WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 5, 468-482. Review Article ISSN 2277– 7105

SOLUBILITY ENHANCEMENT TECHNIQUES: AN OVERVIEW

Himanshi Khatri[1], Md. Sadique Hussain[1*] and Swati Tyagi[2]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan 302017, India.

[2]Department of Pharmacy, Quantum School of Health Sciences, Quantum University, Roorkee, Uttarakhand, 247662, India.

Article Received on
03 March 2022,

Revised on 23 March 2022,
Accepted on 13 April 2022

DOI: 10.20959/wjpr20225-23812

***Corresponding Author**
Md. Sadique Hussain
School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan 302017, India.

ABSTRACT

Solubility is the process by which a solid dissolve in a liquid phase to form a homogeneous mixture. Solubility is a key characteristic in achieving the necessary amount of medication in blood stream in order for pharmacological effect to be demonstrated. The major problem encountered with formulation is low aqueous solubility of new drug molecule. After oral administration, poorly aqueous soluble drugs require high doses to reach maximum therapeutic plasma concentration. Compounds are classified using the biopharmaceutical classification system (BCS) based on their solubility and permeability. This categorization system has been used by regulatory authorities and health organisations to allow dissolution to be used to prove bioequivalence for highly soluble and highly permeable substances. Drugs with poor aqueous solubility cause slow dissolution rates, generally show low bioavailability when orally administered. The purpose of this review article is for the achievement of effective absorption and improved bioavailability.

KEYWORDS: Bioavailability, Solubility, Nanosuspensions, Dispersion, Supercritical fluid.

INTRODUCTION

A variety of approaches can be used to increase the solubilization and bioavailability of poorly water-soluble drugs. Micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, and other procedures are often used for medication solubilization. Solubilization of poorly soluble pharmaceuticals is a common difficulty in novel chemical entity screening investigations as

well as formulation design and development.[1] The ultimate quantity of analyte that may be dissolved in a volume of solvent is known as solubility. It can be characterised both quantitatively and qualitatively. In qualitative term, it can be defined as Spontaneous interaction of two or more substance to form a homogenous dispersion. In quantitative term, Concentration of a substance (solute) in a given volume of solvent at a certain temperature to form homogenous solution. The solubility of drug maybe expressed as percentage, parts, molality, molarity, mole fraction & volume fraction. In pharmaceuticals, solubility equilibria are very important. Drugs having poor water solubility (BCS class II and class IV) shows dissolution related problems.[2]

The BCS is a scientific paradigm for categorising pharmaceuticals based on their water solubility and intestinal permeability. When paired with the drug product's in vitro dissolving properties, the BCS considers three important factors: solubility, intestinal permeability, and dissolution rate, all of which influence the rate and amount of oral drug absorption from sudden release solid oral-dosage forms. According to the BCS which was classified by US Food & Drug Administration (FDA), pharmaceuticals are classified into four fundamental classes based on their solubility and permeability (Table 1). Drugs of class II & class IV are face solubility problem.[3,4] So, increase the solubility turns increase bioavailability of BCS Class II & Class IV drugs.[5]

Table 1: Biopharmaceutical Classification System.

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE L.S IN ABSORPTION
I	High	High	Well absorbed	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Case by Case

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

When in aqueous media solubility of drug is limited, there are various techniques to improve the solubility of poorly soluble drug (Figure 1). There are some traditional and novel techniques to increase the solubility are[6]:

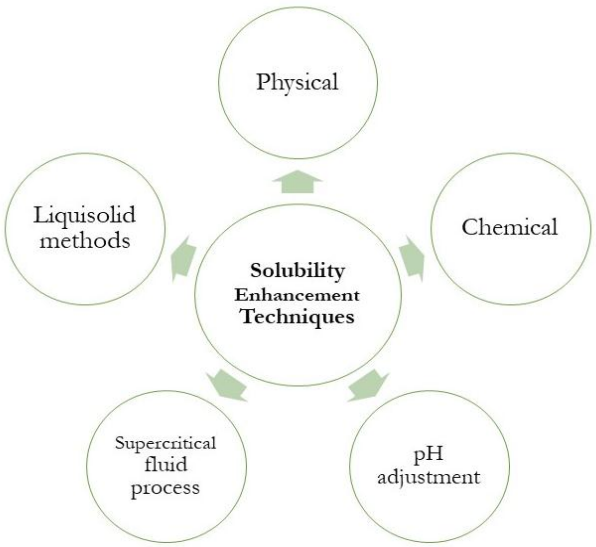

Figure 1: Broad Classification of Solubility Enhancement Techniques.

