EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 2
138-146
Year: 2023

SOLUBILITY ENHANCEMENT TECHNIQUES - AN OVERVIEW

Kanukolanu Aarika*, P. M. M. Naga Lakshmi Varma[1], D. Ooha, J. Kalyani, N. Dharani, Dr. K. Padmalatha[2]

[1]Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada-521108, NTR (Dt), Andhra Pradesh, India.
[2]Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada-521108, NTR (Dt), Andhra Pradesh, India.

***Corresponding Author: Kanukolanu Aarika**
Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada-521108, NTR (Dt), Andhra Pradesh, India.

Article Received on 08/12/2022 **Article Revised on 28/12/2022** **Article Accepted on 18/01/2023**

ABSTRACT
A solid dissolving into a liquid to produce an even molecular dispersion is a phenomenon known as solubility. Nevertheless, the majority of the active medicinal compounds employed are hydrophobic (Poor aqueous soluble). The effectiveness of a medicine is impacted by solubility. As all medications that are absorbed by the body must be in the form of a solution in order to be effective, drug solubility plays a significant role in deciding the concentration of a drug to produce the desired pharmacological response. A common problem that impacts a medicine's bioavailability in the body is drug solubility. Low solubility medications have poor bioavailability because they absorb poorly. For improving a drug's solubility, numerous techniques have been created. Solubility and property development are the most difficult components of formulation development. Poorly water soluble medications are unable to reach their full potential and therapeutic spectrum; as a result, they do not create a finished product. The drug's aqueous solubility altered both its chemical and physical properties. In the formulation of medications, solubility is the most significant idea that shows up as a helpful contribution. To increase the solubility and bioavailability of pharmaceuticals, a variety of procedures and strategies, including physical and chemical alterations, are employed.

KEYWORDS: Homogenous, Hydrophobic, Concentration, Aqueous, Formulation, Bioavailability.

INTRODUCTION
Solubility is the property of a chemical compound, referred to as a solute, to dissolve in a solid, liquid, or gaseous solvent and produce a homogenous solution of the solute in the solvent. Fundamentally, a chemical's solubility is influenced by the solvent used, together with temperature and pressure.

The maximum amount of a drug's solute that can be dissolved in a solvent under a given set of temperature, pH, and pressure conditions is known as the drug's solubility. Drug dissolving rate is a dynamic feature that is more closely related to bioavailability rate than drug solubility in saturated solution, which is a static attribute. Depending on how much of the drug dissolves in the solvent, different descriptive phrases are used to characterize a drug's solubility.[1]

Solubility happens in dynamic equilibrium, which means that it is the outcome of the opposing and concurrent processes of phase joining (such as the precipitation of solids) and dissolution. When the two processes develop an equilibrium in solubility, they do so at a consistent pace.

Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable, can be produced when equilibrium solubility is exceeded under specific circumstances.[2]

Since these processes can happen due to both dissolving and chemical reactions, solubility should not be mistaken with the ability to dissolve or liquefy a substance. For instance, while zinc is insoluble in hydrochloric acid, it does dissolve in it when it chemically reacts with hydrogen to form zinc chloride, which is soluble in the acid. Particle size or other kinetic parameters are not necessary for solubility; given enough time, even massive particles will dissolve.[3]

Table 1: Solubility requirements for USP and BP.

Descriptive	Needed portion of solvent for every component of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 10 to 30
Sparingly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

NEED OF SOLUBILITY

Solubility is one crucial factor in achieving the desired drug concentration in the systemic circulation and achieving the desired pharmacological response is solubility.

The poor bioavailability of oral dose forms, however, presents the biggest design problem. Aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms are some of the variables that affect oral bioavailability. Poor solubility and inadequate permeability are the most common causes of low oral bioavailability.

Other dosage forms, such as parenteral formulations, also heavily rely on solubility. One of the key factors in reaching the desired drug concentration in the systemic circulation and the necessary pharmacological response is solubility. When taken orally, poorly water soluble medications may need high dosages to attain therapeutic plasma concentrations. The main issue in developing formulations for new chemical entities as well as generics is low water solubility.

