has the fundamental benefit of using inexpensive, simple equipment; nevertheless, adding increasing drug crystals to prevent microparticle development is a difficulty. The drug must be soluble in at least one solvent and miscible with an antisolvent in order for this precipitation procedure to work. Furthermore, as drugs are insoluble in both aqueous and nonaqueous fluids, the precipitation approach is inapplicable to them. media grinding. For two to seven days, the milling chamber filled with water, drug, stabiliser, and milling medium is spun at a very high shear rate in a temperature-controlled environment.

b) High Pressure Homogenization: In this technique, a high-pressure homogenizer's nanosized aperture valve is pressed to let the suspension of a medication and surfactant through under pressure.This method's basic idea is based on aqueous phase cavitation. The cavitation forces present in the particles are significant enough to cause the drug microparticles to transform into nanoparticles.

c)Combined Precipitation and Homogenization: The drug nanoparticles that precipitate have a propensity to continue growing into microcrystals. They need homogenization, or the application of high-energy forces. The precipitated particle suspension is then homogenized to maintain the particle size that was achieved following the precipitation step because they are in entirely crystalline, partially crystalline, or entirely amorphous forms, which cause issues with long-term stability and bioavailability. [2,7]

2) Microemulsion

A weakly water-soluble medication is dissolved in an optically clear pre-concentrate by combining a hydrophilic surfactant with a hydrophilic solvent. It is necessary for the surfactant to be non-toxic and compatible with HLB. It results in a translucent emulsion of uniformly sized, little oil droplets that contain the solubilized, poorly soluble medication. The use of microemulsions has increased the solubility of several medications that are totally

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insoluble in water. The optimal formulation is an oil-in-water microemulsion, which allows molecules with poor water solubility to dissolve into the oil phase, increasing solubility. Changes in permeability brought on by surfactants have the potential to increase oral bioavailability. Benefits of Microemulsions: ease of preparation, transparency, filterability, and capacity to include a large variety of medications with different solubilities.[8]

3) Microemulsion and self-emulsifying system

A microemulsion is a pre-concentrate that is optically transparent and is made up of a hydrophilic solvent, oil, and hydrophilic surfactant combination that dissolves drugs that are not very water soluble. When the formulations come into contact with water, they "self emulsify," or spontaneously disperse, to create a highly clear emulsion of uniformly sized, minuscule oil droplets that contain the weakly soluble medication that has been solubilized. Microemulsions are transparent (or translucent), isotropic, thermodynamically stable systems of water, oil, and surfactant. Often, a co-surfactant is added, with droplet sizes typically falling between 20 and 200 nm. These uniform solutions are all low viscosity fluids that may be made across a broad variety of surfactant concentrations and oil to water ratios. A system of microemulsions that is anhydrous is known as a self-microemulsifying drug delivery system (SMEDDS). Some researchers have also called it microemulsion pre-concentrate. It is made up of oil, cosurfactant, and surfactant. When mixed with water and gently stirred, it may generate an o/w microemulsion. Stomach and intestine movements produce the agitation needed for the process of self-emulsification. The theory of insitu emulsion creation in the gastrointestinal tract is applied by self-emulsifying or self-micro emulsifying devices. The oil, cosolvent, surfactant, co-surfactant, and one or more hydrophilic solvents combine to create the self-emulsifying drug delivery system (SEDDS), a clear, isotropic solution. Self-emulsifying drug delivery systems (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) are isotropic solutions of surfactant and oil that, when gently agitated in the presence of water, generate oil-in-water microemulsions. It has been demonstrated that the SEDDS and SMEDDS increase the physical stability profile during long-term storage when compared to ready-to-use microemulsions. [8]

