ejpmr, 2017,5(02), 94-100

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

FORMULATION APPROACHES TO ENHANCE DRUG SOLUBILITY-BRIEF OVERVIEW

Fateh AL Rahman Magbool[1], Elamin Ibrahim Elnima[2], Shayoub M. E.[3] and Salah Eldin Omar Hussein[4]*

[1]PhD Student, Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Khartoum – Sudan.

[2]Professor of Microbiology, Faculty of Pharmacy, University of Khartoum – Sudan.

[3]Associate Professor of Pharmaceutics, Alyarmouk College of Pharmacy – Sudan.

[4]Assistance Professor, Clinical Laboratory Science Department, AL - Ghad International College for Applied Medical Sciences – KSA.

***Corresponding Author: Dr. Salah Eldin Omar Hussein**

Assistance Professor, Clinical Laboratory Science Department, AL - Ghad International College for Applied Medical Sciences – KSA.

Article Received on 28/11/2017 **Article Revised on 18/12/2017** **Article Accepted on 08/01/2018**

ABSTRACT

The solubility of drugs molecules remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has increased solubility. A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. On the basis of solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in the Class II and Class IV of the BCS system. To improve solubility and bioavailability of poorly soluble drug we use various technologies and formulation approaches. This review presents highlight information about the solubility significance, factors affecting solubility, and different formulation approaches used for the enhancement of the solubility of poorly soluble drugs including; pH-adjustment, co-solvents, surfactants, complex formation, lipid-based formulations, nano-suspensions and solid solution/dispersion technologies.

KEYWORDS: Bioavailability, solubility, formulation approaches, Solubility enhancement.

INTRODUCTION

The solution is produced when equilibrium is established between undissolved and dissolved solute in a dissolution process is termed a saturated solution. The amount of substance that passes into solution in order to establish the equilibrium at constant temperature and pressure and so produce a saturated solution is known as the solubility of the substance. It is possible to obtain supersaturated solutions but these are unstable and precipitation of the excess solute tends to occur readily. Drug Solubility is defined as maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The new drug entities with poor aqueous solubility are becoming more prevalent as result of high-throughput screening in drug discovery. Poor aqueous solubility presents significant challenges, as it reduces the oral absorption and bioavailability.[1] Nevertheless, the required solubility to achieve a good bioavailability must be evaluated in view of both the dose and the permeability. Drug absorption relies heavily on two factors; solubility and permeability. As the number of poorly soluble drugs has increased, efforts to enhance solubility have evolved. The Biopharmaceutics Classification System[2] is used to categorize drugs based on solubility and permeability for formulation development. BCS consists of four classes based on solubility and permeability. Both BCS II and IV compounds are of low solubility (Table 1), and class IV compounds suffer from additional poor permeability issue. The solubility class boundary is based on the highest dose strength of a drug product.

Table 1: Biopharmaceutics Classification System (BCS).

Class I	Class II	Class III	Class IV
High solubility	Low solubility	High solubility	Low solubility
High permeability	High permeability	Low permeability	Low permeability

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.[3] Due to advanced research and development, there are varieties of new drugs and their derivatives are available. But more than 40% of lipophilic drug candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmacodynamic activities. The lipophilic drug that reaches market requires a high dose to attain proper pharmacological action. The basic aim of the further formulation & development section is to make that drug available at proper site of action within optimum dose.[4]

SOLUBILITY SIGNIFICANCE

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.[5] Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the most commonly used solvent for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility for most drugs, the pharmacologic response can be related directly to the plasma levels. Thus the term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. It can also be defined as the rate and the extent to which the ingredients or active moiety is absorbed from the drug product and becomes available at the site of action. As per the definition of bioavailability, a drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane, extensive presystemic metabolism.[6] However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role for other dosage forms like parenteral formulations as well.[7] Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.[8] Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.

METHODS OF EXPRESSING SOLUBILITY

Solubilities may be expressed by means of any of the concentration terms. They are expressed most commonly, however, in the terms of the maximum mass or volume of solute that will dissolve in a given mass or volume of solvent at a particular temperature. The British pharmacopoeia (1980) gives information on the approximate Solubilities of official substances in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid or one part by volume of a liquid. The European pharmacopoeia (1982) also uses the expression "parts" in defining the approximate Solubilities that correspond to descriptive terms such as "freely soluble" and "sparingly soluble".