Any medicine that is to be absorbed must be present at the absorption site in the form of an aqueous solution. The preferred solvent for liquid medicinal compositions is water.[4]

A medicinal substance is categorized using the BCS according to its water solubility and intestinal permeability. As opposed to absorption, the rate-limiting phase for BCS class II & IV medications is drug release from the dosage form and solubility in stomach fluid; therefore, increasing solubility also increases bioavailability.[5]

Table 2: Biopharmaceutical Classification System.

CLASS	SOLUBILITY& PERMEABILITY
Class I	High Solubility High Permeability
Class II	Low Solubility High Permeability
Class III	High Solubility Low Permeability
Class IV	Low Solubility Low Permeability

FACTORS AFFECTING THE SOLUBILITY

1. Solute and solvent characteristics

The concentration of the solute in a given amount of solvent at a certain temperature determines the nature of the solute and solvent. As an illustration, 200 grams of zinc chloride may dissolve in 100 grams of water at normal temperature.[5]

2. Temperature

Temperature affects solubility. The solubility will rise with rising temperature if the solution process takes in

energy. The solubility will decrease with rising temperature if the solution process releases energy.[6]

3. Particle size

Effect of particle size on solubility. The surface area to volume ratio rises as particle size decreases. Increased particle surface area results in increased solvent interaction.[7]

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

S-which refers to how easily infinitely big particles can dissolve.
S- stands for a particle's solubility in water.
V-is the molar volume.
G-is the soil surface tension.
R-is the fine particle's radius.

4. Pressure

Although the solubility of solid and liquid solutes is unaffected by pressure changes, the solubility of gaseous solutes increases with increasing pressure and decreases with decreasing pressure.

5. Molecular size

The particle's molecular size has an impact on solubility. Higher molecular weight and larger molecules reduce a substance's solubility since it is more challenging to surround larger molecules with solvent molecules in order to dissolve them.

VARIOUS TECHNIQUES FOR SOLUBILITY ENHANCEMENT TECHNIQUES

To address the problem posed by insoluble substances, numerous technologies have developed, and these technologies have also changed.

Various techniques that are used to overcome the poor drug solubility are discussed under following.[8,9]:

I. CHEMICAL MODIFICATION

1. pH adjustment
2. Salt formation
3. Co-crystallization
4. Co-solvency
5. Solubilizing agents
6. Nanotechnology

II. PHYSICAL MODIFICATIONS

1. Particle size reduction
a. Micronization
b. Nanosuspension

2. Modification of the crystal habit
a. Polymorphs
b. Pseudo polymorphs

3. Complexation
a. Use of complexing agents

4. Solubilization by surfactants
a. Microemulsions
b. Self-micro emulsifying drug delivery system

5. Drug dispersion in carriers.
a. Solid solution
b. Solid dispersion

1. CHEMICAL MODIFICATION

1. pH Adjustment

Drugs that are poorly soluble in water but include molecular components that may be protonated (base) or deprotonated (acid) may be dissolved in water by changing the ph. In theory, both oral and parenteral administration of medications can benefit from pH correction.[10-13]

Advantage

Quick and easy to create, easy to analyses, and only requires minimal amounts of substance.

Disadvantages

Use of a non-physiological pH and extreme pH: Tolerability and toxicity (local and systemic).

