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Solubility enhancement techniques: A comprehensive review

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Abstract

Solubility plays a crucial role whenever a drug's effectiveness depends on its ability to disperse homogeneously in the liquid phase. On the other hand, the majority of active pharmacological substances have low water solubility. One of the most important factors in the success of formulation development is the solubility of the drugs. A difficult challenge in drug development is improving the drug's solubility, dissolution rate and bioavailability; over 40% of novel chemical entities reported to date are poorly water-soluble medications. Despite having promising pharmacokinetic properties, a large number of innovative drugs are unable to enter the market because of poor water solubility. The aqueous solubility of a drug also affects the physical, chemical and dose stability; it sets a standard for purity, dissolution rate and extent of absorption; and it achieves the desired concentration of the drug in systemic circulation in order to achieve the required pharmacological response in the systemic circulation. In this review, solubilization techniques such as chemical modification, physical modification and other methods were discussed as they open up new pathways for the production of potent and marketable drugs in Pharmaceutical Industry.

Keywords: Absorption; Bioavailability; Dissolution; Dispersion; Solubilization techniques

1. Introduction

Poorly water-soluble drugs can benefit from a range of strategies to improve their solubilization and bioavailability. Solid dispersion, co-solvency, micronization, nanonization, chemical modification, hydrotropy, complexation, micellar solubilization, pH adjustment and other methods are mostly used for pharmaceutical solubilization. In Novel Chemical Entities (NCEs) screening investigations as well as formulation design and development, the solubilization of poorly soluble drugs is a frequent challenge.[1,2] The ultimate quantity of solute that may be completely dissolved in a volume of given solvent is known as solubility. It has both quantitative and qualitative characteristics. In qualitative term, it can be described 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 can be expressed as percentage, parts, molality, molarity, mole fraction and volume fraction. In pharmaceuticals, solubility equilibria are very important. The FDA introduced the Biopharmaceutical Classification System (BCS) which divides drugs into four classifications based on permeability and solubility (Table-1). Due to low solubility, Class II and IV of the system encounter dissolution as the rate limiting step for drug absorption.[3] Drugs of class II & class IV have solubility problem.[4,5] Therefore, increasing the solubility of BCS Class II & Class IV drugs also increases their bioavailability. [6]

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Table 1 Biopharmaceutical Classification System

Class	Solubility	Permeability	Absorption pattern
I	High	High	Well absorbed
II	Low	High	Variable
III	High	Low	Variable
IV	Low	Low	Poorly absorbed

2. Importance of solubility

Oral ingestion is the most convenient and most widely used method of drug delivery because of its ease of administration, high patient compliance, cost effectiveness, sterility restrictions and flexibility in dosage form design. Solubility is the essential rate limiting criterion for orally delivered drugs to acquire their required concentration in systemic circulation for pharmacological response. The two most frequent reasons for inadequate oral bioavailability are poor solubility and permeability. The poor bioavailability of oral dosage forms, on the other hand, is a major difficulty in their design. Therefore, for formulation scientists, the problem of solubility is a key concern.[7]

3. Process of solubilization:[8,9]

- Step 1- It involves the breaking of inter- ionic or intermolecular interactions in the solute, the separation of the interactions between the solvent and the solute molecule or ion.
- Step 2 - A solid molecule separates from the bulk.
- Step 3 - It involves integrating the feed of the solid molecule into the hole in the solvent.

4. Methods for solubility enhancement

Poor aqueous solubility is a serious issue, which is analogous to the formulation development of new chemical entities. Any drug that needs to be absorbed should be present in the form of an aqueous solution at the absorption site. For liquid dosage forms, water is the preferred solvent. The majority of drugs have limited aqueous solubility and are weakly basic and acidic. Solubility enhancement is essential since many drug's solubility impacts their bioavailability.[10,11] Several approaches, as shown in Figure 1, are now being used to improve solubility.

