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SOLUBILITY ENHANCEMENT TECHNIQUES OF POORLY WATER-SOLUBLE DRUGS.

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ABSTRACT

Solubility plays an important role when converting any chemical entity to formulation. It is an important parameter to achieve higher bioavailability. Solubility is ultimately affecting the pharmacological activity of drugs. The major challenge with the design of oral dosage forms lies in their poor solubility. The drugs that come under the BCS class II show less solubility in water. This review attempts to encompass the available literature on techniques used to enhance the solubility of poorly water-soluble drugs that come under BCS class II.

Key Words: - Solubility, Solubilization techniques, Permeability, Absorption.

INTRODUCTION [1-2]

Solubility is one of the important parameters to achieve the desired drug concentration in systematic circulation for a pharmacological response. Poor aqueous solubility of lipophilic drugs creates problems in formulation and oral administration. The important phenomenon and as most of the time discussed but a still or not completely resolved issue, solubility enhancement technique remains a most challenging field for the researchers in the formulation design and developmental processes i.e. solubility and dissolution. A few methodologies are adopted to improve the solubility of poorly water-soluble drugs and to improve their bioavailability. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities. The aqueous solubility of the drug plays an important role in drug absorption after oral administration. About 35% of drugs fail to reach the market because of their poor water solubility resulting in poor bioavailability. Because of this reason, solubility is important to increase the therapeutic effectiveness, to attain maximum utility in newly developed drugs.

SOLUBILITY:[3]

The degree to which a substance dissolves in a solvent to make a solution. It is usually expressed as grams of solute per liter of solvent. Currently, only 8% of new drug candidates have high solubility and permeability. Solubility can also be defined as the ability of one substance to form a solution with another substance. In other words, the solubility of solute is the maximum quantity of solute that can be dissolved in a certain quantity of solvent or specified temperature definitions for different solubility terms are given in Table No.01.

IMPORTANCE OF SOLUBILITY: [4]

The most convenient and commonly employed route of drug delivery is the oral route due to its advantages such as ease of administration, high patient compliance, cost-effectiveness, least sterility constraint, and flexibility in the design of dosage form. The major challenge with the design of oral dosage forms lies in their poor solubility. The main cause for low bioavailability is attributed to poor solubility and permeability. The solution is an important aspect for another dosage form like parenteral.

Table 1: B.P. and U.S.P. Solubility Criteria

Descriptive Term	Part of the solvent required per part of the solute
Very Soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

BCS Classification: [5-6]

The Biopharmaceutical Classification System was first developed in 1995 by Amidon & his colleagues. The Biopharmaceutical Classification System is a scientific framework for classifying a drug substance based on its aqueous solubility intestinal permeability and dissolution rate. The BCS is a scientific method that analyzes pharmaceutical substances based on their capacity to dissolve in water and pass through the intestinal lining.

Factor Affecting on BCS Class

I. Solubility
II. Permeability
III. Dissolution

Table No.02. Drug substances are classified based on solubility and permeability.

CLASS	SOLUBILITY	PERMEABILITY	EXAMPLE
Class –I	High	High	Metoprolol, Propranolol, Chloroquine
Class –II	Low	High	Nifedipine, Phenytoin, Ketoconazole
Class –III	High	Low	Cimetidine, Metformin, Captopril
Class -IV	Low	Low	Taxol, Clorthiazole, Furosemide

CLASS -II

- Oral route for administration.
- Drugs are ingested rapidly.
- The drug dissolved slowly.

CLASS -IV

- Poorly absorbed by oral administration.
- Both solubility & permeability limitations.
- The dissolution rate is low.
- Low therapeutic action.

PROCESS OF SOLUBILIZATION: [7-15]

The process of solubilization involves the breaking of inter-ionic or inter-molecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute and interaction between the solvent and the solute molecule or ion.

- The holes get open in the solvent.
- The molecules of the solid start to break down away from the bulk.
- The free solid molecule in the solvent gets integrated into the hole.