2. Salt Formation

It is the most popular and efficient way to speed up how quickly acidic and basic medications dissolve and become soluble in the body. Acidic or basic medications that have been converted to salt have more solubility than the respective medications, such as aspirin, theophylline, and barbiturates.[14]

3. Co-Crystallization

Additionally known as molecular complexes. Co-crystal is the term used when the solvent is a fundamental component of the network structure and creates at least a two component crystal. A co-crystal is a crystalline substance held together by non-covalent forces that comprises of two or more molecular (and electrically neutral) species. Only three of the co-crystallizing agents have been identified as safe and are classified. It contains saccharin, nicotinamide, and acetic acid, which restricts its use in pharmaceuticals.[15]

4. Co-Solvency

Cosolvents are water miscible solvents that can be added to a solution of a medicine that is weakly water soluble to boost the solubility of the drug. Cosolvents are mixes of water and/or more water soluble solvents that are used to make solutions with improved solubility for poorly soluble substances, such as ethanol, PEG 300, or propylene glycol.[16] Due to their high solubilization ability for insoluble medicines and comparatively low toxicity, dimethyl sulfoxide (DMS) and dimethyl acetoamide (DMA) are frequently utilized as cosolvents.[17-19]

Advantage
Easy to formulate and quickly generate.

Disadvantages
The toxicity and tolerability associated with the amount of solvent provided must be taken into account, just like with all excipients.

5. Solubilizing Agents
By using other solubilizing substances, such as PEG 400, the solubility of drugs with low solubility can also be increased. The term "nanotechnology" broadly refers to the study of and application to materials and structures at the nanoscale, generally 100 nanometers (nm) or smaller 35. The technique of "nanonization" involves turning the medication powder into nanocrystals, such as those measuring 200–600 nm in size. Amphotericin B.[20-21] Currently, the fundamental techniques used to create nanoparticles are

- Homogenization in water; grinding (wet milling as in a colloid mill).
- Homogenization in aqueous or non-aqueous media using water-soluble solutions.
- The precipitation

II. PHYSICAL MODIFICATION
1. Size Reduction
The solubility of a solid depends on its size since a smaller particle has a higher surface area to volume ratio. Following equation of how particle size affects solubility.[22]

Log S/ S0 = 2γ V/ 2.303 RTr

S - solubility of essentially infinitely massive particle
So - is the five-particle solubility
V- Molar Volume
g - is the solid's surface tension
r - is the solid's surface tension

a) Micronisation
The solubility of a medicine in micronization is frequently inherently linked to drug particle size.

Decreasing the particle size, the increased surface area enhances the drug's ability to dissolve. Micronization is accomplished through the use of milling processes such as jet milling, rotor milling, stator milling, colloid milling, etc. Micronization is not recommended for medications with high dosage numbers because it does not alter the drug's saturation solubility.[23]

b) Nanosuspension
Is another method to reduce particle size, and it has been used to make drugs including buparvaquone, atovaquone, paclitaxel, tarazepide, and amphotericin-B. Wet milling and homogenization is used to create nanosuspensions.

2. Modification of Crystal Habit
a) Polymorphs
A solid can be either crystalline or amorphous, depending on its interior structure. The various forms are referred to as polymorphs and the phenomenon as polymorphism when a substance occurs in more than one crystalline form.

There are two sorts of polymorphs
Enantiotropic
• An enantiotropic substance, such as Sulphur, is one that can change reversibly into a different form by changing the temperature and pressure.

Monotropic
A monotropic substance is one that is unstable at all pressures and temperatures, such as glyceryl stearates The physical characteristics of the polymorphs, such as their solubility, melting point, density, hardness, and compression characteristics, set them apart from one another. Additionally, polymorphs might be stable or metastable. In comparison to stable polymorphs, metastable polymorphs have greater energy states, lower melting temperatures, and better aqueous solubilities, making them more favored in formulation.

The energy required to move a molecule from the crystal lattice is more than that necessary for a nanocrystalline solid, hence the amorphous forms have better aqueous solubility than the crystalline forms. For example, amorphous novobiocin is 10 times more soluble than crystalline.

b) Pseudo polymorphs
Solvates and trapped solvent are the names for the stoichiometric form of adducts in which the solvent molecules are incorporated into the solid's crystal lattice. The phenomenon known as pseudo polymorphism is the existence of the solvates in many crystalline forms known as pseudo polymorphs.[24]

When water serves as the drug's solvent, the substance is referred to as a solvate or hydrate. Theophylline and ampicillin have higher aqueous solubilities in their anhydrous forms than in their monohydrate and trihydrate concentrates, respectively, since anhydrous forms need less energy to dissolve in water than hydrates do. However, compared to non-organic solvates, organic solvates have a higher aqueous solubility.[25]

3. Complexation
The joining of two or more molecules to create a non-bonded entity with a well-defined stoichiometry is known as complexation. It is supported by relatively weak forces such hydrogen bonds, London forces, and hydrophobic interactions.