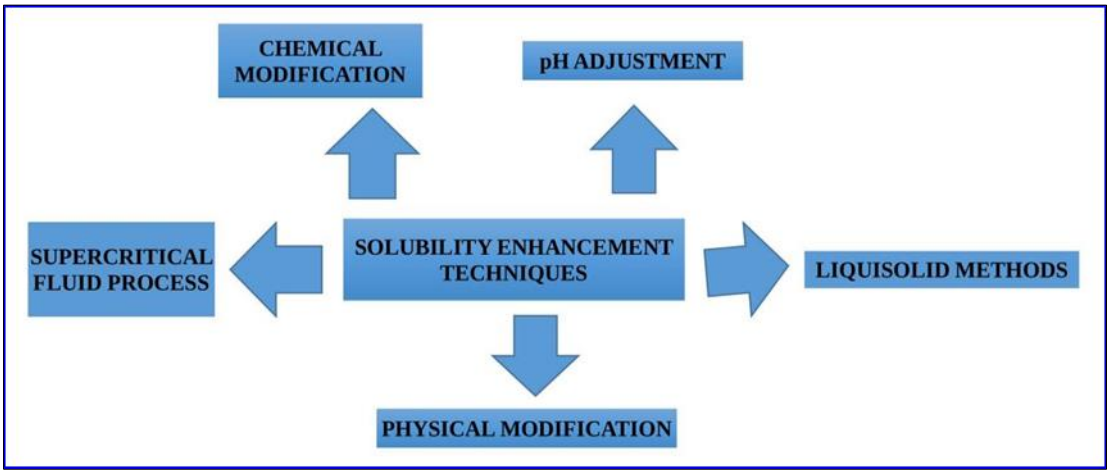

Figure 1 Solubility Enhancement Techniques

i. Physical modification

a) Particle Size Reduction
- Micronization
  Nano-suspension

b) Crystal Habit Modification
- Polymorphs
  Pseudo polymorphs

c) Drug Dispersion in Carrier
  Solid solutions
- Solid dispersions

d) Solubilization by Surfactants
- Microemulsion
- Self-micro emulsifying drug delivery system

e) Complexation

ii. Chemical Modification
- Hydrotrophy
- Co-solvency
- Nanotechnology
- Salt formation
- Co-crystallization

iii. pH adjustment

iv. Supercritical fluid process

V. Liquisolid methods

4.1. Physical modification

4.1.1. Particle Size Reduction

Micronization

A drug's particle size is intrinsically linked to its bioavailability. Increased surface area increases the dissolution properties of a drug by reducing its particle size. Micronization increases the dissolution rate of drugs through increased surface area. Micronization of drugs is done by milling techniques using jet mill, colloid mills, etc. It is inappropriate for drugs with high dosage numbers since it does not modify the drug's saturation solubility.[12] Nowadays, micronization and nano-suspension are the two methods used for reducing the particle size. Drug solubility in micronization is often inversely proportional to drug particle size.

Nanosuspension

This technique is used to dissolve drugs that are poorly soluble and insoluble in water and oils. Nanosuspension is a biphasic system composed of nanosized particles suspended in water. Surfactants stabilize the nano-sized medication particles for parenteral, pulmonary or oral delivery. The average particle size range in nanosuspension is between 200 and 600 nm and the particle size distribution of solid particles is often less than one micron. Various approaches for nanosuspension include Nanocrystals, Dissocubes, Nanopore and Nanoedge.[13]

4.1.2. Crystal Habit Modification

- Polymorphs
- Pseudo Polymorphs

The ability of a solid material to exist in two or more different crystalline forms with different crystal lattice arrangements is known as polymorphism. Different crystalline forms are called polymorphs. Phenomenon in which solvent molecules gets incorporated into crystal lattice of solid are known as solvates. This solvates exist in different crystal form called pseudopolymorphs and the phenomenon is called as pseudo polymorphism. Drugs that exist in crystalline form are chemically identical, but they differ physiochemically in terms of melting point, texture, density, solubility and stability. Similarly, an amorphous form of a drug is more suitable than a crystalline form due to its larger surface area and higher associated energy.[14] Order of different solid form of drugs is Amorphous > Metastable polymorphs > Stable polymorphs.