4) Solid-Lipid Nanoparticles

Drug delivery uses solid-lipid nanoparticles for targeted and coordinated distribution. Their typical particle size is between 50 and 1000 nm, and they are both biocompatible and biodegradable. They consist of a hydrophobic phospholipid covering that is solid. This coating is made up of an aqueous surfactant solution or water dissolved into a lipid matrix that must be solid and at room temperature. The drug-containing solid cores are distributed throughout the lipid matrix. They are probably going to carry both hydrophilic and hydrophobic drugs.[2]

CONCLUSION

The solubility improvement technique of poorly water-soluble drugs plays a vital part in the formulation development to fulfil the therapeutic action and drug bioavailability of the pharmaceutically active ingredient (drug) at the target site. Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. Selection of method for solubility

enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behaviour and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth. By using newer techniques which are discussed above it is possible to improve solubility of poorly water-soluble drugs.

REFERENCES

1) B. K. Abdul Rasool and A. Shahiwala, *Novel Drug Delivery Technologies*, DOI: 10.1007/978-981-13-3642-3.
2) V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. Singh Chandel, Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics, *Biomedicines* **2022**, *10*, 2055.
3) L. Samal, L. Biswal, and A. Kar, Solubility: A Complete and Detailed Review, *Int. J. Dev. Res.* **2019**, *9*(9), 30079-30090.
4) 4)M. G. Bajait, R. Ghatmale, and B. Mundhe, Importance of Solubility and Solubility Enhancement Techniques, *J. Med. Pharm. Allied Sci.* **2019**, *8*(6), 2403-2416.
5) K. T. Savjani, A. K. Gajjar, and J. K. Savjani, Drug Solubility: Importance and Enhancement Techniques, *ISRN Pharmaceutics* **2012**, Article ID 195727.
6) Kumar, A. M. S.; Rajesh, M.; Subramanian, L. Solubility Enhancement Techniques: A Comprehensive Review. *World J. Biol. Pharm. Health Sci.* **2023**, *13*(03), 141-149.
7) A. S. Deshmukh, K. J. Tiwari, and V. R. Mahajan, Solubility Enhancement Techniques for Poorly Water-Soluble Drugs, *Int. J. Pharm. Sci. Nanotechnol.* **2017**, *10*, May-June.
8) S. V. Kadam, D. M. Shinkar, and R. B. Saudagar, Review on Solubility Enhancement Techniques, *Int. J. Pharm. Biol. Sci.* **2013**, *3*(3), 462-475.
9) Deshmukh, A. S. Recent Advances in Self-Emulsifying Drug Delivery System. *Int. J. Pharm. Sci. Nanotechnol.* **2015**, *8*(1), 1-5.
10) Deshmukh, A. S.; Mahajan, V. R. Advanced Delivery of Poorly Water-Soluble Drugs by Lipid-Based Formulation as SMEDDS. *Asian J. Res. Biol. Pharm. Sci.* **2015**, *3*(1), 14-24.
11) Mandawgade, S. D.; Sharma, S.; Pathak, S.; Patravale, V. B. Development of SMEDDS Using Natural Lipophile: Application to Artemether Delivery. *Int. J. Pharm.* **2008**, *362*, 179-183.
12) 12)Chowdary, K. P. R.; Madhavi, B. L. R. Novel Drug Delivery Technologies for Insoluble Drugs. *Indian Drugs* **2005**, *42*(9), 557-564.
13) Patravale, V. B.; Date, A. A.; Kulkarni, R. M. Nanosuspensions: A Promising Drug Delivery Strategy. *J. Pharm. Pharmacol.* **2004**, *56*(7), 827-840.
14) Keck, C. M.; Muller, R. H. Drug Nanocrystals of Poorly Soluble Drugs Produced by High Pressure Homogenisation. *Eur. J. Pharm. Biopharm.* **2006**, *62*(1), 3-16.
15) Muller, R. H.; Bohm, B. H. L.; Grau, J. Nanosuspensions: A Formulation Approach for Poorly Soluble and Poorly Bioavailable Drugs. In *Handbook of Pharmaceutical Controlled Release Technology*; Wise, D., Ed.; Marcel Dekker: New York, NY, 2000; pp 345-357.
16) Leuenberger, H. Spray Freeze-Drying: The Process of Choice for Low Water Soluble Drugs? *J. Nanoparticle Res.* **2002**, *4*(1-2), 111-119.
17) Mumenthaler, M.; Leuenberger, H. Atmospheric Spray Freeze Drying: A Suitable Alternative in Freeze-Drying Technology. *Int. J. Pharm.* **1991**, *72*(2), 97-110.
18) Williams, R. Q. Process for Production of Nanoparticles and Microparticles by Spray Freezing into Liquid. US Patent 20030041602, 2003.