List of complexing agents

TYPES	EXAMPLES
Inorganic	IB
Coordination	Hexamine cobalt(III) chloride
Chelates	EDTA, EGTA
Metal-olefin	Ferrocene
Inclusion	Cyclodextrins, choleic acid
Molecular complexes	Polymers

- **Stacking Complexation**

Complexations known as "stacking" are created when the planar areas of aromatic molecules cross each other. The strong hydrogen bonding interactions of water have the tendency to suck non-polar moieties out of it. Because of this, certain molecules aggregate their hydrocarbon moieties to reduce their interaction with water.[26]

- **Inclusion Complexation**

By inserting a non-polar molecule or non-polar portion of a molecule (referred to as a guest) into the cavity of another molecule or collection of molecules, inclusion complexes are created (known as host). The host's cavity must be both big enough to fit the visitor and small enough to drain the water. Cyclodextrins are the most popular host molecules. By simply mixing the drug and the excipient, lipophilic drug-cyclodextrin complexes, often referred to as inclusion complexes, can be created, improving drug solubilization.[27]

4. Solubilization by surfactants

Surfactants are excellent absorption boosters because they speed up medication permeability and disintegration. By encouraging wetting and penetration of the dissolving fluid into the solid medication particles, they largely increase the rate of dissolution.

a) Microemulsions

Jack H. Shulman coined the phrase "microemulsion" for the first time in 1959. External phase, internal phase, surfactant, and co-surfactant are the four components that make up a microemulsion.

Unlike the cosurfactant, adding surfactant to the internal phase causes the creation of an optically transparent, isotropic, thermodynamically stale emulsion. Because of the internal or disseminated phase's 0.1-droplet diameter, it is known as a microemulsion.

The surfactant and co-surfactant compete with one another and combine to produce a mixed film at the interface, which increases the microemulsion's stability. To guarantee the rapid generation of o/w droplets during production, non-ionic surfactants with high hydrophilic-lipophilic balances, such as tweens and labrafil, are frequently utilized.[28]

b) Self Micro emulsifying Drug Delivery Systems (SMEDDS)

SMEDDS are anhydrous microemulsion systems. Some researchers have also referred to it as microemulsion pre-concentrate. When dispersed in aqueous phase with light agitation, it can produce an o/w microemulsion since it is made up of oil, surfactant, and cosurfactant. The motility of the stomach and intestines is what is agitating you.

The surfactant may not be ionic, such as poly oxyethylene surfactants such as Brij, or it may be an ester of sugar, such as Sorbian mono-oleate (span 80).[29]

5. Drug dispersion in Carriers

The two techniques—using solid solution and employing solid dispersion—permit lowering the size of drug particles to submicron ranges.

a) Solid solution

A solid solute is molecularly distributed in a solid solvent in a binary system known as a solid solution. Solid solutions are also referred to as mixed crystals or molecular dispersion because the two compartments crystallize as a single, homogenous system. Due to the molecular-level reduction in particle size, solid solutions dissolve more quickly and have better water solubility than eutectic and solid dispersions. Typically, the fusion process is used to create them. Melts are a kind of system that is ready for fusion. These systems fall into three categories: continuous solid solutions, substitutional solid solutions, and interstitial solid solutions.[30]

b) Solid Dispersion

A collection of solid products with at least two components, often a hydrophilic matrix and a hydrophobic medicament, is referred to as a solid dispersion. Either the matrix is crystalline or amorphous. The medication can be distributed molecularly as either crystalline or amorphous particles (clusters).[31]