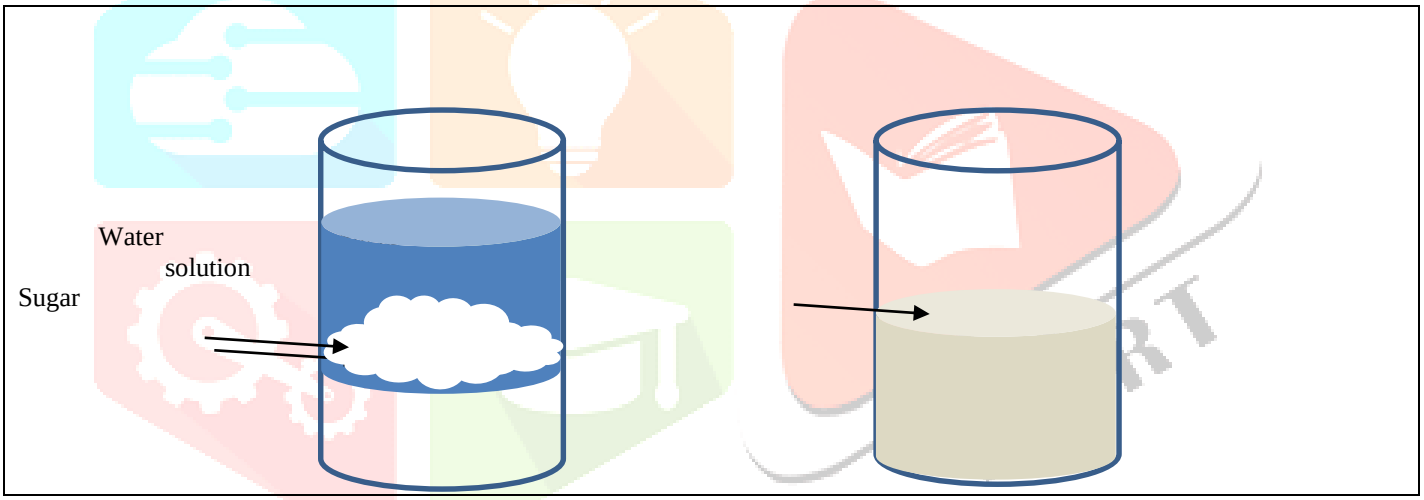

Fig No.01. Dissolving of sugar in water

The solubilization process occurs in three steps.
Step I: Holes open in the solvent.
Step II: Molecules of the solid breaks away from the bulk.
Step III: The free solid molecule is integrated into the hole in the solvent.

Factor Affecting on Solubility of Poorly Water-Soluble Drugs:

I. Temperature
II. Molecular structure of solute
III. Nature of solvent
IV. Crystal characteristics
V. Particle size of the solid
VI. pH
VII. Complex formation
VIII. Solubilizing agent
IX. Polarity
X. Pressure
XI. Polymorphous

I. Temperature

The solubility of a solid in a liquid depends on temperature. In the process of solution, if heat is absorbed, the solubility of the solute rises with a temperature rise. In the case of most of the salts. If a solute gives off heat during the process of solution, the solubility of the solute will decrease with an increase in temperature.

II. Particle size of the solid

The particle size of the solid affects the solubility because, with a decrease in particle size, the surface area of the volume ratio increases. The large surface area of the solute molecule allows more interaction with the solvent. The effect of particle size on solubility can be described.

III. pH

pH of a substance is related to its pKa and concentration of ionized and unionized form of the substance.
It is shown by the given equation,

$$pH = pKa + \log [A^-/HA]$$

Were,

pKa = Dissociation rate constant.

If the substance is brought outside its pKa (pH value where half of the substance is ionized and unionized), the solubility will be changed because of the introduction of new intermolecular forces, mainly ionic attraction forces.

IV. Polarity

The 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. 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.

