INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Mixed Hydrotropic Solid Dispersion Technique - A Green Solubilization Pathway: A Comprehensive Review on Solubility Enhancement Strategies

Athmika Haika*, Neema George, Krishna Haridas, Shabnam Shibu, Aswathy Mohan, Divyamol A.K, Gayathri P.M, Praveena V.A

Department Of Pharmaceutics, Department Of Pharmaceutical Sciences, Rimsr, Cpas, Puthuppally, Kottayam.

ARTICLE INFO

Published: 04 Aug 2026
Keywords:
Mixed hydrotropic solid dispersion, Hydrotropic agents, Solubility Enhancement
DOI:
10.5281/zenodo.21788980

ABSTRACT

The mixed hydrotropic solid dispersion (MHSD) technique represents a sophisticated and eco-friendly approach to enhancing the aqueous solubility and bioavailability of poorly water-soluble drugs. This review explores the integration of solid dispersion technology with the phenomenon of mixed hydrotropy, which utilizes a combination of multiple hydrotropic agents to achieve synergistic solubility enhancement while minimizing individual agent concentrations and associated toxicities. The technique has demonstrated significant efficacy for drugs classified under the Biopharmaceutical Classification System (BCS) as Class II and IV, such as meloxicam, gliclazide, and ornidazole. Various preparation methods, including solvent evaporation, physical mixing, and fusion, are discussed alongside common components like urea, sodium benzoate, and niacinamide. Evaluation parameters such as Fourier-transform Infrared (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD) consistently reveal the conversion of drugs from crystalline to amorphous states, contributing to rapid dissolution. This article provides an in-depth analysis of the components, methods, and evaluation protocols essential for the successful formulation of mixed hydrotropic solid dispersions.

INTRODUCTION

Solubility is a critical factor in the drug development process, as it directly influences the dissolution rate and subsequent oral bioavailability of pharmaceutical agents. Approximately 40% of new chemical entities and many existing drugs suffer from poor aqueous solubility, leading to challenges in formulating effective dosage forms (2, 13). Traditional methods such as

***Corresponding Author:** Athmika Haika
Address: *Department Of Pharmaceutics, Department Of Pharmaceutical Sciences, Rimsr, Cpas, Puthuppally, Kottayam.*
Email ✉: athmikashaika@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

micronization, salt formation, and the use of surfactants often face limitations regarding stability, cost, or solvent toxicity (13, 23).Solid dispersion (SD) technology has emerged as a prominent strategy where a poorly soluble drug is dispersed in a hydrophilic carrier, often leading to improved wetting and particle size reduction (32, 33). However, the choice of carrier is vital; traditional polymers may require large amounts to be effective, which can lead to bulky dosage forms. Hydrotropy, a solubilization phenomenon where the addition of a second solute (hydrotrope) increases the aqueous solubility of a poorly soluble drug, offers a compelling alternative (35, 37). Mixed hydrotropy further refines this by using blends of two or more hydrotropic agents, which provides a synergistic effect and allows for the use of lower concentrations of each individual agent, thereby reducing potential side effects and costs (1, 19, 25)**.**

2. IDEAL DRUG CANDIDATES FOR THIS TECHNIQUE

The mixed hydrotropic solid dispersion technique is particularly suited for drugs belonging to BCS Class II [low solubility, high permeability] and Class IV [low solubility, low permeability] (9, 16). These drugs often exhibit dissolution-limited absorption, meaning any enhancement in their solubility can lead to a significant increase in bioavailability.

Representative drug candidates that have been successfully formulated using this technique include:

- **Anti-inflammatory agents**: Meloxicam (5, 30), Aceclofenac (15, 17), Piroxicam (12) and Ibuprofen (31).
- **Antidiabetic agents**: Gliclazide (18, 22) and Glimepiride (21).
- **Antihypertensive and cardiovascular drugs**: Irbesartan (4), Felodipine (7), and Atorvastatin calcium (24).
- **Antimicrobial and Antifungal agents**: Ornidazole (1), Nevirapine (16), Efavirenz (10), and Miconazole (28).
- **Antipsychotic and CNS drugs**: Lurasidone hydrochloride (11, 14), Flupirtine maleate (3), and Lamotrigine (29).

These drugs typically possess crystalline structures and hydrophobic properties that prevent efficient dissolution in gastric and intestinal fluids. The MHSD technique facilitates their conversion to more soluble forms through molecular dispersion or amorphous transformation (3, 11)**.**

3. ADVANTAGES AND DISADVANTAGES

Advantages

1. Synergistic Solubility Enhancement: The use of mixed hydrotropes often results in a solubility increase that is greater than the sum of the individual effects, allowing for "miraculous" improvements in drug release (10, 27).
2. Reduction in Toxicity: By using a blend of agents, the concentration of each individual hydrotrope can be kept low, minimizing the risk of adverse effects associated with high concentrations of single agents (19, 29).
3. Eco-Friendly and Cost-Effective: Many mixed hydrotropic techniques utilize water as the primary solvent or require minimal organic solvents, making the process greener and reducing manufacturing costs (17, 23, 26).
4. Improved Bioavailability: Rapid dissolution often translates to faster absorption and higher peak plasma concentrations, particularly for mouth-dissolving or fast-disintegrating tablets (5, 20).