Sekiguchi and Obi, who investigated the production and dissolving characteristics of eutectic melts of

sulfonamide medication and a water soluble carrier in the early 1960s, were the ones who first put out the idea of solid dispersion.[32]

A helpful pharmaceutical technique for enhancing the solubility, absorption, and therapeutic efficiency of medicine dose forms is solid dispersion. They can also be referred to as co-precipitates and solid state dispersions, much like Mayersohn and Gibaldi did in their original nomenclature.[33]

Components A and B crystallize simultaneously when combined with composition E and chilled. Other mixtures, however, start to crystallize out one of the components before the other when cold. In order to physically combine the two components into extremely tiny crystals, one of the two compounds is often quickly cooled. When combined with component E, it will dissolve more quickly and have better bioavailability when dissolved in an aqueous medium. This combination has a medicine that is just slightly soluble in water along with a non-toxic, highly water soluble carrier.

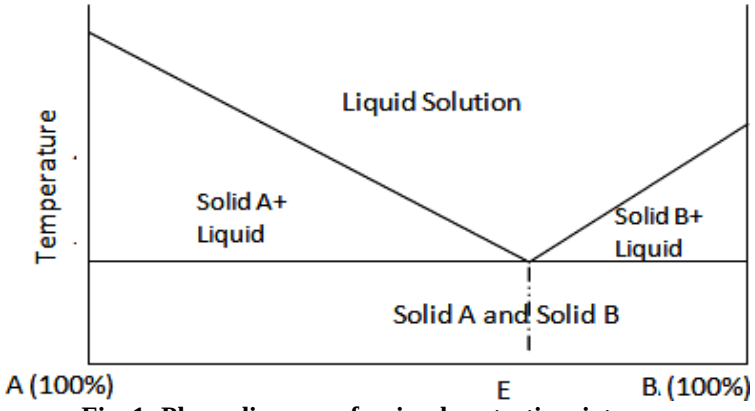

Fig. 1: Phase diagram of a simple eutectic mixtures.

METHODS OF PREPARING SOLID DISPERSIONS

i) Fusion Process

The drug is incorporated into the matrix when the carrier is heated to a temperature just above its melting point. As it cools, the mixture is continuously stirred to evenly distribute the medication throughout the matrix. Enhanced wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form with altered thermodynamic characteristics are additional mechanisms.[34]

ii) Spray Drying

In an appropriate solvent, the carrier and active component are dissolved and suspended. By drying it and applying a stream of warm air to remove the solvent, this solvent is evaporated. Since the droplets have a wide surface area, the solvent quickly evaporates, resulting in the rapid formation of solid dispersion.

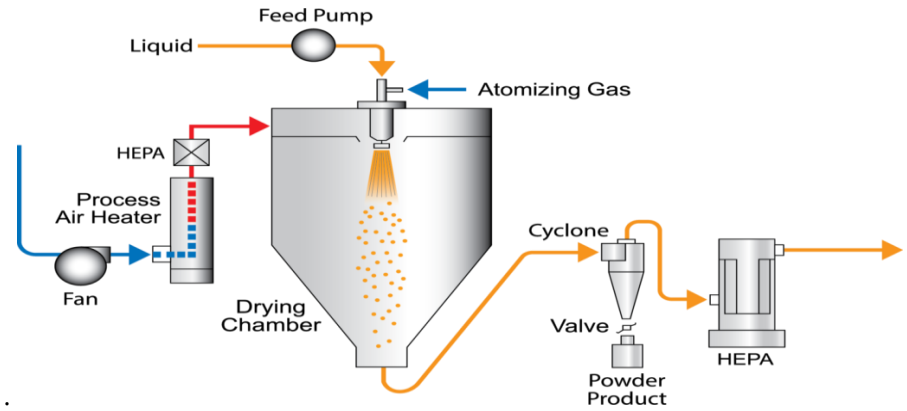

Fig. 2: Spray drying.