V. Pressure

Pressure has a different effect on the solubility of gaseous, solids, and liquid solutes. For solids and liquid solutes, changes in pressure almost do not affect solubility. On the other hand, when pressure in gaseous solutes increases, their solubility increases.

VI. Nature of Solvent

The Solubility of a solute in a solvent depends on the nature of the solute and the solvent. The polarity of the solute and the polarity of the solvent affect the solubility. Example: Polar solvents dissolve polar solutes whereas nonpolar solvents do the same.

VII. Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angle between the faces is always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. The capacity for a substance to crystallize in more than one crystalline form is polymorphism.

METHOD OF SOLUBILIZATION: [16-31]

Although water is widely used as a solvent in pharmaceutical preparations, it may not be possible to ensure complete solubility of all ingredients at all normal storage temperatures.

Strongly ionized materials are likely to be freely soluble in water over a wide pH range. Similarly, weak acids and bases should be adequately soluble at favorable pH.

Various techniques are available to improve the solubility of poorly water-soluble drugs. These techniques can be categorized into three basic approaches are as follows,

I. Traditional techniques.
II. Novel or Newer techniques.
III. Solid dispersion technique.

Table No.03.Techniques of solubility enhancement.

Traditional Techniques		
Hydrotropic	Use of solvent	Micronization
Change in the dielectric constant of the solvent	Nano-suspension	Constant of solvent
Chemical modification of drug	Use of surfactants	Alteration of pH of the solvent
Evaporative precipitation in aq. Solution.	Selective adsorption on insoluble carriers	Solvent precipitation,
Solvent deposition	Use of precipitation inhibitors	Controlled precipitation technology
Co-solvency	Functional polymer technology	Application of ultrasonic waves
Amorphous form	Use of hydrates	Solubilization
Novel Techniques		
Size reduction technology	Nanoparticle technology	Nano-crystal technology
Nano-suspension technology	Cryogenic technology	Supercritical technology
Micellar solubilization	Mixed Micelle	Polymeric Micelle
Porous micro-particle technology	Non-Aqueous solution	Complexation
Solid Dispersion Techniques		
Eutectics	Amorphous Precipitate	Crystallization
Solid solution	Glass solution	Microemulsion technology

I. Traditional techniques

A. Co-solvency

Vehicles used in combination to increase the solubility of a drug are called co-solvents. The solubility of weak electrolytes or non-polar compounds in water can often be improved by altering the polarity of the solvent. This can be achieved by the addition of another solvent that is miscible with water and in which the compound is also soluble and often the solubility in this mixed system is greater than can be predicted from the material's solubility in each solvent.

For example: a blend of propylene glycol and water is used to improve the solubility of co-trimoxazole, and paracetamol is formulated as an elixir using alcohol, propylene glycol, and syrup.

Advantages:

- It is a simple and rapid method to formulate and produce.
- No need for expensive pharmaceutical technology for the formulation of a dosage form.

Disadvantages:

- Toxic effect on renal, central as well as cell lysis, and local tissue irritation.
- As with all excipients, the toxicity and tolerability related to the level of solvent administered must be considered.

B. pH control

Many drugs are either weak acids or weak bases, and therefore their solubilities in water can be influenced by the pH of the system. The solubility of a weak base can be increased by lowering the pH of the solution, whereas the solubility of a weak acid is improved by an increase in pH. In controlling the solubility of a drug in this way, it must be ensured that the chosen pH does not affect the other product requirements.

Example: Phenytoin injection 50mg/ml with propylene glycol 40% and ethanol 10%.

Advantages:

- Simple to formulate and analyze.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluation.

Disadvantages:

- Tolerability and toxicity related to the use of non-physiological pH and extreme pH.

C. Hydrotropy method

Hydrotropy is a solubilization process whereby the addition of a large amount of a second solute increases the aqueous solubility of another. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in each solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "Hydrotropism".

Example: The solubility of Rofecoxib was enhanced by using hydrotropes such as urea and nicotinamide.

