WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 8, 1119-1130. Review Article ISSN 2277–7105

EUTECTIC MIXTURES IN DRUG DELIVERY: INNOVATIONS AND CHALLENGES

Srushti S. Gode*[1], Neha S. Ghosalkar[2], Rini Punathil[3] and Sanket Dharashivkar[4]

[1,2,3,4]Department of Pharmaceutics, St. Wilfred's Institute of Pharmacy, Panvel.

Article Received on
04 March 2025,

Revised on 24 March 2025,
Accepted on 13 April 2025

DOI: 10.20959/wjpr20258-36240

***Corresponding Author**
Srushti S. Gode
Department of Pharmaceutics, St. Wilfred's Institute of Pharmacy, Panvel.

ABSTRACT

Eutectic the new wave in pharmaceutical formulations to solubilize and improve bioavailability of poorly water-soluble drugs. Eutectic systems contain two or more components, and when combined, they have a melting point that is lower than those of their individual compounds, thereby increasing solubility or dissolution rate of active pharmaceutical ingredients. This review showcases the promise of eutectic mixtures to meet formulation hurdles of low solubility and bioavailability. Mechanisms of eutectic formation, preparation methods, and thereby influence on drug-releasing characteristics are discussed. Eutectic mixtures as associated with various formulation approaches would be examined-into solid dispersions, co-crystals, and into amorphous systems-delineating improvement to drug absorption. Case studies are presented in the review for those successful eutectic mixtures in formulation for use prior to clinical. The work also examines other essential hurdles such as stability, scalability, and regulatory hurdles that can be harnessed towards optimizing formulation strategies for maximized therapy. In summary, therefore, eutectic mixtures are not only very versatile but also very potent in terms of enhancing not only solubility but bioavailability in the design of more efficient pharmaceutical formulations.

KEYWORDS: Eutectic mixtures, solubility enhancement, bioavailability, solid dispersions, co-crystals, amorphous systems.

INTRODUCTION

The definition of eutectic formation says: an isothermal, reversible reaction between two (or more) solid phases when a system is heated results in the formation of a single liquid phase.

The term ‘eutectic’ goes back to the Greek word eutektos, which etymologically denotes synthesis at low temperatures or easy fusing. A eutectic mixture (EM) refers to mixing more than one substance, which consequently does not interact to create one new entity, but in a particular ratio shows a lower melting point as compared to the individuals.

Enhancing the effectiveness of Active Pharmaceutical Ingredients (APIs) that are classified under Class II and IV under the Biopharmaceutical Classification System (BCS) is a daunting task for most pharmaceutical industries because of the fact that around 70 and 90 percent of pharmaceutical compounds are poorly soluble in the aqueous solvent and then poorly bioavailable as well. Most of the solid active pharmaceutical ingredients (APIs) exhibit polymorphism, poor bioavailability, inadequate dissolution, and at last a potential inefficacy for treatment. Several methods have been designed based on deep eutectic solvents (DES) and eutectic mixtures, calculated throwing these limitations.[1]

Three general types of eutectics are eutectic salts, eutectic metals, and deep eutectic solvents. They are all eutectic systems and operate under the same eutectic principle. Problematic organic solvents are used for formulation of many drugs while working on developing more benign alternatives. DESs are often wrongly classified as" a subclass of ionic liquids (ILs) due to the two substances having similar physical characteristics".

The organic eutectic solvent systems, also abbreviated as DESs, are combinations of molecules naturally occurring in nature while ionic liquids, or ILs, are usually composed or consist of an inorganic or organic anion and two or more large asymmetric organic cations. Low viscosity, low vapor and low ignition, low cost, biodegradable nature, and low toxicity, broad liquid range, capacity to dissolve a number of solutes along with thermal and chemical stability are shared by the two solvent types. Most of these problems were much aggravated because of EM in the management of many APIs posing problems in their solubility, bioavailability, stability, degree of polymorphism, and formulation-related problems. EM also improved skin permeation for topical dosage forms containing poorly soluble drugs for the local treatment of several infections, much more so by providing reduced side effects with quick drug delivery to the target site, and improving the amount of drug in tissues.