PREDICTION OF SOLUBILITY

Similar types of intermolecular forces may contribute to solute-solvent, solute-solute and solvent-solvent interactions. The attractive forces exerted between polar molecules are much stronger, however than those that exist between polar and non-polar molecules or between non-polar molecules themselves, consequently, a polar solute will dissolve to a greater extent in a polar solvent, where the strength of the solute-solvent interaction will be comparable to that between solute molecules, than in a non-polar solvent, where the solute-solvent interaction will be relatively weak. In addition, the forces of attraction between the molecules of a polar solvent will be too great to facilitate the separation of these molecules by the insertion of a non-polar solute between them, because the solute-solvent forces will again be relatively weak. Thus, solvents for non-polar solutes tend to be restricted to non-polar liquids. The above considerations are often expressed in the very general manner that "like dissolve like". Such a generalization should be treated with caution, because the intermolecular forces involved in the process of dissolution are influenced by factors that are not obvious from a consideration of the overall polarity of a molecule.

INTRINSIC SOLUBILITY

An increase in solubility of the drug in an acidic solution compared with it is aqueous solubility suggests a weak base and an increase in alkali, a weak acid. In both cases dissociation constant will be measurable and salts should form. An increase in both acidic and alkaline solubility suggests either amphoteric or zwitterion behaviour. No change in solubility suggests a non-ionizable, neutral molecule with any measurable dissociation constant. Here solubility manipulations will require either solvents or complexation. When the purity of the drug sample can be assured, the solubility value obtained in acid for a weak acid or alkali for a weak base can be assumed to be the intrinsic solubility".

1. FACTORS AFFECTING THE SOLUBILITY

1.1 Temperature

Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.[9]

1.2 Crystal characteristics

Many drugs exhibit polymorphism "different crystalline forms of the same substance", consequently possess different lattice energies and this difference is reflected by changes in other properties such as solubility and melting point. The effect of polymorphism on solubility is particularly important from a pharmaceutical point of view, because it provides a means of increasing the solubility of a crystalline material and hence it is rate of dissolution. Although the more soluble polymorphs are metastable and will convert to the stable form the rate of such conversion is often slow enough for the metastable form to be regarded as being sufficiently stable from a pharmaceutical point of view. The absence of crystalline structure that is usually associated with a so-called amorphous powder may also lead to an increase in solubility of a drug when compared with that of it is crystalline form. During crystallization process the lattice structures of crystalline materials may be altered by the incorporation of molecules of the solvent from which crystallization occurred, the resultant solids are called solvates (for non-aqueous solvents) or hydrates when the solvent is water and the phenomenon is referred to as solvation although the term pseudopolymorphism is encountered sometimes. There are differences in solubilities between solvated and unsolvated crystals. Hydrated crystals tend to exhibit a lower aqueous solubility than their unhydrated forms. This decrease in solubility can lead to precipitation from solutions of the drugs.

1.3 Molecular structure of solute

The nature of solute will be of paramount importance in determining the solubility of a solid in a liquid. It should be realized that even a small change in the molecular structure of a compound can have a marked effect on it is solubility in a given liquid. In addition, the conversion of a weak acid to it is sodium salt leads to a much greater degree of ionic dissociation of the compound when it dissolves in water. The overall interaction between solute and solvent is increased markedly and the solubility consequently rises. Conversely, the reduction in aqueous solubility of a parent drug by it is esterification may also be cited as an example of the effects of changes in the chemical structure of the solute.

1.4 Polarity and Nature of solvent

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.[10]

1.5 Particle size

The changes in the interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size. The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent.

1.6 Pressure

For solids and liquid solutes, solubility not affected by change in pressure but for gaseous solutes, solubility increases as pressure increases and decrease as pressure decrease.

1.7 pH

If the pH of a solution of either a weakly acidic drug or a salt of such a drug is reduced then the proportion of unionized acid molecules in the solution increases. Precipitation may occur therefore, because the solubility of the unionized species is less than that of the ionized form. Conversely, in the case of solutions of weakly basic drugs or their salts precipitation is favoured by an increase in pH. The relationship between pH and the solubility and pKa value of acidic and basic drugs is given by Eqn,[1]

Acidic drugs: $pH = pKa + \log s\text{-}s0/ s0$

Basic drugs: $pH = pKa + \log s\ 0/ S\text{-}\ s0$

Where pKa = dissociation constant of drug, s0 = solubility of unionised form, moles/litre, S= overall solubility of drug, moles/litre.

1.8 Dielectric Constant

The solubility is a function of dielectric constant of polar and nonpolar medium. Most often, with hydrophobic drugs, the solubility decreases with increasing dielectric constant.