19) Briggs, A. R.; Maxvell, T. J. Process for Preparing Powder Blends. US Patent 3721725, 1973.
20) Rogers, T. L.; Hu, J.; Yu, Z.; Johnston, K. P.; Williams, R. O. A Novel Particle Engineering Technology: Spray-Freezing into Liquid. *Int. J. Pharm.* **2002**, *242*(1-2), 93-100.
21) Buxton, R.; Peach, J. M. Process and Apparatus for Freezing a Liquid Medium. US Patent 4470202, 1984.
22) Cyclodextrins in Pharmaceuticals: An Overview. Available from: http://www.pharmainfo.net/pharma-student-magazine/cyclodextrins-pharmaceuticals-overview-0.
23) Purvis, T.; Mattucci, M. E.; Crisp, M. T.; Johnston, K. P.; Williams, R. O. Rapidly Dissolving Repaglinide Powders Produced by the Ultra-Rapid Freezing Process. *AAPS PharmSciTech* **2007**, *8*(3), Article 58.
24) Williams, H. D.; Trevaskis, N. L.; Charman, S. A.; Shanker, R. M.; Charman, W. N.; Pouton, C. W.; Porter, C. J. Strategies to Address Low Drug Solubility in Discovery and Development. *Pharmacol. Rev.* **2013**, *65*, 315-499.
25) Nidhi, K.; Indrajeet, S.; Khushboo, M.; Gauri, K.; Sen, D. D. J. Hydrotropy: A Promising Tool for Solubility Enhancement: A Review. *Int. J. Drug Dev. Res.* **2011**, *3*, 26-33.
26) Martin, A.; Bustamanate, P.; Chun, A. H. C. *Physical Pharmacy*; BI Wavely Pvt. Ltd.: New Delhi, India, 1994; Vol. 4, p 223.
27) Gennaro, A. R. *Remington's Pharmaceutical Sciences*, 17th ed.; Mack Publishing Co.: Easton, PA, USA, 1985.
28) Krishnaiah, Y. S. Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs. *J. Bioequiv. Availab.* **2010**, *2*, 28-36.
29) Blagden, N.; de Matas, M.; Gavan, P. T.; York, P. Crystal Engineering of Active Pharmaceutical Ingredients to Improve Solubility and Dissolution Rates. *Adv. Drug Deliv. Rev.* **2007**, *59*, 617-630.
30) Sharma, D.; Soni, M.; Kumar, S.; Gupta, G. Solubility Enhancement—Eminent Role in Poorly Soluble Drugs. *Res. J. Pharm. Technol.* **2009**, *2*, 220-224.
31) Kumar, A.; Sahoo, S. K.; Padhee, K.; Kochar, P. S.; Sathapathy, A.; Pathak, N. Review on Solubility Enhancement Techniques for Hydrophobic Drugs. *Pharm. Glob.* **2011**, *3*, 1-7.
32) McMorland, G. H.; Douglas, M. J.; Jeffery, W. K.; Ross, P. L.; Axelson, J. E.; Kim, J. H.; Gambling, D. R.; Robertson, K. Effect of pH-Adjustment of Bupivacaine on Onset and Duration of Epidural Analgesia in Parturients. *Can. Anaesth. Soc. J.* **1986**, *33*, 537-541.
33) Paroha, S.; Chandel, A. K. S.; Dubey, R. D. Nanosystems for Drug Delivery of Coenzyme Q10. *Environ. Chem. Lett.* **2018**, *16*, 71-77.
34) Millard, J.; Alvarez-Núñez, F.; Yalkowsky, S. Solubilization by Cosolvents: Establishing Useful Constants for the Log-Linear Model. *Int. J. Pharm.* **2002**, *245*, 153-166.
35) Rasool, A. A.; Hussain, A. A.; Dittert, L. W. Solubility Enhancement of Some Water-Insoluble Drugs in the Presence of Nicotinamide and Related Compounds. *J. Pharm. Sci.* **1991**, *80*, 387-393.
36) Reddy, A.; Parthiban, S.; Vikneswari, A.; Senthilkumar, G. A Modern Review on Solid Lipid Nanoparticles as Novel Controlled Drug Delivery System. *Int. J. Res. Pharm. Nano Sci.* **2014**, *3*, 313-325.
37) Severino, P.; Pinho, S. C.; Souto, E. B.; Santana, M. H. Polymorphism, Crystallinity and Hydrophilic–Lipophilic Balance of Stearic Acid and Stearic Acid–Capric/Caprylic Triglyceride Matrices for Production of Stable Nanoparticles. *Colloids Surf. B Biointerfaces* **2011**, *86*, 125-130.