iii) Lyophilization (Spray Freeze Drying Method)

Spray freeze drying is a method that has been created to successfully create solid dispersions at ambient temperature and avoid heating while producing medications that are heat-sensitive (SFD). SFD method produces a frozen micronized powder that is subsequently dried from a feed liquid that contains excipients and APIs that are either totally or very slightly soluble in water. In comparison to traditional solid dispersion technology, this approach provides a number of advantages, including amorphous structure and large surface area.[35]

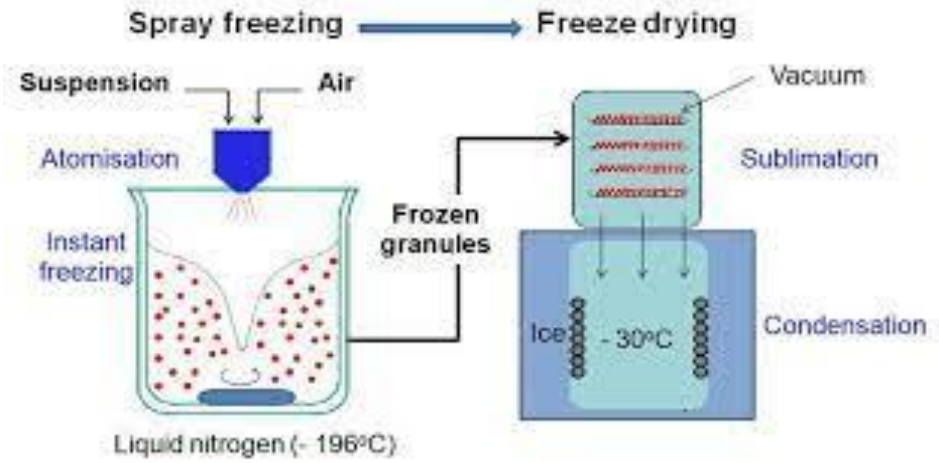

Fig. 3: Spray freeze drying.

iv) Hot-melt Extrusion

In the polymer industry, this is the preferred approach. The first people to apply this technology for pharmacological purposes, however, were Speiser and Huttenrach. These are the sections of a melt extrusion: a feed port for raw materials, a heated barrel with extruder screws to move and mix the ingredients, and an exit port with an optional die to shape the mass while it is being extruded. The heated extruder barrel is continuously loaded with the active chemicals and the carrier. The mixture of active component and carrier is changed into its "fluid like state" when it is forced through heated screws. Because of the strong shear of the extruder screws in this condition, intimate and uniform mixing is possible. The melt is shaped into the desired form, such as granules, pellets, films, or powder, by an optional die in an exit port. The fact that the drug/carrier mixture only experiences an elevated temperature for roughly one minute during the hot melt extrusion procedure allows for the processing of drugs that are somewhat thermolabile.[36]

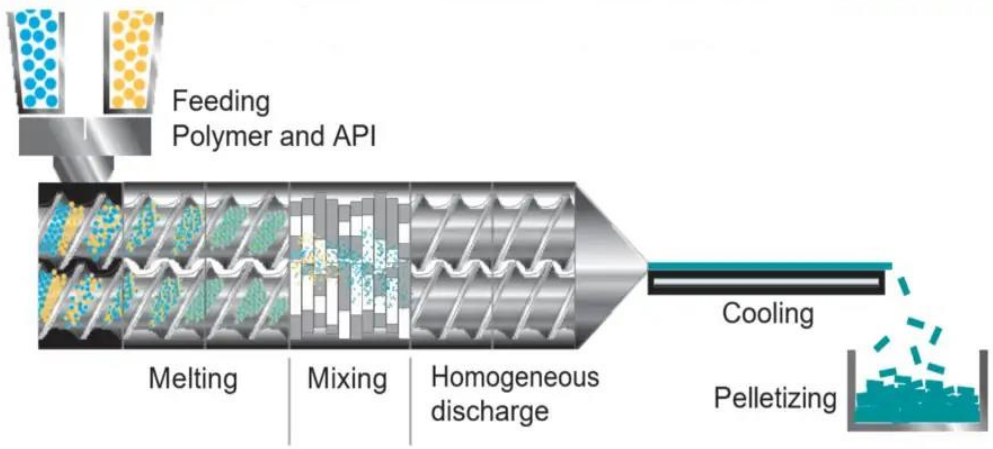

Fig. 4: Hot melt extrusion.