DIFFERENT APPROACHES TOWARD THE ENHANCEMENT OF DRUG SOLUBILITY

Various formulation approaches have been employed to overcome the drug solubility problems that cause the poor absorption and bioavailability including; pH-adjustment, co-solvents, surfactants, complex formation, lipid-based formulations, nano-suspensions and solid dispersion approaches.

Nano-suspension

Drugs can be made into nano-suspensions of particles with diameters less than 100 nanometers (nm).[11,12,13,14] Nano- sized compounds are used to improve solubility of poorly-water-soluble compounds and are sub-micron sized colloidal dispersions of pure drug particles in an outer liquid phase. An added advantage when using nano-suspensions to enhance solubility is this application allows for increased solubility and dissolution rates of the compound. An increase in the dissolution rate can occur because of the increase in surface area. There are various approaches (precipitation, micro-emulsion, high-pressure homogenization and milling methods) to create nano- suspensions, two of the most common ones; solvent diffusion method and melt emulsification methods.

pH- adjustment

solubility enhancing of poorly soluble ionizable can be done either by adjusting the pH of the solution to favor the ionized form whereby the buffer capacity and tolerability of the selected pH are important to avoid drug precipitation, or by using solubilized excipients that modulate the environmental pH (pH-modifier) within the solid dosage form, this pH-modifier should present inside the formulation over the dissolution time of the drug compound, therefore the selection of pH-modifier type and concentration is important. Adjustment of the pH is frequently combined with co-solvents for further increase in solubility.[15] The pH-adjusted formulations are simple to produce and development progresses quickly. The risk of precipitation upon contact with a pH where the drug is less soluble is the major disadvantage of this method.[16, 17] Other disadvantages of this method are tolerability and toxicity may occur due the use of non-physiological pH's. The drug molecules in a pH-adjusted formulation could also become less soluble and precipitate upon dilution in aqueous media and if were administered intravenously, could cause emboli. Moreover, since the drug is less stable chemically in an aqueous environment than in crystalline form, the employed pH may enhance the hydrolysis or catalyze other degradation mechanisms.[18]

Co-solvents

Addition of water miscible solvent can be used enhances drug water-solubility. This procedure is simple to produce and evaluate. The best drug candidates for co-solvent method are compounds that are lipophilic or compounds with a high crystalline structure that are highly soluble in the selection solvent mixture. By using co-solvents, a compound's aqueous solubility can be increased quite significantly than just the compound alone.[18] Co-solvents can be used for drugs that are not suitable for pH-adjustment strategies due to lack of ionizable groups or for drugs that show low affinity for solubilization by surfactants or lipids due to moderate log P (between 1 and 3). Another advantage to co-solvency method is that high concentrations of the compound can be dissolved compared to other methods. The addition of a co-solvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect of a substance has on the energy needed to separate two oppositely charged bodies. Furthermore, co-solvents can be used in combination with other solubilization strategies such as; pH-adjustment, surfactant or lipid-based formulations in order to further enhance the solubility of insoluble compounds. Some disadvantages of this method are the chemical stability of the insoluble drug is worse than in the crystalline state, as with all solubilized forms. The toxicity and tolerability of the excipients must be closely watched. Also, for intravenous administration, uncontrolled amorphous or crystalline precipitation may occur upon dilution with aqueous media. This occurs because the drug is insoluble in water and after precipitation forms the co-solvent mixture is not readily able to re-dissolve. Embolism and local adverse effects are latent risks at the injection site.

Surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small a polar molecule are added they can accumulate in the hydrophobic core of the micelles. High HLB and hydrophilicity of surfactant assists the immediate formulation of o/w droplets and rapid spreading of formulation in the aqueous media. It resembles to some extend Hydrotropism which is a solubilization phenomenon whereby addition of large amount of second solute (hydrotropes) results in an increase in the aqueous solubility of another solute. However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Drugs entrap within the micelles when the surfactants concentration exceeds the critical micelle concentration and this increases the apparent aqueous solubility of drugs. It is a conventional approach to solubilize a poorly soluble substance by reducing the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. Surfactants can be used in combination with other solubilization strategies such as nanosuspension formulations where reducing the particle size of the drug is essential to enhance the surface area and dissolution rate but this creates high free energy, therefore, surfactant in this case act as stabilizers to prevent precipitation by reducing interfacial tension between drug surface and aqueous phase. Furthermore, Surfactants can be used in combination with co-solvents to reduce susceptibility to precipitation upon dilution. The factors that should be considered when using surfactants include the potential of surfactant to induce hypersensitivity after parenteral administration and the

possibility effects of surfactant on transporter/ metabolic enzyme activity.[19, 20]