38) Garud, A.; Singh, D.; Garud, N. Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications. *Int. Curr. Pharm. J.* **2012**, *1*, 384-393.
39) Ekambaram, P.; Abdul Hasan Sathali, A.; Priyanka, K. Solid Lipid Nanoparticles: A Review. *Sci. Rev. Chem. Commun.* **2012**, *2*, 80-102.
40) Westesen, K.; Bunjes, H.; Koch, M. H. J. Physicochemical Characterization of Lipid Nanoparticles and Evaluation of Their Drug Loading Capacity and Sustained Release Potential. *J. Control. Release* **1997**, *48*, 223-236.
41) Westesen, K.; Siekmann, B.; Koch, M. H. J. Investigations on the Physical State of Lipid Nanoparticles by Synchrotron Radiation X-ray Diffraction. *Int. J. Pharm.* **1993**, *93*, 189-199.
42) Mukherjee, S.; Ray, S.; Thakur, R. S. Solid Lipid Nanoparticles: A Modern Formulation Approach in Drug Delivery System. *Indian J. Pharm. Sci.* **2009**, *71*, 349-358.
43) Kalepu, S.; Nekkanti, V. Insoluble Drug Delivery Strategies: Review of Recent Advances and Business Prospects. *Acta Pharm. Sin. B* **2015**, *5*, 442-453.
44) Savjani, K. T.; Gajjar, A. K.; Savjani, J. K. Drug Solubility: Importance and Enhancement Techniques. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3399483/.
45) Vemula, V. R.; Lagishetty, V.; Lingala, S. Solubility Enhancement Techniques. *Int. J. Pharm. Sci. Rev. Res.* **2010**, *5*(1), 41-51.
46) Zavala, J. F.; Sanhenz, L.; Parrila, E. A.; Aguilar, G. A. High Relative Humidity in Package of Fresh Cut Fruits and Vegetables: Advantages or Disadvantages Considering Microbiological Problems and Antimicrobial Delivery Systems. *Institute of Food and Technologies* **2007**, *73*(4), R.41-R-47.
47) Raut, N. A. Enhancement of Aqueous Solubility and Permeability of Poorly Water Soluble Drug. *Pharma Focus Asia* **2018**, *Issue No. 29*, 94-100.
48) Lachman, L.; Liberman, H. A.; Khar, R. K.; Vyas, S. P.; Ahamad, F. J.; Jain, G. K. *The Theory and Practice of Industrial Pharmacy*, 4th ed.; CBS Publishers: 2013; pp 222-236.
49) Fateh, A. L.; Rahman Magbool; Elamin Ibrahim Elnima; Shayoub, M. E.; Salah Eldin Omar Hussein. *EJPMR* **2017**, *5*(02), 94-100.
50) Reddy, R.; Kumar, P.; Sreenivasulu, K.; Srikanth, P. V. S.; Brahmaiah, B.; Sreekanth, N. A Review on Hydrotropy. *2013*, *2*(4), 5-6.
51) Rasool, A. A.; Hussain, A. A.; Dittert, L. W. Solubility Enhancement of Some Water-Insoluble Drugs in the Presence of Nicotinamide and Related Compounds. *J. Pharm. Sci.* **1991**, *80*, 387-393.
52) Badwan, A.; El Khordagui, L. K.; Saleh, A. M.; Khalil, S. A. The Solubility of Benzodiazepines in Sodium Salicylate Solution and a Proposed Mechanism for Hydrotropic Solubilisation. *Int. J. Pharm.* **1983**, *13*, 67-74.
53) Roy, K.; Moulik, S. P. Functions of Hydrotropes (Sodium Salicylate, Proline, Pyrogallol, Resorcinol and Urea) in Solution with Special Reference to Amphiphile Behaviours. *Colloids Surf.* **2002**, *203*, 155-166.
54) Patil, M. S.; Godse, S. Z.; Saudagar, R. B. Solubility Enhancement by Various Techniques: An Overview. *World J. Pharm. Pharm. Sci.* **2013**, *2*(6), 4558-4572.
55) Babu, P. R. S.; Subrahmanyam, C. V. S.; Thimmasetty, J.; Manavalan, R.; Valliappan, K.; Kedarnath, S. Solubility Enhancement of Cox-II Inhibitors by Co-solvency Approach. *Dhaka Univ. J. Pharm. Sci.* **2008**, *7*(2), 119-126.
56) Prasad, B. S. G.; Gupta, V. R. M.; Devanna, N.; Rama, D. M.; Rao, G. V. V.; Harish, N. Mixed Co-Solvency Concept: A Promising Tool to Enhance Solubility of Poorly Soluble Drug Aceclofenac. *Int. J. Pharm. Chem. Biol. Sci.* **2012**, *2*(3), 338-342.