1. Physical Modification

I. Particle Size Reduction

- Micronization
- Nanosuspension

II. Modification of Crystal Habit

- Polymorphs
- Pseudo polymorphs

III. Drug Dispersion in Carrier

- Solid solutions
- Solid dispersions

IV. Solubilization by Surfactants

- Microemulsion
- Self-micro emulsifying drug delivery system

V. Complexation

2. Chemical modification

I. Hydro trophy

II. Co-solvency

III. Nanotechnology

IV. Salt formation

3. pH adjustment

4. Supercritical fluid process

5. Liquisolid methods

1. Physical Modification

I. PARTICLE SIZE REDUCTION

Solubility of drug is also related to particle size of drug. By reducing particle size, surface area increases which improves the dissolution property of drug. Drug particle size is often related to bioavailability of poorly soluble drugs. Particle size reduction is done by milling techniques using colloid mill, jet mill etc. The saturation solubility of drug does not change, this is not suitable for drugs having a high dose number. Particle size reduction can be achieved by nanosuspension & Micronization.[7]

- Micronization: In Micronization technique, dissolution rate of drugs increased through increase surface area of particles. But equilibrium solubility does not increase. Increasing the surface area of these drugs which cause decrease in particle size, enhance their rate of dissolution.

These processes were applied to progesterone, fenofibrate, Griseofulvin, spironolactone & diosmin. For these drugs, improved their bioavailability, digestive absorption & clinical efficacy.[8]

Advantages

- Gives uniform particle with narrow particle size distribution and increase in surface area.

Disadvantages

- High energy process, causes disruption in drug crystal lattice and in the final product amorphous or disordered regions is present
- Disordered/Amorphous regions are thermodynamically unstable and upon storage in hot and humid conditions these are susceptible to recrystallization.[2,8]

- Nanosuspension: This technology is used to poorly soluble drugs that are insoluble in water & oils. Nanosuspension is biphasic system which consists nano size particle in aqueous vehicle. For parenteral and Pulmonary administration or oral and tropical use nano size drug particles are stabilized by surfactant. In nano suspension, particle size distribution of solid particle is usually less than one micron. And average particle size range is 200 and 600nm. This process applied to tarazepide, atovaquone, amphotericin &

paclitaxel and buparvaquone. Various methods for nanosuspension preparation include Nanocrystals, DissoCubes, Nanopore and Nano edge.[9]

Advantages

- Size of drug particles is reduced which increase the surface area, which in turn increase dissolution, solubility & bioavailability.
- Nanosuspension increase drug permeability.
- Nanosuspension increase duration of action of residence.
- Nanosuspension increase bio adhesion of drug
- It exerts advantage of high drug loading.
- Avoidance of organic solvent.

Disadvantage

- The main problem suffer in nanosuspension is instability due to crystal growth, agglomeration, Ostwald ripening.[10]

II. MODIFICATION OF CRYSTAL HABIT

a) Polymorphs

b) Pseudo polymorphs

- Polymorphism is the ability of solid material to exist in 2 or more different crystalline forms with different arrangements in crystal lattice. Polymorphs are different crystalline forms. Crystalline forms of drugs are chemically same but they have different physiochemical properties like melting point, texture, density, solubility, stability. Similarly, amorphous form of drug is more suitable than crystalline form. Due to more surface area and high associated energy.[11]

Order of different solid form of drugs.

Amorphous > Metastable polymorphs > Stable polymorphs.