4.1.3. Drug Dispersion in Carrier

Solid Solutions

It is blend of two crystalline solids that exist as a new crystalline solid. The two components crystallise simultaneously in a homogeneous one-phase solution, resulting in a mixed crystal. As a result, it is expected to yield higher rates of dissolution than simple eutectic systems.[15]

Solid Dispersion

In the early 1960s, Sekiguchi and Obi initially proposed the idea of solid dispersions. The term "solid dispersion" refers to a group of solid products that are formed of at least two different parts, often a hydrophilic matrix and a hydrophobic drug.[11] It is a useful pharmaceutical approach for increasing the rate of drug absorption, solubility and therapeutic effectiveness. Polyvinyl pyrrolidone, plasdone S-630 and PEGs are mostly used as hydrophilic carriers. Surfactants are sometimes used during the solid dispersion formation process.[16,17] Examples include Docusate sodium, Myrj-52, Tween 80, Sodium lauryl sulphate and Pluronic F-68. Halofantrine, Celecoxib and Ritonavir also undergo this technique to improve their solubility. The following methods are used to prepare solid dispersion of hydrophobic drugs to increase their aqueous solubility:

Fusion Method

The first to suggest a melting method for preparing fast-release solid dispersion dosage forms were Sekiguchi and Obi in 1961. This method involves heating the carrier above its melting point while mixing the drug into the matrix. The mixture is then cooled to disperse the drug throughout the matrix.[18]

Solvent Evaporation Method

The carrier and active component are dissolved in an appropriate organic solvent. To produce a solid residue, the solvent is evaporated at a high temperature in a vacuum.[19] Commonly used solvents are ethanol, chloroform or a mixture of dichloromethane and ethanol.

Hot-Melt Extrusion

It is similar to fusion method, except that the extruder causes intense component mixing instead. However, unlike the conventional fusion method, this approach enables continuous production, making it suitable for large-scale production. Additionally, since the form can be changed for the next processing stage without grinding at the extruder's output, the product is easier to handle.[20]

4.1.4. Solubilization by Surfactants

Microemulsion

A hydrophilic surfactant and a hydrophilic solvent combine to dissolve a poorly water-soluble drug in an optically transparent pre-concentrate. The surfactant needs to be non-toxic and HLB-compatible. It produces a transparent emulsion of small, homogeneous oil droplets containing the poorly soluble drug that has been solubilized. Numerous drugs that are completely insoluble in water have been made more soluble by the use of microemulsions. An oil-in-water microemulsion is the best formulation because it increases solubility by permitting molecules with low water solubility to dissolve into the oil phase. Oral bioavailability can be enhanced as a consequence of surfactant-induced permeability alterations.

Advantages of Microemulsions

- Simplicity of preparation, clarity, ability to be filtered and incorporate a wide range of drugs of varying solubility.[21]

Self-Micro Emulsifying Drug Delivery System (SMEDDS)

The self-emulsifying drug delivery system is made up of a transparent isotropic solution, which is a combination of oil, surfactant, co-surfactant, one or more hydrophilic solvents and a co-solvent. Oil-in-water microemulsions are produced by the Self-emulsifying drug delivery systems (SEDDS) and Self-microemulsifying drug delivery systems (SMEDDS), which are isotropic solutions of oil and surfactant. When taken orally, these novel colloidal formulations behave like microemulsions of oil in water.

4.1.5. Complexation

Cyclodextrins (CDs) have been complexed with drugs to enhance their water solubility and drug stability. In pharmaceutical formulations, the most common cyclodextrin derivatives with improved water solubility are used. Cyclodextrins with molecular weights greater than 1000 Da are large and unlikely to easily permeate the skin. It has been observed that cyclodextrin complexation can both increase and decrease skin penetration. In addition to their use in enhancing solubility, CDs can also be used as stabilizers and membrane permeability enhancers. Cyclodextrins significantly improve permeability through biological membranes.[22]

4.2. Chemical modification

4.2.1. Hydrotrophy

The phenomenon of solubilization occurs when a large amount of a second solute is added, increasing the solubility of the first solute in water. It improves solubility more directly through a process known as complexation, which involves weak interactions between hydrotropic substances such as sodium benzoate, sodium acetate, sodium alginate, urea and drugs that are poorly soluble. Hydrotropic agents are ionic organic salts.[23] Many salts with large anions or cations that are also very soluble in water, a phenomenon known as "hydrotropism," cause the "salting in" of non-electrolytes known as "hydrotropic salts." A weak contact exists between the hydrotropic agent and the solute in hydrotropic solutions, which are non-colloid. [24,25]