Eutectic mixtures have long been known in pharmaceutical applications, while their use as systems to improve solubility and dissolution of poorly water-soluble drugs remains largely unexplored. The number of studies relating to the preparation of eutectic mixtures to improve

the solubility and the oral bioavailability of poorly soluble active pharmaceutical ingredients has increased very dramatic in recent years-possibly including drug carrier and drug-drug mixtures as shown in (fig 1.1). The present review discusses the possibility of conversion of eutectic mixtures towards hollow pharmaceutical solid systems for enhancing drugs solubility, dissolution rates, or oral bioavailability. Other aspects such as historical, physico-chemical, microstructural characteristics, preparation techniques, mechanisms of solubility/dissolution enhancement, solid-state characterization techniques, in vivo studies, advantages, limitations are and formulation perspectives also discussed.[2]

These problems highlight the urgent need to create a eutectic mixture (EM) dosage form for pharmaceuticals. An EM is a mixture of at least two substances that, in most cases will not combine to create new chemical compounds but, at specific ratios, will somehow prevent one another from crystallizing and form a system with melting point below any of the components. Eutectic temperature is the temperature above which the system exists as liquid and below which it exists as solids or is combined into a multi-component emulsion made up of at least two liquid solids which show immiscibility in the solid state and do not combine in order to produce a new chemical complex.

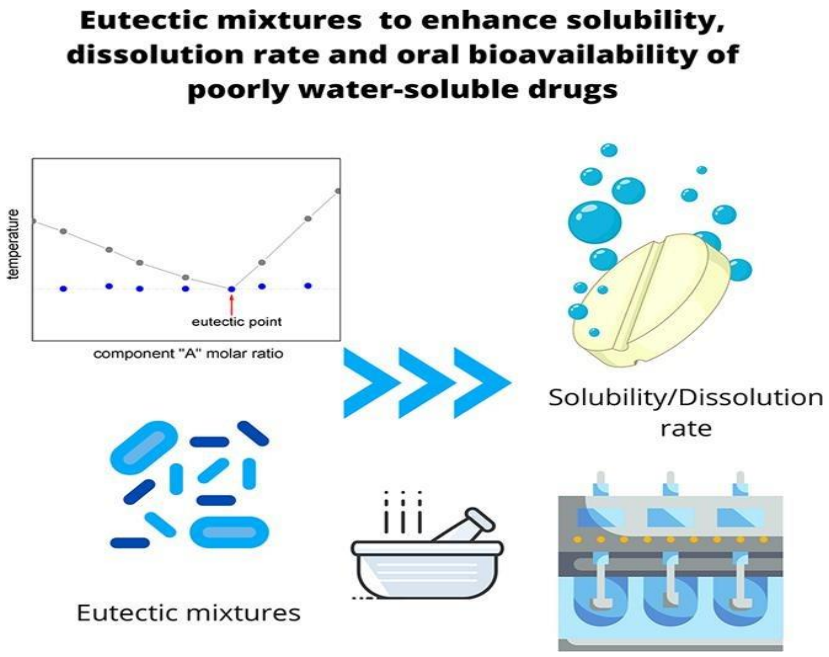

Fig 1.1 Eutectic Mixture to enhancing solubility.

Still, at a specific rate, the eutectic composition will show a melting point or solidification point vastly lower than its ingredients. At the eutectic composition, the two factors parade reduction in flyspeck size and are unevenly circulated, therefore contributing to adding the

rate of bioavailability and dissolution of the medicine. The melting point depression explication and boost in entropy makes it veritably clear for an understanding.[3]

ADVANTAGES OF EUTECTIC MIXTURE[4]

- **Enhanced solubility:** Eutectic mixture increases the solubility of some poorly soluble drugs by forming a novel solvate, thereby increasing solubility in water or other solvents. This has a direct effect on the bioavailability and efficacy of the compound.
- **Stability:** Eutectic mixtures help stabilize drugs by protecting them against degradation or oxidation, and thus extending the shelf life. Together with their synergistic effects due to a partial therapeutic use, the drug in the eutectic mixture could also logically decrease the dosage required when compared with its ordinary dosage. Lesser dosages would further curtail the side effects, and thus promote better patient compliance.
- **Formulation:** Eutectic mixtures favorably affect how drugs get formulated, leading to a more homogeneous and consistent mixture, thus augmenting the manufacturing process and minimizing variability between batches. A lesser amount of drug can stabilize a poorly soluble drug through formation of a eutectic mixture with another similarly therapeutic compound. Hence, a reduced amount of drug may even lower the side effects profile and favor acceptance of treatment by the patient.
- **Enhanced formulating**: The Eutectic Mixture is yet another avenue along which new possibilities for formulation may arise through enhanced drug homogeneity and consistency, thus facilitating manufacturing with concomitantly reduced batch-to-batch variability.
- **Flexibility:** This sets up Amorphous Eutectic Mixtures to be extremely flexible in the sense that the combinations can be made to combine with drugs of wholly different physical and chemical properties in such a way as to arrive at new combinations with synergistic effects.