Limitations of Solid Dispersions

- The method of preparation is costly and time-consuming
- Formulation in to dosage forms is challenging
- Scaling up manufacturing process is challenging
- Reproducibility of its physicochemical attributes is challenging
- The amorphous condition may crystalline during storage or processing.

CONCLUSION

We can conclude that the solubility of any molecule is critical and plays a significant role in pharmaceutical formulation and development. The rate of oral absorption of weakly water-soluble drugs is determined by drug dissolution, and solubility is also a main criterion for the formulation and development of different dosage forms of different drugs.

All of the techniques or methods discussed above, which can be employed alone or in conjunction with others, aid in improving or enhancing the solubility of the molecule or any poorly soluble drugs. Many drugs bioavailability is affected as a result of their solubility issues, requiring solubility improvement. The choice of any method for increasing solubility is determined by the drug's nature and properties, such as chemical nature, physical nature, pharmacokinetic behaviour, and so on. With the use of

numerous procedures, such as those stated above, it is now possible to enhance the solubility of poorly soluble medications.

ACKNOWLEDGMENT

The authors acknowledge to Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada for their valuable support to complete the review work in a successful manner.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. L. Lachman, H. Lieberman, and J. L. Kanig, The Theory And Practise of Industrial Pharmacy, Lea & Febiger, 3rd edition, 1986.
2. P. B. Myrdal and S. H. Yalkowsky, "Solubilization of drugs in aqueousmedia," in Encyclopedia of Pharmaceutical Technology J. Swarbrick, Ed., p. 3311, Informa Health Care, New York, NY, USA, 3rd edition, 2007.
3. Patil MS, Godse SG, Saudagar RB. Solubility Enhancement by Various Techniques: An Overview. World Journal of Pharmacy and Pharmaceutical Sciences, 2013; 2(6): 4558-4572.
4. Godse SZ, Patil MS, Kothavade SM, Saudagar RB. Techniques for Solubility Enhancement of Hydrophobic Drugs: A Review, *J Adv. Pharm. Edu. & Res.*, 2013; 3(4): 403-414.
5. Patil S.K., Wagh K.S., Parik V.B., Akarte A.M., Baviskar D.T., Strategies for solubility enhancement of poorly soluble drug. *Int J pharm Sci Rev Res*, 2011; 8(2): 74-80.
6. Blagden N., de Matas M., Gavan P.T., York P., Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv Drug Del Rev*, 2007; 59(7): 617–630.
7. 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 Edu Res*, 2012; 2(1): 32-67.
8. Shinde A: Solubilization of poorly water soluble drugs. Pharma Info. Net, 2007; 5(6).
9. Perett S and Venkatesh G: Enhancing the bioavailability of insoluble drug compound. http:// www.eurand. Com/ pdf/Eurx_article_technology_2006.pdf
10. Gennaro A.R: Remington, The science and practice of pharmacy. Lippincott, Williams and Wilkins, 2005; 21st edition: 867-868.
11. Fiese EF and Hagen TA: Preformulation, In: Lachman L, Liberman H.A and Kanig J.L, The theory and practice of industrial pharmacy. Bombay, Varghees Public house, 1990; 3rd edition: 171-196.
12. Allen LV, Popovich NG and Ansel HC: Ansel's Pharmaceutical Dosage Forms and drug delivery system, Lippincott, Williams and Williams, 2005; 100-101.