Advantages

- Hydrotrophy's solvent nature is pH independent, has high selectivity and does not require emulsification.
- It does not require the production of an emulsion system or the use of organic solvents.[26]

4.2.2. Co-Solvency

A drug whose solubility in water is weak can have its solubility increased by the use of co-solvents, which are water-miscible solvents in which the drug has a high solubility. Co-Solvents are liquid solutions of one or more water-miscible solvents and water that improve the solubility of insoluble substances. Cosolvent techniques may be suitable for poorly soluble compounds that are lipophilic or highly crystalline and have a high solubility in the solvent mixture. Cosolvents have the ability to increase the solubility of weakly soluble compounds by thousands of times when compared to the drug's water solubility alone. Dimethyl sulfoxide (DMSO) and dimethylacetamide (DMA) have been used extensively as cosolvents due to their significant solubilization capacity for drugs that are difficult to dissolve and low toxicity.[27] Weak electrolytes and nonpolar molecules frequently have poor water solubility. These types of solutes are more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as co-solvency; and the solvents that, in combination increases the solubility of the solute are called co-solvents.

E.g- Phenobarbitone is insoluble in water. A clear solution is obtained by dissolving in mixture of Alcohol, Glycerin and Propylene glycol. This process of improving solubility of solute by addition of combination of solvents is known as co-solvency and the solvent used is known as co-solvents. Examples of commonly used co-solvents are ethanol, sorbitol, glycerin, propylene glycol, polyethylene glycol, etc.

Advantages

- It offers a high solubilization capacity for drugs that are poorly soluble and is simple to formulate, produce and evaluate.

Disadvantages

- As with other excipients, it is important to take into account the toxicity and tolerance of the given solvent level.
- As with all solubilized forms, the insoluble material has lower chemical stability when compared to a crystalline state.[28]

4.2.3. Nanotechnology

Nanotechnology is the study and use of materials and structures at the nanoscale level of about 100 nanometers (nm) or less. Since micronized products have a very small effective surface area for dissolving, the next stage was nanonization because the improvement in oral bioavailability through micronization is insufficient for many Novel Chemical Entities (NCEs) with limited solubility. The preparatory procedures that can be used include sonication, high-pressure homogenization, vacuum deposition and high-temperature evaporation.[29]

Advantages

- It results in the formation of spherical particles with smooth surfaces, narrow particle size distributions and large specific surface areas, which boosts solubility and the dissolution rate.[30]

4.2.4. Salt formation

An API is frequently unable to be created in its purest form because of different instability problems. This conversion results in the formation of salts, cocrystals, solvates, hydrates and polymorphs. Poorly soluble drug candidates (weak acids and bases) have been improved through salt formation. Salts are produced when a substance ionises in solution. It works well in solid dosage forms as well as parenteral and other liquid formulations. When an acidic or basic medication is converted into a salt with a higher solubility than the basic medicine, a salt is formed. E.g- Diclofenac is insoluble in water but Diclofenac sodium is soluble in water.[31,32]

4.2.5. Co-Crystallization

Co-crystallization influences molecular interactions, which may be used to enhance therapeutic value. A co-crystal is defined as a multi-component crystal formed between two substances that are solids at ambient conditions, with at least one component being an acceptable ion or molecule. To select the ideal co-crystal, analytical methods and a rational physicochemical study might be applied. Solvates and co-crystals are only physically distinguishable from one another. When one component is liquid and the other is solid, solvates are formed. When both components are solid, co-crystals are produced. Various co-crystallization methods are 1) Solvent evaporation 2) Grinding 3) Slurry co-crystallization 4) Solvent-drop grinding 5) High-throughput co-crystallization 6) Hot melt extrusion and 7) Sonocrystallization method.

4.3. pH adjustment

Drugs that are insoluble in water can be made water soluble by adjusting the pH. When using this technique to achieve solubility, consideration must be given to the buffer's capacity and the pH's tolerance. As a result, alkalizing excipients may improve the solubility of weakly acidic drugs, whereas the solubility of weakly basic drugs may be improved by decreasing the pH.[33] It can also be used on lipophilic and crystalline compounds that are poorly soluble.[34] Theoretically, pH adjustments can be used for parenteral as well as oral delivery systems. The poorly soluble medication may precipitate after intravenous injection since blood is a potent buffer with a pH between 7.2 and 7.4.