Advantages:

- Less toxic compared to other organic solvent.
- Facile recovery of the solute from hydrotrope solutions by simple dilution.
- For solubility of poorly water-soluble drugs mixed hydrotropy have a synergistic effect on the solubility of the substance.

Disadvantages

- There are chances of a weak interaction between the hydrotropic agent and drugs. As there is the use of water as a solvent, complete removal of water cannot be achieved.
- The use of hydro-tropes is limited for some hydrotropic agents because of toxicity.

D. Solvent deposition:

Reduction of particle size remains the accepted method for increasing dissolution rates.

However, upon micronization, hydrophobic drugs tend to form clumps when exposed to the dissolution medium.

Sekiguchi and Obi proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water-soluble carriers would increase the dissolution rate and absorption of the drug.

Example: The poorly aqueous soluble drug such as Nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch.

Advantages:

- Uses small quantities of compound.
- Simple to produce.
- Simple to analyze.

Disadvantages:

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity (local and systemic) related to the use of a non-physiological pH and extreme pH.

II. Novel or Newer Techniques

A. Size reduction technology

The size and shape of very small particles, if less than 1 micrometer diameter, can affect their solubility. As particle size decreases solubility will increase and molecular dispersions of drugs in solid/solid solutions can exhibit improved availability due to the increase in solubility of the dispersed drug.[17] The bioavailability is intrinsically related to drug particle size. Particle size reduction is done by milling techniques using a jet mill, rotor-stator colloid mills, etc.

Advantages:

- Typically, low excipient-to-drug ratios are required.
- A method to consider for stubborn compounds that defeat previous attempts to increase solubility.
- Generally, crystal forms are chemically and physically more stable than amorphous particles.

Disadvantages:
- Technically, the development of sterile intravenous formulations is even more challenging.
- Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.

B. Supercritical technology

Another novel nanosizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid technology. Supercritical fluids are fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp), allowing them to assume the properties of both a liquid and a gas. Commonly used supercritical solvents are carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water.

Advantages:
- The low operating conditions (temperature and pressure) make supercritical fluids attractive for pharmaceutical research.
- The flexibility and precision offered by supercritical fluid processes allow micronization of drug particles within narrow ranges of particle size, often to sub-micron levels.

Disadvantages:
- Lack of standard extraction procedure.
- Difficulties in extracting polar compounds.
- Inefficiency in cleaning.

C. Nano-suspension

A pharmaceutical nano-suspension is a biphasic system made up of drug particles that are nano in size and stabilized by a surfactant. It is intended for either oral and topical application or parental and pulmonary delivery. Having particles that range in size from 200 to 600 nanometers on average, solid particles in nano-suspensions typically have a particle size distribution of less than 1 micron.

There are two methods for the preparation of nano-suspension:

1. Bottom-up technology
2. Top-down technology

Advantages
- Use of simple and low-cost equipment.
- Large scale is possible to some extent.
- Higher saturation solubility is the advantage for precipitation compared to other methods of nano-suspension preparation.

Disadvantages
- The solvent needs to be miscible with at least one non-solvent.
- Solvent residues need to be removed, thus increasing production costs.
- The duration of the process not being very production friendly.
- Potential growth of germs in the water phase when milling for a long time.

D. Micellar solubilization

The micellar solubilization approach is because surfactants, owing to their amphiphilic nature, associate spontaneously in anisotropic clusters known as 'micelles.' These contain a hydrophobic center and hydrophilic surfaces. Poorly soluble or water-insoluble drugs are enclosed in the hydrophobic centers of micelles and thus become solubilized. It is noteworthy that the association or aggregation of surfactant molecules occurs at a particular concentration called the 'critical micelle concentration' (CMC). The lower the CMC value of a particular surfactant, the more stable a micelle is formed.

Examples: Repaglinide, rosiglitazone, glyburide, and glimepiride.

Advantages
- Increase drug loading.
- Increase penetration.
- Targeted drug delivery.
- Improve the dissolution of the lipophilic drug in aqueous medium.