DISADVANTAGES OF EUTECTIC MIXTURE[3,4]

- It is possible that the limited compatibility of drugs may lead to drug degradation or inactivation.
- Dosage variability: Control of drug doses in eutectic mixtures may become difficult since the melting temperature of the mixtures might get altered with variations in temperature, humidity, and other environmental conditions.

- Difficulty in manufacturing: The manufacture of eutectic mixtures, compared with other dosage forms, would become a more complicated and, therefore, a more expensive process.
- Stability problems: Eutectic mixtures may be susceptible to moisture, oxidation, and other environmental factors, which could lead to instability or shorter shelf-life.
- Regulatory problems: The presentation of eutectic mixtures in drugs may bring about regulatory problems due to safety and efficacy issues.

CHARACTERISTICS ARE TYPICALLY RESPONSIBLE FOR EM FORMATION

- Solid state immiscibility and liquid state miscibility between components
- Requires direct contact between materials making up the eutectics for contact-induced melting point depression.
- Intermolecular hydrogen - Physical bond that results from two contact with -chemical group.
- It could form eutectic mixes having the ability to relate with the modified VantHoff equation according to the integrated molecules.[5]

About that eutectic temperature: it is the minimum melting temperature regardless of the proportional relationships. Once this temperature is reached by a superlattice, their components will evaporate and the mixture will melt. In contrast to a eutectic mixture, a non-eutectic mixture will penetrate before the entire mix solidifies, so portions will solidify in a lattice at its temperature.[6]

Eutectic compositions are formed by means of geometric dilution and compose at least two elements that exhibit the same melting and freezing characteristics. A mixture gets formed due to crystallization, whereby the material behaves as an entity. The materials can create a dense crystal lattice and thereby dissolve together with no discrimination. The advantages of EM include (a) cheapness (b) chemically inert with water (c) easy to prepare by virtue of their being prepared simply by mixing 2 components, thus bypassing all the environmental problems of waste disposal and purification confronted with ILs; (d) they are biodegradable, bio-compatible, and completely non-toxic, rendering the use of these media safe for all.[7]

METHODS OF PREPARATIONS OF EUTECTIC MIXTURES

Eutectic mixtures are generally prepared by the various methods that are as follows:

- **Melting method (fusion method)**

Melting method is also called as fusion method. This method was firstly employed by Sekiguchi and Obi to prepare a physical mixture composed of sulfathiazole and urea. The process of formation of physical solution involved heating the components until melting. While continuously stirring, the molten mixture settles quickly at low temperature level of an ice bath. The sudden cooling on an ice bath achieves the supersaturation of the mixture. Under these conditions, the molecules of the substance become "trapped" into the matrix of the rapidly solidifying system. The solid mass formed is then pulverized and sieved to ensure standardization of the size of grains obtained. This technique enhances the dispersion of crystals within the eutectic mixture. In spite of its widespread use, the fusion method has some limitations. It can only be used when the drug substance and the carrier mix homogeneously upon heating. Another important limitation of this method is thermal degradation of the drug and carrier. High temperatures can also cause the loss of a volatile drug or carrier. One possible solution to preventing degradation is to conduct both heating and/or melting under vacuum. Alternatively, the process can be carried out in an inert atmosphere such as nitrogen to avoid oxygen-induced degradation of the drug or carrier. Another unfavorable aspect to this method pertains to modification of the mutual miscibility of the components on cooling, which leads to phase separation issues. Crystallization of the drug has been observed when the mixture is cooled slowly. Conversely, fast cooling favors the formation of amorphous solid dispersions.[8]