Advantages

- Simple to formulate and analyse.
- Simple to expedite and create.
- Low chemical usage makes it appropriate for high-throughput testing.[35]

Disadvantages

- When diluted in an aqueous medium with a pH lower than the compound's solubility, precipitation risk exists. This might result in oral variability and intravenous emboli.
- Tolerance and toxicity (both local and systemic) associated with non-physiological pH and extreme pH.[36]

4.4. Supercritical fluid process

Super Critical Fluids (SCFs) can dissolve nonvolatile solvents, with carbon dioxide serving as the critical point. Above its critical temperature and pressure, a SCF exists as a single phase. SCFs are intermediates between pure liquids and gases, giving them properties that are helpful for product processing. Additionally, near the critical points, even small changes in operating temperature, pressure, or both have a significant impact on density, transport qualities like viscosity, diffusivity and other physical properties like dielectric constant and polarity. The most widely used supercritical solvents include water, ethanol, ammonia, nitrous oxide, ethylene, propylene and n-pentane. Compressed fluid antisolvent, rapid expansion of supercritical solutions, impregnation or infusion of polymers with bioactive materials, precipitation with compressed antisolvents (PCA), gas antisolvent recrystallization, solution enhanced dispersion by supercritical fluid (SEDS) and aerosol-based SCF processing have all been developed to address different aspects of these problems.[37]

Advantages

- With the flexibility and accuracy provided by SCF techniques, drug particles can be micronized within specific particle size ranges, frequently to sub-micron levels.
- Once the drug particles have been solubilized in the SCF, it is possible to recrystallize them with significantly smaller particle sizes.
- Nano suspensions with a diameter of 10-100 nm have been produced using current SCF methods.[38]

4.5. Liquisolid methods

Both absorption and adsorption happen when a drug dissolved in a liquid vehicle is introduced to a carrier material with a porous surface and fibres inside, like cellulose. Specifically, the liquid first absorbs into the interior of the particles and is captured by their internal structure; once this system reaches saturation, the liquid is adsorbed onto the internal and external surfaces of the porous carrier particles. A liquid drug can be transformed into a dry, non-adherent, free-flowing, compressible powder by blending it with specific powder excipients, like the carrier and coating material. Microcrystalline and amorphous cellulose, as well as silica powders, are used as coating materials.[39,40]

Advantages

- Used in the production of liquid or oil-based drugs.
- Different carriers and additives, such as PVP, PEG 6000, Hydroxypropyl methylcellulose and Eudragit, among others, can be used to modify drug release.
- It improves the bioavailability and solubility of water-insoluble medications when administered orally.
- A variety of drugs with poor solubility can be formulated into the system.
- This system is specifically designed for powdered liquid drugs.[41]

Disadvantages

- For large doses of insoluble drugs (>100 mg), it is not applicable.
- It requires recipients with strong adsorption and specific surface area characteristics.[42]

5. Conclusion

Since solubility is necessary for drug absorption from the GIT, drug dissolution is the rate-determining step for the oral absorption of medications that are weakly water-soluble. Solubility is a critical concern for formulation scientists to overcome. To increase the solubility of medications, the various techniques listed above can be used alone or in combination. Choosing the best solubility enhancement technique is essential for achieving the objectives of a successful formulation, including excellent oral bioavailability, reduced dose frequency and improved patient compliance, while retaining a low production cost. Nanosuspension, supercritical fluid, cryogenics and inclusion complex formation are the most alluring methods to use among the various solubility alternatives when it comes to overcome the solubility problem of hydrophobic medications. Drug properties like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behaviour, etc., as well as dosage form requirements like tablet or capsule formulation, strength, immediate, or modified release, greatly impact the method of solubility enhancement. This review overall conclude that every molecule's solubility is crucial and has a big impact on the development of pharmaceutical formulations.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

References

[1] Vemula, V.R., Lagishetty, V. and Lingala, S., 2010. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research, 5(1), pp.41-51.

