Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

https://doi.org/10.36673/IJRPNS.2021.v10.i01.A04

VARIOUS TECHNIQUES FOR SOLUBILITY ENHANCEMENT: AN OVERVIEW

B. Hemalatha*[1], K. Manasa[1], P. Kavya[1], T. Pavani Priya[1], K. Padmalatha[2]

[1*]Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada, Andhra Pradesh, India.

[2]Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada, Andhra Pradesh, India.

ABSTRACT

The success of formulation depends on how capably it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability which ultimately depends upon the solubility of drug molecules in case of oral formulations. So, solubility enhancing techniques like co-solvency, hydrotropy, co-crystallisation, salt formation, change in pH, addition of solubilizing agent, micronization, complexation, modification of crystal habit, solid dispersion have to be used to enhance solubility of poorly soluble drugs. The intention of this article is to describe the solubilisation techniques for improving bioavailability of poorly soluble drugs.

KEYWORDS

Soluble drugs, Techniques and Enhancing techniques.

Author for Correspondence:

Hemalatha B,
Department of Pharmaceutics,
Vijaya Institute of Pharmaceutical Sciences for Women,
Vijayawada, Andhra Pradesh, India.

Email: balahemalatha25@gmail.com

INTRODUCTION

The therapeutic effectiveness of any drug depends upon its bioavailability and thus ultimately upon the solubility of those drug molecules. Solubility is important parameter to attain the desired concentration of drug in the systemic circulation to prove its pharmacological response. The solubility of a solute is defined as the maximum quantity of solute that can dissolve in a certain amount of solvent at a specific temperature. The solubility is defined as the capability of one substance to form a solution with another substance. The substance which is to be dissolved is called the solute and the dissolving fluid in which that solute dissolves is

called the solvent. Solute and solvent together form a solution. Thus, the process of dissolving the solute into the solvent is called as solution. If the solvent is water, this process is known as hydration. The solubility of a drug is represented by various concentration expressions such as the molarity, molality, percentage volume fraction, mole fraction. Also the pharmacopoeia expresses the solubility in terms of the number of millilitres of the solvent required to dissolve 1g of the solute. The descriptive terms given in the Indian Pharmacopoeia are given in Table No.1. Solubility is a physical property referring to the total strength of a given solute to get dissolve in a solvent[1] (Amrit Kaur *et al*, 2016).

Solvent

Solvent is the main constituent of a solution and should be able of dissolving another substance to form a consistently disperse mixture at a molecular level.

Solute

Solute is a substance present in small quantity and dissolves in the solvent.

Process of Solubilisation

The process of solubilisation involves three steps:

1. The separation of solvent molecules to provide the space in the solvent for solute.
2. The breaking of the intermolecular bonds or inter-ionic bonds in the solute.
3. The interaction between the separated solvent molecules and the broken solute molecules or ion.

Need for solubility

According to the recent estimates, approximately 40-50% of the new chemical entities are being rejected because of their poor solubility; as solubility is one of the key parameter to achieve the desired concentration of drugs or active ingredient in the systemic circulation. Because the therapeutic effectiveness of any drug molecule depends upon the solubility as well as on the bioavailability of that drug molecule.

Bioavailability can be defined as the rate and extent of the therapeutically active drug that reaches to the systemic circulation in the unchanged form and is available at the site of action. The absorption of drugs from the GI tract can be affected by poor aqueous solubility and poor membrane permeability of the drug molecule. Thus, when any drug or an active agent is administered orally, it must first get dissolved in the gastric or in the intestinal fluids before it get permeated through the membranes of the GIT to reach the systemic circulation. So, to improve the oral bioavailability of drugs, there is a necessitate to enhance the solubility and dissolution rate of poorly water soluble drugs.

According to BCS classification of drugs, class II and IV drugs are poorly water soluble drugs and thus dissolution of these drugs is the rate limiting step when administered. The BCS classification of drugs is described in Table No.2.

FACTORS AFFECTING SOLUBILITY

The solubility of any drug or other components depends upon given points:-

- Nature and composition of the solvent medium
- Physical form of the solid
- Temperature and pressure of system

The factors which influence the process of solubility include the following.