III. DRUG DISPERSION IN CARRIER

- Solid solution: In this two crystalline solid are blend that exist as a new crystalline solid. In homogenous one phase system, two components are crystallized together to form a mixed crystal. As compare to simple enteric system it yields much higher rate of dissolution.[12]
- Solid dispersion: The concept of solid dispersion was proposed by Sekiguchi & Obi. Solid dispersion is a useful pharmaceutical technique for enhance the rate of dissolution,

absorption & therapeutic efficacy of drugs. Solid dispersion term refers to a group of solid products generally consists a hydrophilic matrix & a hydrophobic drug. Commonly used hydrophilic carriers are polyethylene glycols, polyvinyl pyrrolidone, plasdone-S630. In the formation of solid dispersion surfactants are many times used.[13,14]

Example - Myrj-52, Tween-80, Sodium lauryl sulphate, Pluronic-F68 and Docusate sodium. This process was applied to halofantrine, celecoxib, ritonavir to increase the solubility. Techniques to prepare solid dispersion of hydrophobic drugs to enhance their aqueous solubility are following:

- Fusion process: In this process, carrier is heated above its melting point temperature and drug is incorporated into matrix with constant stirring mixture is cooled to disperse the drug throughout the matrix.[15]
- Solvent evaporation method: In a suitable organic solvent, carrier and active ingredient are dissolved. Solvent is evaporated at an elevated temperature under vacuum conditions to produce a solid residue.[16]

Commonly used solvents are chloroform, ethanol, or a mixture of dichloromethane and ethanol.

Advantages

- The thermal decomposition of drugs and carrier can be prevented.

Disadvantages

- Expensive
- Difficult to remove complete liquid solvent
- Difficult to find out common solvent

- Hot-melt extrusion: In polymer industry this method is commonly used. In hot melt extrusion method, the mixing of components is induced by extruder. Like fusion process, drug and carrier are immiscible. The drug/carrier combination is only exposed to an elevated temperature for about one minute with the hot melt extrusion method, which allows for the processing of drugs that are slightly thermolabile.[2,9]

IV. SOLUBILISATION BY SURFACTANTS

- Microemulsion: A microemulsion is an optically clear, transparent, thermodynamically stable, isotropic translucent system, contain a mixture of oil, surfactant and hydrophilic

solvent which dissolve a poorly aqueous soluble drug. HLB and non-toxicity are the parameters for selecting a surfactant. When the formulations come into contact with water, they self-emulsify, forming a highly clear emulsion of small, homogeneous oil droplets carrying the solubilized weakly soluble medication. Microemulsions have been used to improve the solubility of numerous medications that are nearly insoluble in water, as well as to incorporate proteins for oral, parenteral, and intravenous administration. The most suited formulation is an oil-in-water (o/w) microemulsion, which is intended to enhance solubility by dissolving molecules with low water solubility into an oil phase solubility.[17,18]

Advantages

- Drug release from well-developed microemulsion pre-concentrates is usually not dependent on digestion. As a result, without the need for meal co-administration, optimum bioavailability and repeatability can be expected.[19]

Disadvantages

- Validation becomes more difficult for formulations with several components.[20]
- Self-emulsifying drug delivery system: The mixture of oil, surfactant, co-surfactant, and one or more hydrophilic solvents in the absence of an external phase (water) and the cosolvent produce a clear isotropic solution. The self-emulsifying solution is a type of solution that has the ability to emulsify itself. Some researchers have also called it "microemulsion pre-concentrate." When taken orally, these new colloidal compositions behave like oil-in-water microemulsions.[21,22]

V. COMPLEXATION

Drugs have been complexed with cyclodextrins to improve water solubility and drug stability. In pharmaceutical formulations, the most often used β-cyclodextrin derivatives with improved water solubility are utilised. Because cyclodextrins are big molecules with molecular weights larger than 1000 Da, they are unlikely to penetrate the skin easily. Skin penetration has been reported to increase and decrease as a result of cyclodextrin complexation. CDs can also be utilised as membrane permeability enhancers and stabilising agents in addition to their solubility enhancement application. The presence of cyclodextrins improves permeability through biological membranes. In pulmonary drug delivery systems, CDs can also be used as a permeability enhancer.[23]