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57) Nayak, A. K.; Panigrahi, P. P. Solubility Enhancement of Etoricoxib by Cosolvency Approach. *ISRN Phys. Chem.* **2012**, Article ID 820653, 1-5.
58) Dhapte, V.; Mehta, P. Advances in Hydrotropic Solutions: An Updated Review. *St. Petersburg Polytechnical University J. Phys. Math.* **2015**, *1*, 424-435.
59) Kapadiya, N.; Singhvi, I.; Mehta, K.; Karwani, G.; Dhrubo, J. Hydrotropy: A Promising Tool for Solubility Enhancement: A Review. *Int. J. Drug Dev. Res.* **2011**, *3*(2), 26-33.
60) Pentewar, R. S.; Utikar, M.; Gaikwad, S. S.; Thonte, S. S.; Bhange, M.; Sugave, R. V. A Review on Extraction of Herbal Drugs and the Enhancement of Solubility by Hydrotropy Technique. *World J. Pharm. Res.* **2015**, *4*(9), 614-623.
61) Wu, C. Y.; Benet, L. S. 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.
62) Chaudhari, A.; Nagachi, U.; Gulati, N.; Sharma, V. K.; Khosa, R. K. Enhancement of Solubilisation and Bioavailability of Poorly Soluble Drugs by Physical and Chemical Modification: A Recent Review. *J. Adv. Pharm. Educ. Res.* **2012**, *2*(1), 32-67.
63) Blagden, N.; de Matas, M.; Gavan, P. T.; York, P. Crystal Engineering of Active Pharmaceutical Ingredients to Improve Solubility and Dissolution Rates. *Adv. Drug Deliv. Rev.* **2007**, *59*(7), 617-630.