Particle Size

The particle size affects the solubility for the reason that the decrease in particle size increases the surface area to volume ratio. The larger surface area of solute molecules allows more interaction with the solvent[3] (Honey Kansara *et al*, 2015).

Molecular Size

The molecular size will affect the solubility of the drug as larger the molecule or higher the molecular weight of the drug, less is the solubility of that substance[4] (S. V. Kadam *et al*, 2013). In organic compounds, the amount of carbon branching increases the solubility as more branching will decrease the size of molecule and make it easier for the solvent to solvate the molecules.

Temperature

With the increase in temperature, the process of solution absorbs the energy and hence solubility will get increased however if the process of solution releases the energy with the increase in temperature

then it will reduce the solubility. A small number of solid solutes are there which are less soluble in warm solutions. In case of gases, the solubility get decreased when temperature of solution is increased[4] (Jinal N. Patel *et al*, 2012).

Pressure

In case of solids and liquid solutes, there is no effect of pressure on the solubility but in case of gaseous solutes, when the pressure is enhanced, there is an increase in the solubility and with the decrease in pressure there is a decrease in solubility[5] (Rakesh Tiwle *et al*, 2012).

Nature of solute and solvent[6] (Vilas P Bharti *et al*, 2015)

There is a lot of difference in the solubility of two or more different substances on the basis of their natures. For example: In 100grams of water at room temperature only 1 gram of Lead (II) chloride can be dissolved where 200grams of Zinc chloride can be dissolved in same amount of water i.e. 100 grams of water at same room temperature.

Polarity

The polarity of solute and the solvent molecules will impinge on the process of solubility.

Usually the polar solute molecules will get dissolved in polar solvent system as well as non-polar solute molecules will get dissolved in non-polar solvent system. Thus if the solute molecule is polar in nature it must have both positive and negative ends and if the solvent is also of polar nature then it also consist of both the ends, thus the positive ends of solute molecule gets attracted towards the negative ends of the solvent molecules. These type of attractions are known as dipole-dipole interactions which is a type of intermolecular force[7] (Sharma Neha *et al*, 2011).

Polymorphs

Solids have a rigid form and a definite shape. The shape or crystal habit of a given solid may vary but angles between the faces remains constant[8] (Blagden N *et al*, 2007). A crystal is made up of ions, atoms or molecules in a lattice or in a regular geometric arrangement constantly repeated in three dimensions. This repetitive arrangement is called as unit cell. The ability of a substance to crystallize in more than one crystalline form is known s polymorphism. The polymorphs can vary in their melting points. As the melting point of any solid is related to its solubility, the polymorphs will have different solubility[9] (Singhal D *et al*, 2004).

Rate of solution

The rate of solution can be defined as the measure of how fast the substance dissolves in a solvent.

The various factors that affect the rate of solution are:

- Size of particles
- Temperature
- Amount of solute already dissolved
- Stirring

TECHNIQUES TO ENHANCE SOLUBILITY

The techniques that enhance poor drug solubility are discussed below.

Physical Modifications

Particle size reduction

- Micronization
- Nanosuspension
- Sonocrystallization
- Spray drying

Modification of the crystal habit

- Polymorphs
- Pseudo polymorphs
- C. Drug dispersion in carriers
- Eutectic Mixtures
- Solid dispersions

Complexation

- Use of Complexing agents
- E. Solubilization by surfactants:
- Micro emulsions
- Self microemulsifying drug delivery systems

Chemical Modifications

- Change in pH
- Use of buffer
- Salt Formation

Other Methods

- Co-crystallisation
- Co-solvency
- Hydrotropy

Physical Modifications

Particle size reduction

Particle size reduction can be attained by techniques like micronization, nanosuspension, sonocrystallization and spray drying. Each technique employs diverse equipments for reduction of the particle size.

Micronization

The solubility of drug is essentially related to drug particle size. If the particle size reduces, the surface area increases which improves the dissolution properties of the drug. Usual methods of particle size reduction, for instance comminution and spray drying depend upon mechanical stress to disaggregate the active compound. Micronisation enhances the dissolution rate of drugs through increased surface area; however it does not increase equilibrium solubility. Size reduction of drugs is performed by milling techniques using jet mill, rotor stator colloid mills etc. Micronization does not fit for drugs having a high dose number because it does not change the saturation solubility of the drug[10] (Chaumeil J. C *et al*, 1998).

Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug that are stabilised by surfactants. The advantage of nanosuspension is increased dissolution rate due to larger surface area exposed. The absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor[11] (Prabhakar Ch *et al*, 2011).

The techniques for the production of nanosuspensions are,

Homogenization

The homogenizers are normally used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors. The suspension is forced under pressure through a valve. This causes bubbles of water to form which collapses as they come out of valves which cracks the particles.

Wet milling

Wet milling 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.

Sonocrystallisation

Recrystallization of poorly soluble materials using liquid solvents and antisolvents is employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation[12] (Perrut M *et al*, 2005). Sonocrystallisation makes use of ultrasound power characterised by a frequency range of 20-100 kHz for inducing crystallisation. It augments the nucleation rate and is an effective means of size reduction. Most applications utilize ultrasound in the range 20 kHz - 5 MHz.

Spray drying

Spray drying is a generally used method of drying a liquid feed through a hot gas. This hot gas is air however sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used instead. The liquid feed differs depending on the material being dried and is not restricted to food or pharmaceutical products and might be a solution, colloid or a suspension. This process of drying is a one pace rapid process and eradicates additional processing.

Modification of the crystal habit

Polymorphism is the capability of an element to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, although they exhibit diverse physicochemical properties including solubility, melting point, density, texture, stability etc. Generally polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, one polymorphic form can

alter reversibly into another at a definite transition temperature below the melting point, whereas no reversible transition is possible for monotropes. Once the drug has been characterized under one of this type, advance study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and as a result higher solubility. In the same way the amorphous form of drug is more suitable than crystalline form due to higher energy associated and increase surface area[13] (Pinnamaneni S *et al*, 2002). In general, the anhydrous form of a drug has better solubility than the hydrates since the hydrates are already in interaction with water and as a result have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for additional interaction with water. Alternatively, the organic (non-aqueous) solvates have greater solubility than the non-solvates. Hence, the order for dissolution of diverse solid forms of drug is Amorphous >Metastable polymorph >Stable polymorph. Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug[14] (Forster A *et al*, 2001).

Drug dispersion in carriers

Eutectic mixtures

In 1961, Eutectic mixture was primary described as solid dispersions by Sekiguchi and Obi. Eutectic mixtures are produced when the drug and polymer are miscible in their molten condition, but on cooling, they crystallize as two different components with negligible miscibility. Both drug and carrier be present in the finely divided state, which results in the higher surface area and increase the dissolution rate of the drug, for instance, sulfathiazole-urea mixture[15] (D. Christopher Vimalson *et al*, 2016).

Solid Dispersions

The phrase solid dispersion refers to a group of solid products consisting no less than two different components, normally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[16] (Hamsaraj *et al,* 2006).

When the solid dispersion is uncovered to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. This augments surface area of dissolution rate and consequently bioavailability of poorly water soluble drugs. Drug in soluble hydrophilic carrier enhances the dissolution rate by reducing particle size and increasing the particle porosity. Residual drug is in amorphous state and improving wettability and for this reason bioavailability for poorly water soluble drug. The potential benefit of this technique is huge. In recent times, surfactants have been included for betterment of formulation as in many cases. Thermodynamic instability and recrystalisation of drug becomes a difficulty. Thus surfactants are used to avoid recrystalization and potentiating their solubility[17] (Chiou WL *et al*, 1971).

The methods to prepare solid dispersions are:

Fusion Method

The amount of carrier is weighed accurately and are placed in an aluminium pan on a hot plate and is liquefied with the constant stirring at about 60°C temperature. Then the accurately weighed active drug is mixed into the molten carrier with stirring to establish homogeneity[18] (Juppo A M *et al*, 2003). This mixture is then heated until a clear homogeneous melt is obtained. Then, the pan is removed from the hot plate to cool the mixture to room temperature. The limitation of this method is that, at high temperature some drugs may get degraded[19] (Emara L H *et al*, 2002).

Solvent Evaporation Method

Both the drug and the carrier are to be dissolved in a common solvent and then evaporate the solvent under vacuum to generate a solid solution. A major requirement for the make of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying[20] (Kai T *et al*, 1996).