2. Chemical modification

I. HYDROTROPHY

Hydrotrophy is a solubilization process in which a high amount of a second solute is added to increase the aqueous solubility of a third solute. The method by which it improves solubility is more directly associated with complexation, which involves a weak contact between hydrotropic agents such as sodium alginate, sodium acetate, sodium benzoate, urea and poorly soluble drugs. The "salting in" of non-electrolytes known as "hydrotropic salts" is caused by many salts with large anions or cations that are themselves extremely soluble in water, a process known as "hydrotropism." Hydrotropic solutions are non-colloid and have a weak contact between the hydrotropic agent and the solute.[24,25]

Advantages

- Hydrotrophy has a high selectivity and doesn't require emulsification, and its solvent nature is independent of pH
- It does not need the use of organic solvents, or the preparation of an emulsion system.[26]

II. CO-SOLVENCY

Co-solvency is a mixture of one or more miscible liquids used to improve the solubility of drugs. The addition of a co-solvent solution can improve the solution's solubility and miscibility, as well as its dissolution. In comparison to the simple drugs, the co-solvent enhanced the low solubility drug by almost a thousand times.[27] A co-solvent technique may be appropriate for poorly soluble lipophilic or highly crystalline molecules with a high solubility in the solvent mixture. Because of the low toxicity of many co-solvents and their relative ability to solubilize nonpolar pharmaceuticals, it has primarily been used in parenteral dosage forms. To lower the solvent content before administration, parenteral formulations may require the addition of water or a dilution step using an aqueous media. To improve the solubility of weakly soluble substances, co-solvents can be coupled with various solubilization procedures and pH adjustments.[28] The use of co-solvents to improve the solubility of poorly soluble pharmaceuticals is a very useful strategy. Propylene glycol, ethanol, glycerin, and polyethylene glycol are the most common low-toxicity cosolvents used in parenteral administration. Because of their considerable solubilization capacity for poorly soluble drugs and their comparatively low toxicity, dimethyl sulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely employed as cosolvents.[29]

Advantages

- It is easy to formulate, produce, and evaluate, and it has a high solubilization capability for poorly soluble medicines.

Disadvantages

- Toxicity and tolerability in relation to the amount of solvent used must be taken into account
- The chemical stability of the insoluble substance is worse than in a crystalline state, as it is with all solubilized forms.[30]

III. NANOTECHNOLOGY

The study and use of materials and structures at the nanoscale level of around 100 nanometres (nm) or less is referred to as nanotechnology. Oral bioavailability increase via Micronization is insufficient for many new chemical entities with limited solubility because micronized products have a relatively small effective surface area for dissolving, hence the next stage was nanonization.[31]

Advantages

- It leads to the development of nano or micro sized spherical particles with smooth surfaces, narrow particle size distributions, and large specific surface areas, which increases the dissolving rate and solubility.[32]

Disadvantages

- The problem of agglomeration is basic and difficult to resolve.[33]

IV. SALT FORMATION

Improvements in drug solubility and dissolution are achieved via salt generation techniques. This method is used to observe the effects of various drugs or chemical reactions. When a medication is ionised, salt is produced. It works effectively in parenteral and other liquid dose forms, as well as solid dosage forms. Between 1995 and 2006, the FDA approved over 300 novel chemical entities for marketing, 120 of which were salt forms. Furthermore, hydrochloric acid was used to produce 54 of the 101 approved salts of basic drugs, showing that the hydrochloride salt form was the most common. The acidic or basic drugs water solubility as a function of pH determines whether the chemical will form acceptable salts. It uses several methods, such as physiochemical properties, to alter the drug's stability,

bioavailability, purity, and manufacturability. For many years, salt production of low soluble medication candidates has been used to improve solubility.[34] Examples- Aspirin, Barbiturates, Theophylline etc. Progesterone, a water-insoluble steroid that is soluble in peanut oil, is a commercially accessible example of this method.[35]