[2] Akhgari, A., Shakib, Z. and Sanati, S., 2017. A review on electrospun nanofibers for oral drug delivery. Nanomedicine Journal, 4(4).

[3] Khatri, H., Hussain, M.S. and Tyagi, S., 2022. Solubility enhancement techniques: An overview.

[4] Cook, J., Addicks, W. and Wu, Y.H., 2008. Application of the biopharmaceutical classification system in clinical drug development—an industrial view. The AAPS journal, 10, pp.306-310.

[5] Brahmankar DM and Jaiswal SB. Biopharmaceutics and Pharmacokinetics, 2009; 349-357.

[6] Sharma, D.K., 2007. Solubility Enhancement strategies for poorly water-soluble drugs in solid dispersions: A review. Asian Journal of Pharmaceutics (AJP), 1(1).

[7] Barradas, T.N. and de Holanda e Silva, K.G., 2021. Nanoemulsions of essential oils to improve solubility, stability and permeability: A Review. environmental chemistry letters, 19(2), pp.1153-1171.

[8] Singh, J., Walia, M. and Harikumar, S.L., 2013. Solubility enhancement by solid dispersion method: A review. Journal of Drug Delivery and Therapeutics, 3(5), pp.148-155.

[9] Vimalson, D.C., et, al. 2016, Enhance solubility of hydrophobic drugs. Asian Journal of Pharmaceutics, 10(2), pp.67-74.

[10] Ting, J.M., Porter III, W.W., Mecca, J.M., Bates, F.S. and Reineke, T.M., 2018. Advances in polymer design for enhancing oral drug solubility and delivery. bioconjugate chemistry, 29(4), pp.939-952.

[11] Zhang, Y., Wang, S., Dai, M., Nai, J., Zhu, L. and Sheng, H., 2020. Solubility and bioavailability enhancement of oridonin: A review. molecules, 25(2), p.332.

[12] Kale, A.R., Kakade, S. and Bhosale, A., 2020. A Review on: Solubility enhancement techniques. Journal of Current Pharma Research, 10(2), pp.3630-3647.

[13] Singh, N., Allawadi, D., Singh, S. and Arora, S.S., 2013. Techniques for bioavailability enhancement of BCS class II drugs: A review. International Journal of Pharmaceutical and Chemical Sciences, 2(2), pp.1092-1101.

[14] Shah, R., Eldridge, D., Palombo, E. and Harding, I., 2015. Lipid nanoparticles: production, characterization and stability (Vol. 1, pp. 23-43). New York, NY, USA:: Springer International Publishing.

[15] Laitinen, R., Lobmann, K., Grohganz, H., Strachan, C. and Rades, T., 2014. Amino acids as co-amorphous excipients for simvastatin and glibenclamide: physical properties and stability. Molecular pharmaceutics, 11(7), pp.2381-2389.

[16] 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. International Journal of Polymeric Materials and Polymeric Biomaterials, 69(7), pp.407-418.

[17] Mohit and 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.

[18] Patel, B.B., Patel, J.K., Chakraborty, S. and Shukla, D., 2015. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharmaceutical Journal, 23(4), pp.352-365.

[19] Donnell PB and McGinity JW. Preparation of microspheres by the solvent evaporation technique. Advanced Drug Delivery Reviews, 1997; 28(1): 25-42.

[20] Khansary MA, Shirazian S and Walker G. Molecular engineering of co-crystallization process in hot melt extrusion based on kinetics of elementary molecular processes. International Journal of Pharmaceutics, 601, p.120495.

[21] Bind, A., Das, S., Singh, V.D., Kumar, R., Chourasia, A. and Saha, P., 2020. Natural bioactives for the potential management of gastric ulceration. Turkish Journal of Physiotherapy and Rehabilitation, 32(3), pp.221-226.

[22] Dhapte V and Mehta P. Advances in Hydrotropic Solutions: An updated review. st. petersburg polytechnical university Journal: Physics and Mathematics, 2015; 1: 424-435.