Disadvantages
- High concentration of surfactant, making them unsuitable for intravenous administration.
- Sometimes precipitation may occur.
- Mixed micelles may have a bad test.

III. Solid dispersion techniques

A. Eutectics:

This mixture is composed of two compounds in the liquid state that are completely miscible but in the solid state only to a very limited extent. It is prepared through fat solidification of the fused melt of the two components, giving a complete liquid miscible product and very little solid-solid solubility. Such a system is thermodynamically intimately mixed with the physical mixture of its two crystalline compounds.

B. Solid solutions

Depending on the miscibility the two types of discontinuous solid solutions and continuous solid solutions. In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the components is stronger than the bonding between the individual components. Discontinuous solid solutions in discontinuous solid solutions, the solubility of each of the components in the other component is limited in nature.

Conclusion

The present review shows that various techniques are used to enhance the solubility of poorly water-soluble drugs. Solubility is a rate-determining step for oral absorption of poorly water-soluble drugs. It further shows the number of techniques with their process and concerns their increased systemic availability of drugs. Newer techniques are mentioned in the review they significantly enhance the solubility of poorly water-soluble drugs.

References

1. Deshmukh, A. S., Tiwari, K. J., & Mahajan, V. R. (2017). Solubility enhancement techniques for poorly water-soluble drugs. Int. J. Pharm. Sci. Nanotechnol, 10(8).
2. Mahapatra, A. P., Patil, V., & Patil, R. (2020). Solubility enhancement of poorly soluble drugs by using novel techniques: A comprehensive review. Int J Pharm Tech Res, 13(2), 80-93.
3. Bhamare, V., Joshi, R., & Amrutkar, R. (2021). Solubility enhancement of BCS class II drugs. International Journal of Pharmaceutical Science and Research, 12(9), 5057-5064.
4. Kovvasu, S. P. (2018). Cyclodextrins and their application in enhancing the solubility, dissolution rate and bioavailability. Innoriginal: International Journal of
Sciences, 25-34.
5.Chavda, H., Patel, C., & Anand, I. (2010). Biopharmaceutics classification system. Systematic reviews in pharmacy, 1(1), 62.
6. Bajpai, Y. K., Singh, S., Bisht, V., Butola, K., Awasthi, A., & Kumar, S. (2022). BCS Class II Drug & Its Solubility Enhancement: A Review. Journal for Research in Applied Sciences and Biotechnology, 1(5), 48-58.
7.Kolhe, S, Chipade, M., & Chaudhari, P. D. (2012). Solubility and Solubilization Techniques-A Review. International journal of pharmaceutical and chemical sciences, 1(1), 129-150.
8. Pote, S. V., Bavaskar, K., & Jain, A. (2022). Solubility enhancement of poorly soluble drug by using different techniques.
9. Kaur, A., Prasad, D. N., Dua, J. S., Menra, M., & Sharma, N. (2016). ASPECTS OF SOLUBILISATION: A REVIEW. World Journal of Pharmaceutical Research, 5(6), 741-758.
10. Behera, A. L., Sahoo, S. K., & Patil, S. V. (2010). Enhancement of solubility: A pharmaceutical overview. Der Pharmacia Lettre, 2(2), 310-318.
11. Patil, S. K., Wagh, K. S., Parik, V. B., Akarte, A. M., & Baviskar, D. T. (2011). Strategies for solubility enhancement of poorly soluble drugs. Int J Pharm Sci Rev Res, 8(2), 74-80.
12. Shah, P., Goodyear, B., & Michniak-Kohn, B. B. (2017). A review: Enhancement of solubility and oral bioavailability of poorly soluble drugs. Adv Pharm J, 2(5), 161-173.