Complex Formation

The apparent solubility of a solute in a particular liquid may be increased or decreased by the addition of a third substance which forms an intermolecular complex with the solute. The solubility of the complex will determine the apparent change in the solubility of the original solute. Among all the solubility enhancement approaches and techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule known as guest into the cavity of another molecule or group of molecules known as host. The most commonly used host molecules are cyclodextrins. Cyclodextrin (CD) are macrocyclic oligosaccharides consisting of a hydrophilic outer surface and a hydrophobic inner cavity where guest molecules having a lipophilic nature can be accommodated.[21] Thus, the drugs get encapsulated in the cavity and results in improved aqueous solubility and enhanced dissolution rates. The formation of cyclodextrin complexes requires specific molecular properties which may not work for certain compounds, and the toxicity of cyclodextrin complexes at high concentrations which limits the dose level are the major limitations of this method.[19] An advantage to this method of enhancing solubilization by complexation is that it is achieved through specific interaction rather than changes in the bulk solvent properties. Unlike co-solvents, pH adjustments, and emulsion solubilizing systems, the dissociation is very rapid and quantitative which makes it predictable. An added significant advantage is that commonly used complexating agents like hydroxyl propyl beta cyclodextrin are not as toxic compared to other solubilizing agents such as surfactants.[18] A major disadvantage of the use of cyclodextrins is for formulating the ionizable drugs.

Lipid-based formulations

Lipid-based formulations consist of a drug dissolved in a blend of two or more excipients such as triglyceride oils, partial glycerides, surfactants or co-surfactants.[22] Lipid-based formulations can be solutions, suspensions, emulsions, micro-emulsions, micellar solutions, liposomes, lipid nanoparticles, or nano-emulsions. Among those formulations solid lipid nanoparticles (SLNs, which possess a solid lipid core) and its second generation nanostructured lipid carriers (NLCs, which possess a core of solid lipid and liquid lipid) have attracted a significant level of interest during the recent years. SLNs and NLCs are mainly produced by high pressure homogenization (HPH), have an average particle size below 500 nm and revealed several advantages such as: controlling the drug release and improving the drug stability. Furthermore, SLNs and NLCs are safe carriers and easily produced on large scale.[23, 24]

Solid dispersions

In 1961, Sekiguchi and Obi first introduce the solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs.[25,26] Solid solutions are analogous to liquid solutions that contain one phase. In solid dispersion a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug which can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products.[27,28] A eutectic system has a large surface area, which will enhance the dissolution, resulting in improved solubility and bioavailability.

Salt formation

Sat formation is most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Dissolution rate of particular salt is usually different from that of parent compound. Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms.

The Liquisolid formulations

The Liquisolid techniques are considered as pleasantly flowing and compressible powdered forms of liquid medications. These liquid medications may be regenerated into dry – looking or moistureless, non-adherent free-flowing and readily compressible powders by a simple admixture with selected carriers and coating materials. In this technique, the liquid portion which can be liquid drug, drug suspension or drug solution in a suitable nonvolatile liquid vehicle can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. The acceptable flowing and compressible powder form of liquid medication is liquisolid compact. When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.[29] Drug is solubilized in a maximum molecularly dispersed state. Therefore, this is due to their significantly increased wet- ting properties and increased surface area of drug available for dissolution. Water insoluble or poorly water soluble drugs may be expected to have increased dissolution rate properties as well as improved bioavailability. The liquisolid is newer and promising approach because of

simple manufacturing process, low production coast, and applicable for industry due to good flow and compact property of liquisolid formulation.

CONCLUSION

Solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different 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. The selection of suitable method for solubility enhancement is depends on drug properties. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. The different formulation techniques described above alone or in combination can be used to enhance the solubility of the drug.