3. pH adjustment

A drug that is poorly water soluble may be able to dissolve in water if the pH is changed. The buffer capacity and tolerability of the chosen pH must be considered when obtaining solubility using this method.[36] Excipients that increase the pH of the environment within the dosage form to a level higher than the pKa of weekly acidic pharmaceuticals increase the drug's solubility; excipients that function as alkalizing agents may increase the solubility of weekly basic drugs. It can be used on crystalline and lipophilic poorly soluble substances as well.[37]

Advantages

- Formulation and analysis both are simple
- Small amounts of chemical are used, making it ideal for high-throughput testing.[38]

Disadvantages

- Tolerance and toxicity (both local and systemic) associated with non-physiological pH and extreme pH
- When diluted in aqueous fluid with a pH lower than the compound's solubility, there is a chance of precipitation. This can create emboli intravenously, and it can also cause variability when taken orally.[39]

4. Supercritical fluid process

With the critical point of carbon dioxide, supercritical fluids (SCFs) can dissolve non-volatile solvents. Above its critical temperature and pressure, a SCF exists as a single phase. It is safe, eco-friendly, and cost-effective. SCFs are appealing for pharmacological research because of their low operating conditions (temperature and pressure). SCFs have qualities that are advantageous in product processing since they are intermediate between pure liquid and pure gas. Furthermore, near the critical points, slight changes in operating temperature, pressure, or both affect density, transport qualities (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity). Carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water are all common

supercritical solvents. Precipitation with compressed antisolvents process (PCA), Gas Antisolvent Recrystallization, Rapid Expansion of Supercritical Solutions, Precipitation with Impregnation or infusion of polymers with bioactive materials, Gas Antisolvent Recrystallization, Solution enhanced Dispersion by Supercritical Fluid, Compressed Fluid Antisolvent, solution enhanced dispersion by SCF (SEDS), and aerosol based SCF processing have all been developed to address individual aspects of these shortcomings.[40,41]

Advantages

- The drug particles can be recrystallized at much smaller particle sizes once they've been solubilized in SCF. Current SCF techniques have showed the ability to produce nano suspensions with particle diameters ranging from 5-2,000nm
- SCFs are interesting for pharmacological research because of their low operating conditions (temperature and pressure)
- SCF methods allow drug particles to be micronized within limited particle size ranges, typically to sub-micron levels, due to their flexibility and precision.[42]

5. Liquisolid methods

When a drug dissolved in a liquid vehicle is introduced into a carrier material with a porous surface and fibres in its interior, such as cellulose, both absorption and adsorption occur; that is, the liquid is initially absorbed in the interior of the particles and is captured by its internal structure, and after this process has reached saturation, the liquid is adsorption onto the internal and external surfaces of the porous carrier particles. By blending a liquid medication with specified powder excipients such as the carrier and coating material, a liquid medication can be turned into a dry, non-adherent, free-flowing, compressible powder. Coating materials include microcrystalline and amorphous cellulose and silica powders.[43,44]

Advantages

- A variety of medications that are poorly soluble can be formulated into the system
- In comparison to the creation of soft gelatine capsules, the cost of production is minimal
- Allows liquid drugs to be pulverised in a flowable and compressible manner
- This method is useful in the manufacture of greasy and liquid drugs
- The method improves the solubility and bioavailability of orally administered water insoluble and can be used in the industry
- This technique is required for powdered liquid pharmaceuticals only.[45]

Disadvantages

- It is not suitable to insoluble medicines with high doses (>100 mg)
- It necessitates recipients with high specific surface area and adsorption characteristics.[46]

CONCLUSION

We conclude in this review paper 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.

CONFLICT OF INTEREST

None declared.

FUNDING

None.