[23] Maheri, A., Ghanbarpour, P., Rahimpour, E., Acree Jr, W.E., Jouyban, A., Azarbayjani, A.F. and Kouhkan, M., 2021. Solubilisation of dexamethasone: experimental data, co-solvency and polarised continuum modelling. physics and chemistry of liquids, 59(6), pp.817-826

[24] Nidhi K, Indrajeet S, Khushboo M, Gauri K and 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 and 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 and Saudagar RB. Review on solubility enhancement techniques. International Journal of Pharmacy and Biological Sciences, 2013; 3(3): 462-575.

[27] Shi H, Xie Y, Xu J, Zhu J, Wang C and Wang H. Solubility enhancement, solvent effect and thermodynamic analysis of pazopanib in co-solvent mixtures. The Journal of Chemical Thermodynamics, 155, p.106343.

[28] Patel MSN, Ahmed MH, Saqib M and Shaikh SN. Chemical Modification: A unique solutions to solubility problem. Journal of Drug Delivery and Therapeutics, 2019; 9(2): 542-546.

[29] Jagtap S, Magdum C, Jadge D and Jagtap R. Solubility enhancement technique: A Review. Journal of Pharmaceutical Science and Research 2018;10:2205-11.

[30] Chopra, H., Bibi, S., Islam, F., Ahmad, S.U., Olawale, O.A., Alhumaydhi, F.A., Marzouki, R., Baig, A.A. and Emran, T.B., 2022. Emerging trends in the delivery of resveratrol by nanostructures: applications of nanotechnology in life sciences. Journal of Nanomaterials, 2022, pp.1-17.

[31] Tran, P., Pyo, Y.C., Kim, D.H., Lee, S.E., Kim, J.K. and Park, J.S., 2019. Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs and application to anticancer drugs. Pharmaceutics, 11(3), p.132.

[32] Repka MA, Bandari S, Kallakunta VR, Vo AQ, McFall H and Pimparade MB . Melt extrusion with poorly soluble drugs an integrated review. International journal of pharmaceutics, 535(1-2), pp.68-85.

[33] Goonoo N, Bhaw-Luximon A and Jhurry D. drug loading and release from electrospun biodegradable nanofibers. Journal of biomedical nanotechnology 2014; 10:2173–2199.

[34] Young OA, Zhang SX, Farouk MM and Podmore C. Effects of pH adjustment with phosphates on attributes and functionalities of normal and high pH beef. Meat Science, 2005; 70: 133-139.

[35] McMorland, G.H., Douglas, M.J., Jeffery, W.K., Ross, P.L., Axelson, J.E., Kim, J.H., Gambling, D.R. and Robertson, K., 1986. Effect of pH-adjustment of bupivacaine on onset and duration of epidural analgesia in parturients. Canadian Anaesthetists' Society Journal, 33, pp.537-541.

[36] Jain A, Ran Y and Yalkowsky SH. Effect of pH-sodium lauryl sulfate combination on solubilization of PG-300995 (an anti-hiv agent). AAPS PharmSciTech., 2004; 5(3): 45-48.

[37] Abuzar, S.M., Hyun, S.M., Kim, J.H., Park, H.J., Kim, M.S., Park, J.S. and Hwang, S.J., 2018. Enhancing the solubility and bioavailability of poorly water-soluble drugs using supercritical antisolvent (sas) process. International journal of pharmaceutics, 538(1-2), pp.1-13.

[38] Campardelli R, Baldino L and Reverchon A. Supercritical fluids applications in nanomedicine. The Journal of Supercritical Fluids, 2015; 101: 193-214.

[39] Burra S, Yamsani M and Vobalaboina V. The liquisolid technique: an overview. Brazilian Journal of Pharmaceutical Sciences, 2011; 7(3): 475-482.

[40] Javadzadeh Y, Jafari-Navipour B and Nokhodchi A. liquisolid technique for dissolution rate enhancement of a high dose water – insoluble drug (carbamazepine). International journal of pharmaceutics., 2007; 341: 26-34.

[41] Kulkarni AS, Aloorkar NH, Mane MS and Gaja JB. Liquisolid systems: a review. International Journal of Pharmaceutical Sciences and Nanotechnology, 2010; 3(1): 795-802.

[42] Lu M, Xing H, Jiang J, Chen X, Yang T and Wang D. Liquisolid technique and its applications in pharmaceutics. Asian Journal of Pharmaceutical Sciences, 2017; 12: 115-123