- **Solvent method**

The solvent method was first applied by Tachbani and Nakamura who prepared a solid solution of liophilic β-carotene in a hydrophilic carrier, polyvinylpyrrolidone. In this method, a physical mixture of a drug and a carrier is dissolved in a volatile solvent, that is chloroform or dichloromethane. Then, solvent was completely evaporated at the range of 23–650C, the Solid dispersion dissolved solids form a layer of solid dispersion. The film obtained was dried and pulverized. Solvent used and its rate of removal are two very important parameters affecting the dissolution of the drug substance in the solid dispersion obtained. They thus affect crystallographic structure of the resulting system. By far the major advantage of this method of preparation is that it allows the drug substance to be preserved from degradation due to the low temperature necessary for vaporization of the organic solvent. The

disadvantages include production costs that are extremely high, difficulties regarding the selection of a low boiling volatile solvent and its complete removal, possible side effects of solvent residues that may influence the chemical stability of the substance, and also the problem inherent in the reconstruction of the crystalline form.[9]

- **Melt extrusion method**

Recently, the melt-extrusion technique for the preparation of solid dispersions has started gaining acceptance. Therefore, the method has been considered particularly useful in producing dispersions of drug substances that exist in different polymorphic forms with varying degrees of bioavailability. In essence, the melt-extrusion method yields solid dispersions in which drug substances must dissolve in the polymer and stay as molecular-level dispersions until solidification of the polymer. Melt extrusion is considered a variant of the melting technique. Melt extrusion comprises various sub-processes such as introduction of substrates into extruder, mixing and grinding to reduce particle size, concentration of the mass into form suitable for extrusion and of solid consistency, melting of the mass, homogenization, and forcing the melt through the extrusion die. The substances acting as carriers, for example, the polymer, are fed into the feed section of the extruder from a dosing hopper. Mechanical solutions allow for easy transport of the material through the machine via either a single- or twin-screw system. In transit the material is preheated by external heat sources, which consist of the heater bands along the wall of the cylinder and friction. Outside heater bands must keep at a constant temperature. The advanced substrates are now mixed, kneaded, and melted. After this, a part of the extruder is for degassing; therefore, degassing can proceed, followed by homogenization, before the intermediate reaches the degassing zone. It is, therefore, important that the mass flow through the cylinder towards the receiver section is kept uniform to guarantee uniform thickness of the product. The final stage in this process involves the milling for a minute of the extrudate so that the particles larger than 355 µm could be separated using sieving. Tablet, granule, or pellet form is given clearly to the product soon after extrusion. Melt-extrusion may, like the traditional melting method, suffer from problems concerning the mutual mixing of the components and their temperature sensitivity; but since the exposure time to high temperature (approximately one minute) is short, this technique could be adopted for producing solid dispersions with heat-sensitive substances. The extrusion method enables scaling up the production of solid dispersions from a lab-based scale.[10]

- **Melt agglomeration method**

In this method, when the carrier fulfills also the role of a binder, solid dispersions are formulated. Here, solid dispersions may be obtained by simultaneously mixing a preheated carrier (binder), drug and excipients in a high-speed mixer above the melting point of the carrier. Alternately, solid dispersions can be prepared by introducing to the molten, heated carrier the drug dispersed together with the excipients, or adding a molten carrier-drug mixture to the preheated excipients. Such parameters as type of a binding agent, method of preparation, and particle size are considered critical in a solid dispersion preparation using this technique. Particle size governs the solubility of the resultant system, together with the mechanism of agglomerate formation, their size, distribution, and concentration.[11]

- **Melt evaporation method**

This method of preparing solid dispersions consists of dissolving a drug in solvent and incorporating this solution into polyethylene glycol melted at a temperature lower than 75°C. The two solutions are blended together and the solvent evaporated to leave behind a product layer that is dried until it attains a constant weight. The limitation of this technique is that it must have solvents in which the drug has limited solubility for mixing with the melted polyethylene glycol. Studies, however, confirm that between 5 and 10% of the liquid ingredients become incorporated into PEG 6000 without significant loss in solid characteristics. Furthermore, the liquid solvent used in this technique has the potential to lead to the formation of polymorphic drug forms, which then precipitate out from the solid dispersion formed as a result. The converse of this is that the limited incorporation of drug into solid dispersion stands between 5 and 10% of the whole system.[12]

- **Compaction method**

Here, in this technique, the formation of eutectic mixture during the process of tablet formation, i.e., wet granulation or compression, sometimes happens inadvertently. This may be brought about by the very intimate contact between the components or may become effective due to the rise in temperature during punching.[13]

- **Grinding method**

This method is to be used on a laboratory scale for the preparation of eutectic mixtures. The grinding can be accomplished using mortar pestle. Use of vibratory mills, mechanical

grinders are for large scales. This process has some limitations hence it is not commonly used.[14]

PHASE TRANSITION OF THE EUTECTIC SYSTEM

It is a phase transition when something goes from one state to another. There is a precise temperature and pressure under which each element or substance can phase change from one phase to another.