Complexation

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stochiometry[21] (Rawat S *et al*, 2004). Complexation relies on reasonably weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are chelates - EDTA, EGTA, molecular complexes- polymers, inclusion complexes with cyclodextrins.

Complexes are two categories:

Stacking complexes is driven by alliance of non polar area of drug and complexes agent. This results in exclusion of the non polar area from contact with water, thus reducing total energy of the system. Stacking can be homogeneous or mixed, but outcomes in clear solution.

Inclusion complexes are formed due to the capability of a compound to include in another complex. There are no forces involved connecting them and are called as no-bond complexes.

Solubilization by surfactants

Surfactants are molecules with discrete polar and non-polar regions. Most surfactants have a hydrocarbon segment coupled to a polar group. The polar group can be anionic, cationic, zwitterionic or non-ionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles[23] (Mohini S. Patil *et al*, 2013). This process of solubilization is very vital in industrial and biological processes. The presence of surfactants may lesser the surface tension and increase the solubility of the drug in an organic solvent.

Microemulsions

The word "microemulsion" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant molecules. Surfactant molecules have both a polar as well as a polar group. Therefore they exhibit a very unusual behaviour, firstly, they get adsorbed at the interface, where they can fulfill their dual affinity with hydrophilic groups situated in aqueous phase and hydrophobic groups in oil or air. Secondly, they lessen mismatching with solvent by Micellization Process. The dispersed phase normally comprises of small particles or droplets, with a size range of 5nm - 200nm and has extremely low oil/water interfacial tension. As the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. The microemulsion is formed readily and sometimes spontaneously, commonly without high-energy input. In several cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase.

Self - Microemulsifying Drug Delivery System

Self - Microemulsifying Drug Delivery Systems (SMEDDSs) are isotropic and thermodynamically stable solutions consisting of an oil, surfactant, cosurfactant and drug mixtures that spontaneously form oil-in-water (o/w) microemulsions when mixed with water under gentle stirring. The motility of stomach and intestine provides the agitation required for self-emulsification *in vivo*. SMEDDS spreads readily in the GI tract and the digestive motility of the stomach and the intestine provides the agitation required for self-emulsification. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the tiny size of the formed droplet presents a great interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps develop bioavailability by affecting the drug absorption[24] (Shailesh T. Prajapati *et al*, 2013).

CHEMICAL MODIFICATIONS

- Change in the pH
- Use of buffer
- Salt Formation

Change in the pH

The most effective and the simplest mean of growing the aqueous solubility of organic solute which is ionisable, is the change in the pH of the system. For example:

In case of the weakly acidic drugs, at low pH, the solute is in unionised form and so produces insoluble precipitates where at higher pH it is in ionised form which leads to the more soluble drug.

In case of weakly basic drugs, at low pH, the solute is in ionised form, so more soluble drug but when the pH is high then the solute is in unionised form which will end in insoluble precipitation.

Use of buffer

Buffers are used to preserve the pH of solution over the time and also used to reduce or to eliminate the potential for the precipitation which might occur upon dilution. When dilution of a solution is finished then pH variation occurs which results in the decreased solubility.

Salt Formation

The dissolution rate of diverse salts is usually unlike from their parent compounds. Salt formation is the most widespread and successful method of increasing solubility and dissolution rates of acidic and basic drugs[25] (Yogesh S. Thorat *et al*, 2011). Acidic or basic drug transformed into salt have more solubility than respective drug. Examples include Aspirin, Theophylline and Barbiturates.

Other Methods

- Co-crystallisation
- Co-solvency
- Hydrotropy

Co-crystallisation

It is a new approach available for increasing the drug solubility through the appliance of co-crystals, also referred as molecular complexes. A co-crystal is a crystalline material which consists of two or more molecular species which are electrically neutral and are held collectively by non-covalent forces. The co-crystallizing agents are generally recognised and classified as safe (GRAS) which includes nicotinamide, saccharin and acetic acid.

Co-solvency[26] (Md. Mofizur Rahman *et al*, 2014)

The solubilisation of drugs in co-solvents is a method for improving the solubility of poorly soluble drug. It is familiar that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. The majority co-solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups warrant water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, dropping the overall intermolecular attraction of water. By disturbing waters self-association, cosolvents lessen 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 nonpolar like the solute, cosolvents smooth the progress of solubilisation.