REFERENCES

1. Vemula VR, Lagishetty V, Lingala S. Solubility Enhancement Techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41-51.
2. Kshirsagar S, Choudhari M, Sathyan R, Dhore S. Solubility Enhancement by Various Techniques based on Pharmaceutical and Medicinal Chemistry Approach: An Overview. Asian Journal of Pharmacy and Technology, 2019; 9(2): 141-146.
3. Yasir M, Asif M, Kumar A, Aggarval A. Biopharmaceutical Classification System: An Account. International Journal of PharmTech Research, 2010; 2(3): 1681-1690.
4. Cook J, Addicks W, Wu YH. Application of the Biopharmaceutical Classification System in Clinical Drug Development—An Industrial View. The AAPS Journal, 2008; 10(2): 306-310.
5. Brahmankar DM, Jaiswal SB, Biopharmaceutics and Pharmacokinetics, 2009; 349-357.

6. Sharma D. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A review. Asian Journal of Pharmaceutics, 2016; 1(1).
7. Loh ZH, Samanta AK, Heng PWS. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian journal of pharmaceutical sciences, 2015; 10(4): 255-274.
8. Kasimedu S, Thoppani SR, Pommala N, Orugonda G, Yelamanda J. A Review on Solubility Enhancement Techniques. J. Compr. Pharma, 2015; 2(2): 36-41.
9. Singh N, Allawadi D, Singh S, Arora S. Techniques for Bioavailability Enhancement of BCS Class II Drugs: A Review. International Journal of Pharmaceutical and Chemical Sciences, 2013; 2(2): 1092-1101.
10. Sunder S, Nair R. Methods of nanonization of drugs for enhancing their dissolution. Eur J Adv Eng Technol, 2016; 3(8): 101-110.
11. Shah R, Eldridge D, Palombo E, Harding I. Introduction Lipid Nanoparticles: Production, Characterization and Stability, Springer, 2015; 960: 1–7.
12. Kim KN, Son JH, Kim HS. Solution solubilization composition of insoluble material and method for solubilizing insoluble material using same. Google Patents. 2019.
13. Veni DK, Gupta NV. Development and evaluation of Eudragit coated environmental sensitive solid lipid nanoparticles using central composite design module for enhancement of oral bioavailability of linagliptin. Int. J. Polym. Mater. Polym. Biomater, 2020; 69: 407–418.
14. Mohit, Hussain MS. A Brief Review on Buccal Drug Delivery System: Advantages, Limitations, and Impact on Healthcare system. World Journal of Pharmaceutical Research, 2021; 10(5): 558-576.
15. Patel BB, Patel JK, Chakraborty S, Shukla D. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharmaceutical Journal, 2015; 23(4): 352-365.
16. Donnell PB, McGinity JW. Preparation of microspheres by the solvent evaporation technique. Advanced Drug Delivery Reviews, 1997; 28(1): 25-42.
17. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews, 2000; 45: 89-121.
18. Hussain MS, Mohit, Kaur G, Pamma P. Overview of Controlled Drug Delivery System. Advances in Bioresearch, 2021; 12(3): 248-255.
19. Acharya DP, Hartley PG. Progress in microemulsion characterization. Current Opinion in Colloid & Interface Science, 2012; 17(5): 274-280.