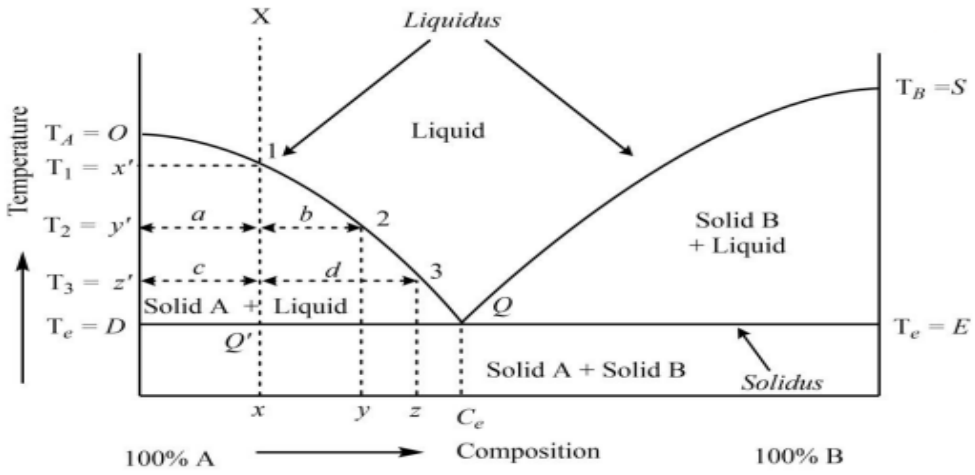

Figure 1.2 Two components form a compound: Solid- liquid Equilibria.

The parameters used to define the eutectic point are number ratio at eutectic percentage (on the atomic or molecular ratio axis (X-axis) of the diagram) and eutectic temperature (on the Y-axis of the diagram) as shown in (Fig 1.2). Not all binary alloys have a eutectic point because the valence electrons of the component species are not always compatible in any of the mixing ratios to form a new type of joint crystal lattice of the combination. The melting point and freezing point of the silver-gold eutectic system meet at the pure element endpoints of the atomic ratio axis while significantly separating in the mixed area of the axis.[15]

APPLICATION OF EUTECTIC MIXTURES

Analyzing or identifying such entities in terms of a eutectic mixture is made possible by the assumption that similar melting points of components can form a eutectic mixture. The eutectic point is different for these paired compounds with similar melting points and is slightly lower than either of the compounds. This fact can help one to recognize Ergotamine, Allobarbital as these are capable of forming eutectic mixtures with benzanilide.

Cosmetics are made using this fact to make the constituents liquefied and measurable properties through decreasing their melting point. For example, a eutectic composition prepared by mixing n-butyl-phthalimide and iso-propyl-phthalimide with 1, 3, 5-triazine derivatives was used in another anti-sun formulation due to the unique stability it showed. A eutectic composition was used in scalp itch formulations that indicated improved deposition of the monoethanolamide's eutectic compositions on the scalp in relation to the pure amides.[12] The eutectic system is the best alternative in the pharmaceutical field to improve solubility, absorption, and permeation of poorly water-soluble drugs, or used as an oil phase in an emulsion system. It was suitable as a deep eutectic solvent (DES) since it was cheap, biodegradable, non-flammable, and non-toxic. Liquid eutectic systems, produced from combinations of quaternary ammonium salts and organic components, were used as deep eutectic solvents (DES).[16]

CONCLUSION

Among the novel approaches adopted in drug delivery, eutectic mixtures present a huge promise in terms of advantages including increased solubility, increasing drug bioavailability, and better drug stability. It further dissolves active pharmaceutical ingredients (APIs) and provides a lower melting temperature, resulting in better dissolution rates. Such formulations are therefore useful particularly for drugs that exhibit poor solubility in water. Another advantage is that they can form stable, amorphous systems of drugs, which can help alleviate issues with crystallization and degradation of drugs. Nevertheless, many challenges arise from the complex formulation optimization, physical and chemical stability issues, and regulatory issues surrounding eutectic drug formulations. To produce given therapeutic outcomes, a proper selection of co-formers along with accurate control over the composition and processing conditions should be done. Future advances in nanotechnology, computational modeling, innovative formulation techniques, will probably drive innovation in the field of eutectic drug delivery systems. These advances may make it possible to overcome the existing challenges that inhibit eutectic mixture resolution in their potential to revolutionize drug formulation and patient outcomes.