Hydrotropy

Hydrotropy is a solubilization phenomenon in which adding together of large amount of a second solute results in an increase in the aqueous solubility of another solute. A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Classically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) although the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self aggregation all of a sudden starts to occur. As an alternative, some hydrotropes aggregate in a step-wise self-aggregation process, slowly increasing aggregation size. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to augment the aqueous solubilities of lots of poorly water soluble drugs[27] (Sandeep Kumar *et al*, 2016).

Advantages of hydrotropy

It is superior to other solubilization methods such as miscibility, micellar solubilization, cosolvency and salting in since the cosolvent character is independent of pH, has high selectivity and does not oblige emulsification[28] (Sandhiya Jatwani *et al*, 2012).

It simply requires mixing the drug with the hydrotrope in water[29] (Varun Raj Vemula *et al*, 2010).

It does not call for chemical modification of hydrotropic drugs, use of organic solvents, or preparation of emulsion system[30] (Satish K. Patil *et al*, 2011).

Table No.1: Definition of solubility

S.No	Definition	Parts of solvent required for one part of solute
1	Very soluble	<1
2	Freely soluble	1 - 10
3	Soluble	10 - 30
4	Sparingly soluble	30 - 100
5	Slightly soluble	100 - 1000
6	Very slightly soluble	1000 - 10, 000
7	Insoluble	>10, 000

Table No.2: Biopharmaceutical Classification System (BCS)

S.No	Class	Permeability	Solubility
1	Class I	High	High
2	Class II	High	Low
3	Class III	Low	High
4	Class IV	Low	Low

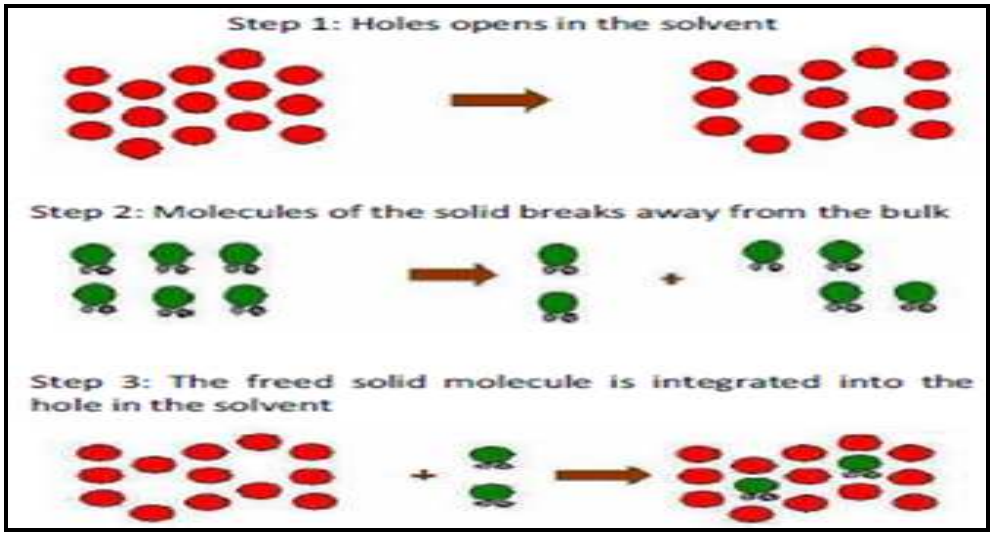
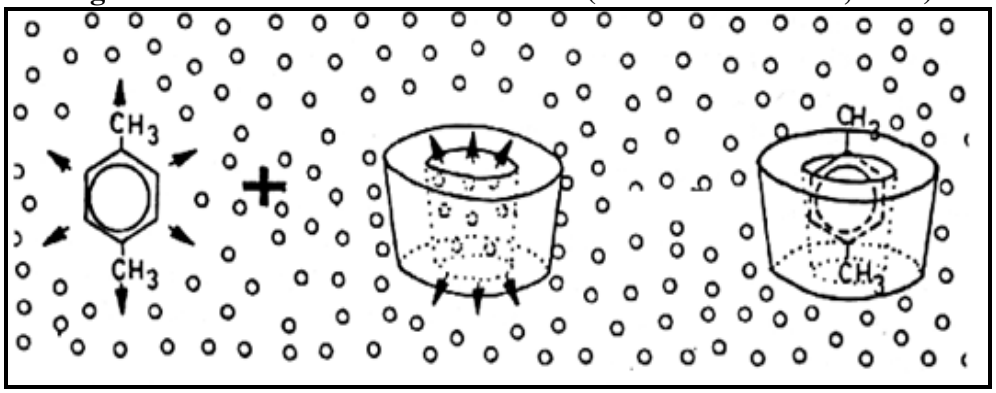