13. Krishna Shailaja, M. Usha, P. Sankeerthana, R. Jaya Sri, S. Niharika and S. Madhuri (2023), Review on Solubility Enhancement Techniques for Poorly Soluble Drugs, J. Pharmaceutics and Pharmacology Research, 6(3); DOI:10.31579/ 2693-7247/126.
14. Kshirsagar, S., Choudhari, M., Sathyan, R., & Dhore, S. (2019). Solubility enhancement by various techniques based on pharmaceutical and medicinal chemistry approach: an overview. Asian Journal of Pharmacy and Technology, 9(2), 141-146.
15. Gupta, J., & Devi, A. (2019). Solubility enhancement techniques for poorly soluble pharmaceuticals: a review. Indian Journal of Pharmaceutical and Biological Research, 7(02), 09-16.
16. Singh, N., Allawadi, D., Singh, S., & Arora, S. S. (2013). Techniques for bioavailability enhancement of BCS class II drugs: a review. International Journal of Pharmaceutical and Chemical Sciences, 2(2), 1092-1101.
17. Dixit, G. R.,Upadhye, K. P., Bakhle, S. S. (2019). Solubility enhancement techniques: Pharmaceutics-I, VBD Publication, of Technical Pharmacy Series (TPS), 179-184.
18. Doke, V. V., Kunwarpuriya, A. S., Gupta, K., & Khutle, N. M. (2020). Co-Solvency and Anti-Solvent Method for The Solubility Enhancement: An Overview. World Journal of Pharmaceutical Research, 9(5), 584-600.
19. Vemula, V. R., Lagishetty, V., & Lingala, S. (2010). Solubility enhancement techniques. International journal of pharmaceutical sciences review and research, 5(1), 41-51.
20. Namdev, B., Venkatachalam, S., Jawahar, N., & Chorsiya, A. (2022). A Brief Review on Solubility Enhancement Technique: Hydrotropy. Indian Journal of Pharmaceutical Education and Research, 56(2), 347-355.
21. Sikarra, D., Shukla, V., Kharia, A. A., & Chatterjee, D. P. (2012). Techniques for solubility enhancement of poorly soluble drugs: an overview. JMPAS, 1, 1-22.
22. Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: importance and enhancement techniques. International Scholarly Research Notices, 2012.
23. Jagtap, S., Magdum, C., Jadge, D., & Jagtap, R. (2018). Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research, 10(9), 2205-2211.
24. Bin, L. K., Janakiraman, A. K., Abd Razak, F. S., Uddin, A. H., Sarker, M. Z. I., Ming, L. C., & Goh, B. H. (2020). Supercritical fluid technology and its pharmaceutical applications: A revisit with two decades of progress. Indian J. Pharm. Educ. Res, 54, s1-s3.
25. Kumar, L. A., Pattnaik, G., Satapathy, B. S., Patro, C. S., Naik, S., & Dash, A. K. (2022). SOLUBILITY ENHANCEMENT TECHNIQUES: UPDATES AND PROSPECTIVES. Journal of Pharmaceutical Negative Results, 2847-2855.
26. Khandbahale, S. V. (2019). A review-Nanosuspension technology in drug delivery system. Asian Journal of Pharmaceutical Research, 9(2), 130-138.
27. Ansari, M. J. (2019). An overview of techniques for multifold enhancement in solubility of poorly soluble drugs. Curr. Issues Pharm. Med. Sci, 32(4), 203-209.
28. Guptaa, S. K., Guptaa, R. K., Pandeya, N. K., Singha, S. K., & Kumara, B. (2018). Solubility Enhancement Techniques: A Comparative Study.
29. Kumar, S., Dilbaghi, N., Saharan, R., & Bhanjana, G. (2012). Nanotechnology is an emerging tool for enhancing the solubility of poorly water-soluble drugs. Bionanoscience, 2, 227-250.
30. Malkawi, R., Malkawi, W. I., Al-Mahmoud, Y., & Tawalbeh, J. (2022). Current trends on solid dispersions: past, present, and future. Advances in Pharmacological and Pharmaceutical Sciences, 2022.
31. Sharma, K. S., Sahoo, J., Agrawal, S., & Kumari, A. (2019). Solid dispersions: A technology for improving bioavailability. J. anal. pharm. res, 8(4), 127-133.