13. Venkatesh S Y, Rao V and Anderson BD: Intrinsic solubility estimation and pH solubility behavior of CoDalane, an extremely hydrophobic diprotic acid, pharmaceutical research, 1996; 13(10): 1453-1459.
14. Sinho PJ: Martin's Physical pharmacy and pharmaceutical sciences, 2006; 5(9): 232-234.
15. Shinde A: Solubilization of poorly water soluble drugs. Pharma Info. Net, 2007; 5(6).
16. Stickery RG: Solubilizing exicipient in oral and injectable formulations. Pharmaceutical Research, 2004; 21: 201-230.
17. Krishna G, Chen K.J, Linc C and Nomeir AA: Permeability of lipophilic compound in drug discovery using invitro human absorption model Caco-2m. *Int J Pharm Pharma Sci.*, 2001; 222: 77-89.
18. Seethala R and Fernandes PB: Handbook of Drug Screening New York, Marcel Dekker. Inc., 2001; 597-601.
19. 29. Seedhar N, Bhatia S: Solubility enhancement of Cox-2 inhibitors using various solvent systems. AAPS Pharmaceutical Scientific Technology, 2003; 4: 33.
20. Swar Brick J: Encyclopedia of Pharmaceutical Technology, 2006; 3314-3316.
21. Mezzola L, Commercializing Nantechnology, Nat Biotechnol, 2003; 10: 1137-1143.
22. Adam M, Perskey and Jeffrey A: Hurgnet, Salutions and solubility, http://www.cop.ufl.edu/sofezone/pnokai/pha5100/ pha5110.htm.
23. Chaumeil JC: Micronization, a method of improving the bioavailability of poorly soluble drugs, methods and findings in experimental and clinical pharmacology. *Euro J Pharma Sci.*, 2000; 10: 17-28.
24. Singhal D, Curatolo W: Drug polymorphism and dosage form design, a practical perspective. Advanced Drug Delivery Review, 2004; 56: 335-347.
25. Biopharmaceutics and pharmacokinetics A Teratise, 1st Edition, 27-29.
26. Sangwi R, Evans D, Sanmel H and Yarkowsky: Stacking complexation by nicotinamide; A useful way of enhancing drug solubility. *Int J Pharmaceutics*, 2007; 336: 35-41.
27. Loftsson T and Brewster ME: Pharmaceutical applications of cyclodextrins and drug solubilization and stabilization. *J Pharma Sci.*, 1996; 85: 1017-25.
28. Lawrence MJ and Rees GD: Microemulsions based media as novel drug delivery systems. *Adv Drug Deliv Rev.*, 2000; 45: 89-121.
29. Holm R, Porter LJH, Edward GA, Mullertz A, Kristensen HG and Chorman WN:Examination of oral absorption and lymphatic transport of holofantin is a triple canulated canine model after administration in SMEDDS containing structured triglycerides. European Journal of Pharmaceutical Sciences, 2003; 20: 91-97.

30. Swarbrick J: Encyclopedia of Pharmaceutical Technology, 2006; 3: 777-779.
31. Chion WL and Riegelman S: Pharmaceutical applications of solid dispersion systems. *J Pharma Sci.*, 1971; 60(9): 1281-1302.
32. Sekiguichi K and Obi N, Studies on absorption of eutectic mixtures, I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chemical Pharmaceutical Bull, 1961; 9: 866-872.
33. Habib MJ. Pharmaceutical solid dispersion Technology, Technomic Publishing Company, Inc. Lancaster, Pennsylvania (U.S.A.), 2001; 1-36.
34. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor watersoluble drugs, Drug Discov. Today, 2012; 12(23-24): 1068-1075.
35. Rogers TL, Hu JH, Yu ZS, Johnston KP, Williams RO, III A novel particle engineering technology: spray-freezinginto liquid. *Int J Pharm*., 2002; 242: 93-100.
36. Kumar P, Singh C. A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs, *Am. J. Pharmacol*. *Sci.*, 2013; 1(4): 67-73.