Figure No.1: Process of solubilisation[2] (Jinal N. Patel *et al*, 2012)



Drug Cyclodextrin Drug - Cyclodextrin complex

Figure No.2: Complex formation by cyclodextrin[22] (Dordunoo Stephen K *et al*, 1996)

CONCLUSION

A drug administered in solution form is efficiently absorbed than the same amount of drug administered in a solid dosage form such as tablet or capsule. Solubility is a most key parameter for the oral bioavailability of poorly soluble drugs. Dissolution is the rate determining step for oral absorption of the poorly water soluble drugs, which will consequently affect the *in vivo* absorption of drug. Currently merely 8-10% of new drugs have both high solubility and permeability. As the solubility problem of many drugs affects the bioavailability, solubility enhancement becomes obligatory. By using the above mentioned techniques, the solubility can be enhanced for poorly soluble drugs.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada, Andhra Pradesh, India for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Amrit Kaur, Prasad D N, Dua J S, Muse Menra and Neha Sharma. Aspects of solubilisation: A review, *World Journal of Pharma Rese,* 5(6), 2016, 741-758.
2. Jinal N. Patel, Dharmendra M. Rathod, Nirav A. Patel and Moin K. Modasiya. Techniques to improve the solubility of poorly soluble drugs, *International Journal of Pharmacy and Life Sciences,* 3(2), 2012, 1459-1469.
3. Honey Kansara, Riddhi Panola, Amul Mishra. Techniques used to enhance bioavailability of BCS class II drugs: A review, *Int. J. Drug Dev and Res,* 7(1), 2015, 82-93.
4. Kadam S V, Shinkar D M, Saudagar R B. Review on solubility enhancement techniques, *International Journal of Pharma and Biological Sciences,* 3(3), 2013, 462-475.
5. Rakesh Tiwle, Ajazuddin, Tapan Kumar Giri, Dulal Krishna Tripathi, Vishal Jain and Amit Alexander. An exhaustive review on solubility enhancement for hydrophobic compounds by possible applications of novel techniques, *Trends in Applied Sciences Research,* 7(8), 2012, 596-619.
6. Vilas P. Bharti, Vinayta R Attal, Anirudha V Munde, Arunadevi S Birajdar, Sanjay Bais. Strategies to enhance solubility and dissolution of a poorly water soluble drug, *Journal of Innovations in Pharmaceuticals and Biological Sciences,* 2(4), 2015, 482-494.
7. Sharma Neha, Bharkatiya Meenakshi. Solubility enhancement techniques: A Review, *International Journal of Pharmaceutical Erudition,* 1(3), 2011, 40-53.
8. Blagden N, Matas M, Gavan P T, York P. Crystal Engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, *Advanced Drug Delivery Reviews,* 59(7), 2007, 617-630.
9. Singhal D, Curatolo W. Drug polymorphism and dosage form design a practical perspective, *Adv. Drug. Deliv. Rev,* 56(3), 2004, 335-347.
10. Chaumeil J C. Micronisation: A method of improving the bioavailability of poorly soluble drugs, *Methods and Findings in Experimental and Clinical Pharmacology,* 20(3), 1998, 211-215.
11. Prabhakar Ch, Bala Krishna K. A review on nanosuspensions in drug delivery, *International Journal of Pharma and Biosciences,* 2(1), 2011, 549-558.
12. Perrut M, Jung J, Leboeuf F. Enhancement of dissolution rate of poorly soluble active ingredients by supercritical fluid processes part II: Preparation of composite particles, *International Journal of Pharmaceutics,* 288(1), 2005, 11-16.
13. Pinnamaneni S, Das N G, Das S K. Formulation approaches for orally administered poorly soluble drugs, *Pharmazie,* 57(5), 2002, 291-300.