REFERENCES

1. Lipinski, C.A., 2000. Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Methods, 44: 235–249.
2. Dahan A, Miller JM, Amidon GL (2009) Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. AAPS J, 11: 740-746.
3. Shinde AJ. et al, "Solubilization of poorly solubledrugs: A Review", Pharmainfo.net, 2007; 6.
4. Shiv M. Solubility Enhancement: Needpharmainfo.net, 2009.
5. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41–51
6. Sharma D, Soni M, Kumar S, Gupta G. Solubility enhancement—eminent role in poorly soluble drugs. Research J Pharm and Tech, 2009; 2(2): 220–224.
7. K. H. Edward and D. Li, "Solubility," in Drug Like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization, p. 56, Elsevier, 2008.
8. V. R. Vemula, V. Lagishetty, and S. Lingala, "Solubility enhancement techniques," International Journal of Pharma- ceutical Sciences Review and Research, 2010; 5(1): 41–51.
9. Blagden N., de Matas M., Gavan P.T., York P., Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced Drug Delivery Reviews, 2007; 59(7): 617–630.
10. Swarbrick J, Encyclopedia of Pharmaceutical Technology, 2006; 3: 3314-33287.
11. Enriquez GG, Rizvi SA, D'Souza MJ, Do DP (2013) Formulation and evaluation of drug-loaded targeted magnetic microspheres for cancer therapy. Int J Nanomedicine, 8: 1393-1402.
12. Angra PK, Rizvi SAA, Oettinger CW, D'Souza MJ (2011) Novel approach for preparing nontoxic stealth microspheres for drug delivery. European Journal of Chemistry, 2: 125-129.
13. Kolluru LP, Rizvi SA, D'Souza M, D'Souza MJ (2013) Formulation development of albumin based theragnostic nanoparticles as a potential delivery system for tumor targeting. J Drug Target, 21: 77-86.
14. Do DP, Pai SB, Rizvi SA, D'Souza MJ (2010) Development of sulforaphane- encapsulated microspheres for cancer epigenetic therapy. Int J Pharm, 386: 114-121.
15. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S (2011) Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm, 420: 1-10.
16. Vemula, V.R., Lagishetty, V., Lingala, S., 2010. Solubility enhancement techniques. Int. J. Pharm. Sci. Rev. Res, 5: 41-51.
17. Siepe, S., Lueckel, B., Kramer, A., Ries, A., Gurny, R., 2008. Assessment of tailor-made HPMC-based matrix minitablets comprising a weakly basic drug compound. Drug Dev. Ind. Pharm, 34: 46–52.
18. Vemula VR, Lagishetty V, Lingala S (2010) Solubility Enhancement Techniques. International Journal of Pharmaceutical Sciences Review and Research, 5: 41-51.
19. Kerns, E.H., Di, L., 2008. Drug-like Properties: Concepts, Structure Design and Methods, in: Drug-like Properties: Concepts, Structure Design and Methods. Elsevier.
20. Williams, H.D., Trevaskis, N.L., Charman, S. a, Shanker, R.M., Charman, W.N., Pouton, C.W., Porter, C.J.H., 2013. Strategies to address low drug solubility in discovery and development. in: Pharmacological Reviews, 315–499.
21. Loftsson, T., Brewster, M.E., 1996. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J. Pharm. Sci, 85: 1017–1025.
22. Pouton, C.W., 2000. Lipid formulations for oral administration of drugs: Non-emulsifying, self-emulsifying and "self-microemulsifying" drug delivery systems. Eur. J. Pharm. Sci, 11: S93-S98.
23. Müller, R.H., Mäder, K., Gohla, S., 2000. Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. Eur. J. Pharm. Biopharm, 50: 161-177.
24. Mäder, K., Mehnert, W., 2001. Solid lipid nanoparticles: production, characterization and applications. Adv. Drug Deliv. Rev, 47: 165–96.
25. Arora S.C., Sharma P.K. et al., Development, characterization and solubility study of solid dispersion of cefixime trihydrate by solvent

evaporation method. International Journal of Drug Development & Research, 2010; 2: 424-430.
26. Ahire B.R., Rane B.R., Bakliwal S.R., Pawar S.P., Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Techniques. International Journal of Pharm tech Research, 2010; 2: 2007-2015.
27. Craig D.Q.M., The mechanisms of drug release from solid dispersion in water soluble polymers. International journal of pharmacy, 2002; 203: 131-144.
28. Sekiguchi K., Obi N., Studies on absorption of eutectic mixture-I: A comparison of the behaviour of that of ordinary sulfathiazole eutectic mixture of sulfathiazole. Chemical and Pharmaceutical Bulletin, 1961; 9: 866-872.
29. Fahmy R.H., Kassem M.A., Enhancement of Famotidine Dissolution Rate Through Liquisolid Tablets Formulation: In Vitro and in Vivo Evaluation. European Journal of Pharmaceutics and Biopharmaceutics, 2008; 69: 993–1003.