20. Tehrani-Bagha A, Holmberg K, Solubilization of Hydrophobic Dyes in Surfactant Solutions. Materials, 2013; 6(2): 580-608.
21. Gursoy RN, Benita S. Self-Emulsifying Drug Delivery Systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine & Pharmacotherapy, 2004; 58: 173–182.
22. Nigade PM, Patil SL, Tiwari SS. Self-Emulsifying Drug Delivery Systems (SEDDS): A Review. International Journal of Pharmacy and Biological Sciences, 2012; 2(2): 42-52.
23. Dhapte V and Mehta P. Advances in Hydrotropic Solutions: An Updated Review. St. Petersburg Polytechnical University Journal: Physics and Mathematics, 2015; 1: 424-435.
24. Nidhi K, Indrajeet S, Khushboo M, Gauri K, Sen DJ. Hydrotropy: A Promising tool for solubility Enhancement. International Journal of Drug Development & Research, 2011; 3(2): 26-33.
25. Yadav NK, Shukla T, Upmanyu N, Pandey SP, Khan MA. Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate. Journal of Drug Delivery and Therapeutics, 2018; 8(5): 481-488.
26. Kadam SV, Shinkar DM, Saudagar RB. Review on solubility enhancement techniques. International Journal of Pharmacy and Biological Sciences, 2013; 3(3): 462-575.
27. Doke VV, Kunwarpuriya AS, Gupta K, Khutle NM. Co-Solvency and Anti-Solvent Method for The Solubility Enhancement: An Overview. World Journal of Pharmaceutical Research, 2020; 9(5): 584-600.
28. 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.
29. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41–51.
30. Patel MSN, Ahmed MH, Saqib M, Shaikh SN. Chemical Modification: A unique solutions to Solubility problem. Journal of Drug Delivery and Therapeutics, 2019; 9(2): 542-546.
31. Kataria T, Hussain MS, Kaur G, Deb A. Emerging Nanoparticles in the Diagnosis of Atherosclerosis. International Journal of Pharmaceutical Sciences Review and Research, 2021; 70(2): 46-57.
32. Sarangi M, Padhi S. Solid Lipid Nanoparticles A Review. Journal of Critical Reviews, 2016; 3(3): 5-12.
33. Hussain MS. Nanotoxicology: Nano toxicity in humans. Academia Letters, 2021; 4331.

34. Desale SL, Deshmukh AS and Mahajan VR. Solubility enhancement of poorly water-soluble drug Fenofibrate by inclusion complex. World Journal of Pharmacological Research and Technology, 2015; 4(3): 242-255.
35. Karmarkar AB. Effect of Ceolus KG-802 on the dissolution rate of fenofibrate liquisolid tablets: Preformulation and formulation development studies. Drug Discov. Ther., 2010; 4: 493-498.
36. Zhu LG, Brewer MS. Effects of pH and temperature on metmyoglobin solubility in a model system. Meat Science, 2002; 61(4): 419-424.
37. Young OA, Zhang SX, Farouk MM, Podmore C. Effects of pH adjustment with phosphates on attributes and functionalities of normal and high pH beef. Meat Science, 2005; 70: 133-139.
38. Graham H, McMorland M, Joanne D, Wayne K, Peggy LE, James EA, et al. Effect of pH-adjustment of bupivacaine on onset and duration of epidural analgesia in parturients. Canadian Journal of Anaesthetics, 1986; 33(5): 537-541.
39. Jain A, Ran Y, Yalkowsky SH. Effect of pH-Sodium Lauryl Sulfate combination on solubilization of PG300995 (an Anti-HIV Agent), AAPS PharmSciTech., 2004; 5(3): 45-48.
40. Campardelli R, Baldino L, Reverchon E. Supercritical fluids applications in nanomedicine. J. Supercrit. Fluids, 2015; 101: 193–214.
41. Brunner G. Applications of Supercritical Fluids. Annual Review of Chemical and Biomolecular Engineering, 2010; 1: 321-342.
42. Campardelli R, Baldino L, Reverchon A. Supercritical fluids applications in nanomedicine. The Journal of Supercritical Fluids, 2015; 101: 193-214.
43. Burra S, Yamsani M, Vobalaboina V. The Liquisolid technique: an overview. Brazilian Journal of Pharmaceutical Sciences, 2011; 7(3): 475-482.
44. Javadzadeh Y, Jafari-Navipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water – insoluble drug (carbamazepine). Int. J. Pharm., 2007; 341: 26-34.
45. Kulkarni AS, Aloorkar NH, Mane MS, Gaja JB. Liquisolid Systems: A Review. International Journal of Pharmaceutical Sciences and Nanotechnology, 2010; 3(1): 795-802.
46. Lu M, Xing H, Jiang J, Chen X, Yang T, Wang D, et al. Liquisolid technique and its applications in pharmaceutics. Asian Journal of Pharmaceutical Sciences, 2017; 12: 115-123.