14. Forster A, Hempenstall J, Rades T. Characterization of glass solutions of poorly soluble drugs produced by melt extrusion with hydrophilic amorphous polymers, *J. Pharm. Pharmacol,* 53(3), 2001, 303- 315.
15. Christopher Vimalson D, Parimalakrishnan S, Jeganathan N S, Anbazhagan S. Techniques to enhance solubility of hydrophobic drugs: An overview, *Asian Journal of Pharmaceutics,* 10(2), 2016, 67-75.
16. Hamsaraj Karanth, Vikram Subraya Shenoy, Rayasa Ramachandra Murthy. Industrially feasible alternative approaches in the manufacture of solid dispersions: A technical report, *AAPS Pha Sci Tech,* 7(4), 2006, 31-38.
17. Chiou W L, Riegelman S. Pharmaceutical applications of solid dispersion systems, *J. Pharm. Sci,* 60(9), 1971, 1281-1302.
18. Juppo A M, Boissier C, Khoo C. Evaluation of solid dispersion particles prepared by SEDS, *Int. J. Pharm,* 250(2), 2003, 385-401.
19. Emara L H, Badr R M, Elbary A A. Improving the dissolution and bioavailability of Nifedipine using solid dispersions and solubilizers, *Drug. Dev. Ind. Pharm,* 28(7), 2002, 795-807.
20. Kai T, Akiyama Y, Nomura S, Sato M. Oral absorption improvement of poorly soluble drug using solid dispersion technique, *Chem. Pharm. Bull,* 44(3), 1996, 568-571.
21. Rawat S, Jain S K. Solubility enhancement of celecoxib using β-cyclodextrin inclusion complexes, *Europe Journal of Pharmaceutics and Biopharmaceutics,* 57(2), 2004, 263-267.
22. Dordunoo Stephen K, Burt Helen M. Solubility and stability of taxol: Effects of buffers and cyclodextrins, *International Jour of Pharm,* 133(1-2), 1996, 191-201.
23. Mohini S. Patil, Sheetal Z. Godse, Dr. R. B. Saudagar, Solubility Enhancement by various techniques: An overview, *World Journal of Phar and Pharma Sci,* 2(6), 2003, 4558-4572.
24. Shailesh T. Prajapati, Harsh A. Joshi and Chhaganbhai N. Patel, Preparation and characterization of self – microemulsifying drug delivery system of olmesartan medoxomil for bioavailability improvement, *Journal of Pharmaceutics,* 2(13), 2012, 1-9.
25. Yogesh S. Thorat, Indrajeet D. Gonjari and Avinash H. Hosmani. Solubility enhancement techniques: A review on conventional and novel approaches, *International Journal of Pharmaceutical Sciences and Research,* 2(10), 2011, 2501-2513.
26. Md. Mofizur Rahman, Abul Bashar Ripon Khalipha, Md. A. K. Azad, Sophia Hossain and Sanjida Haque. Methods of solubility and dissolution enhancement for poorly water soluble drugs: A review, *World Journal of Pharmacy and Pharmaceutical Sciences*, 3(5), 2014, 107-130.
27. Sandeep Kumar, Pritam Singh, Various techniques for solubility enhancement: An overview, *The Pharma Innovation Journal,* 5(1), 2016, 23-28.
28. Sandhiya Jatwani, Avtar Chand Rana, Gurpreet Singh and Geeta Aggarwal. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach, *International Journal of Pharmaceutical Sciences and Research,* 3(4), 2012, 942-956.
29. Varun Raj Vemula, Venkateshwarlu Lagishetty, Srikanth Lingala. Solubility enhancement techniques*, International Journal of Pharmaceutical Sciences Review and Research,* 5(1), 2010, 41-51.
30. Satish K. Patil, Kalpesh S. Wagh, Venkatesh B. Parik, Anup M. Akarte, Dheeraj T. Baviskar. Strategies for solubility enhancement of poorly soluble drugs, *International Journal of Pharmaceutical Sciences Review and Research,* 8(2), 2011, 74-80.

Please cite this article in press as: Hemalatha B *et al.* Various techniques for solubility enhancement: An overview, *International Journal of Research in Pharmaceutical and Nano Sciences,* 10(1), 2021, 29-38.