ACKNOWLEDGEMENT

I sincerely appreciate the valuable contributions and support of all those who made this review possible. I am grateful to my fellow colleagues and mentors for the very stimulating discussions and programs they provided in their feedback. Also, I acknowledge the

intellectual effort from the peer reviewers who provided comments that led to improvements in the present work.

REFERENCE

1. Balakrishnan I; Jawahar N; Senthil Venkatachalam; Debosmita Datta. A Brief Review on Eutectic Mixture and Its Role in Pharmaceutical Field. International Journal of Research in Pharmaceutical Sciences, 2020; 11(3): 3017–3023.
2. azzo, G. C.; Pezzini, B. R.; Stulzer, H. K. Eutectic Mixtures as an Approach to Enhance Solubility, Dissolution Rate and Oral Bioavailability of Poorly Water-Soluble Drugs. International Journal of Pharmaceutics, 2020; 588: 119741.
3. Abulfadhel jaber neamah; Rashid, A. M.; Ghareeb, M. M. Eutectic Mixtures: A Promising Solvent in Drug Delivery System. 2022; 1.
4. Dheyab, A. S.; Abu Bakar, M. F.; AlOmar, M.; Sabran, S. F.; Muhamad Hanafi, A. F.; Mohamad, A. Deep Eutectic Solvents (DESs) as Green Extraction Media of Beneficial Bioactive Phytochemicals. Separations, 2021; 8(10): 176.
5. Satya Girish Avula; Alexander, K.; Riga, A. Predicting Eutectic Behavior of Drugs and Excipients by Unique Calculations. Journal of Thermal Analysis and Calorimetry, 2010; 99(2): 655–658.
6. Dissolution Rate Enhancement and Physicochemical Characterization of a Fenofibric Acid–Nicotinamide Eutectic Mixture. Tropical Journal of Natural Product Research, 2021; 5(9): 1614–1618.
7. Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. Deep Eutectic Solvents: Syntheses, Properties and Applications. Chemical Society Reviews, 2012; 41(21): 7108.
8. Urbanetz, N. A. Stabilization of Solid Dispersions of Nimodipine and Polyethylene Glycol 2000. European Journal of Pharmaceutical Sciences, 2006; 28(1-2): 67–76.
9. Argade, P. Solid Dispersion: Solubility Enhancement Technique for Poorly Water-Soluble Drugs INTRODUCTION.[1,2] Technique-for-poorly-water-soluble-drugs. pdf. Leuner, Christian, and Jennifer Dressman. "Improving drug solubility for oral delivery using solid dispersions." European journal of Pharmaceutics and Biopharmaceutics, 2000; 50.1: 47-60.
10. Bhavna Dilipbhai, K.; N Shah, C.; Upadhyay, U. Solid Dispersion: A Novel Technique to Enhancement of Solubility. International Journal of Science and Research (IJSR)., 2024; 13(9): 13–19.

11. Sunita; Vikas Budhwar; Choudhary, M. Pharmaceutical Eutectics: A Promising Drug Delivery System. Research Journal of Pharmacy and Technology, 2020; 13(11): 5515–5523.
12. Bi, M.; Sung Joo Hwang; Morris, K. R. Mechanism of Eutectic Formation upon Compaction and Its Effects on Tablet Properties. Thermochimica Acta., 2003; 404(1-2): 213–226.
13. Cherukuvada, S.; Nangia, A. Fast Dissolving Eutectic Compositions of Two Anti-Tubercular Drugs. CrystEngComm., 2012; 14(7): 2579.
14. G. Kalyani; P. Bhuvaneswari; B. Hemalatha; K. Padmalatha. Hydrotropy: A Promising Tool for Solubility Enhancement. Asian Journal of Pharmacy and Technology, 2022; 146–150.
15. Tuntarawongsa, S. and Phaechamud, T. (2012) "Polymeric eutectic drug delivery system," Journal of Metals, Materials and Minerals: No. 2, Article 5, 2012; 22: 27-32.
16. Gala, U.; Pham, H.; Chauhan, H. Pharmaceutical Applications of Eutectic Mixtures. Semantic Scholar, 2013.