5. Versatility: The technique can be applied to a wide range of chemical classes and can be integrated into various final dosage forms, including tablets, gels, and orodispersible systems (20, 26).

Disadvantages

6. Hygroscopicity: Some hydrotropic agents (e.g., urea) are hygroscopic, which may affect the stability and flow properties of the solid dispersion if not properly handled (21, 28).
7. Carrier Load: Achieving significant solubility might still require a relatively high ratio of hydrotropes to drug, which can impact the size of the final tablet (11).
8. Stability Concerns: While many studies report stability, the potential for recrystallization of the amorphous drug back to its crystalline form during storage remains a general challenge for solid dispersions (3,17,20).
9. Permeability Interplay: In some cases, high levels of hydrotropes might slightly reduce the apparent permeability of the drug, although this is often outweighed by the massive gains in solubility (12).

4. IMPORTANCE AND FEATURES

The MHSD technique is distinguished by several unique features that make it a "novel science of solubility enhancement" (19).

Synergetic Effect

The primary feature is the synergy between different hydrotropes. For example, a blend of sodium acetate, sodium benzoate, and sodium citrate has been shown to enhance the solubility of candesartan cilexetil more effectively than any of these agents alone (23). Similarly, ternary and quaternary blends have shown exponential increases in solubility for atorvastatin, with quaternary blends reaching nearly 1000-fold enhancement (24).

Amorphous Transformation

A key mechanism of MHSD is the disruption of the drug's crystalline lattice. Evaluation through XRD and DSC typically shows a reduction or disappearance of characteristic drug peaks, indicating a transition to an amorphous or molecularly dispersed state (3, 21). This state has higher internal energy and lower thermodynamic stability, facilitating faster dissolution into the aqueous environment (11).

Solvent Minimization

Unlike traditional solid dispersion methods like solvent evaporation that may rely heavily on organic solvents, mixed hydrotropy often employs aqueous solutions of hydrotropes to dissolve the drug, thereby "precluding organic solvents" and their associated residues (17, 29).

5. COMPONENTS USED (HYDROTROPIC AGENTS AND POLYMERS)

The success of the MHSD technique depends on the selection and ratio of hydrotropic agents and, occasionally, the inclusion of hydrophilic polymers to stabilize the dispersion.

Hydrotropic Agents

These agents are typically small organic molecules or salts that increase the solubility of hydrophobic drugs in water. Common agents include:

- **Organic Acid Salts:** Sodium benzoate, sodium salicylate, sodium acetate, and trisodium citrate (11, 18, 21, 22).
- **Amides and Related Compounds:** Urea and Nicotinamide (Niacinamide) (1, 3, 8, 20).
- **Polyols and Sugars:** Mannitol and Lactose (9, 16).
- **Others:** Resorcinol and Piperazine (24, 25, 12).

Hydrophilic Polymers and Carriers

Polymers are often used to inhibit recrystallization and provide a matrix for the drug. Examples include:

- **Polyethylene Glycols (PEG):** PEG 4000 and PEG 6000 are frequently used for their wetting properties (2, 8).
- **Cellulose Derivatives:** Hydroxypropyl Methylcellulose (HPMC) and its various grades (e.g., HPMC 2910) (26, 30).
- **Vinyl Polymers:** Polyvinylpyrrolidone (PVP) (2).
- **Natural Carriers:** Skimmed milk has also been explored as a novel carrier in combination with urea (15).

Excipients for Final Dosage Forms

For tablets, additional components like super disintegrants (Croscarmellose sodium, Crospovidone) and subliming agents (Camphor) are used to achieve fast disintegration (5, 20).

6. METHODS OF PREPARATION

Several methods are employed to prepare mixed hydrotropic solid dispersions, each offering different advantages in terms of scale-up and drug stability.

Solvent Evaporation Method

This is the most common laboratory technique. The drug and hydrotropic agents are dissolved in a common solvent (often water or an aqueous-organic mixture), followed by the removal of the solvent using techniques such as:

- **Rotary Evaporation:** Used for bulk removal of solvents under vacuum (9, 24).
- **Freeze-Drying (Lyophilization):** Produces a highly porous and amorphous mass (9).
- **Drying and Trituration:** The solution is evaporated to a semisolid mass, dried, and then triturated into a fine powder (18).

Fusion (Melt) Method

In this method, the hydrotropic agents (if they have suitable melting points, like urea) are melted, and the drug is dissolved or dispersed in the molten mass. The mixture is then cooled rapidly to form a solid dispersion (1, 13). A variation is the Fusion-Solvent Method, which combines the two approaches (1).

Physical Mixing / Grinding

The drug and hydrotropes are physically blended or subjected to intense trituration (kneading) to reduce particle size and ensure intimate contact. While simple, this method may not always achieve the same level of amorphous conversion as solvent-based methods (9, 21, 28).

Sublimation and Other Specialized Techniques

For orodispersible tablets, sublimation techniques using agents like camphor are used to create porous structures that enhance disintegration (5). Advanced methods like Hot-Melt Extrusion (HME) and supercritical antisolvent processes are also mentioned in broader solid dispersion contexts (34, 36, 13).

7. COMMON EVALUATION PARAMETERS

Thorough characterization is essential to verify the formation of a solid dispersion and assess its performance.

In-Vitro Dissolution Studies

Dissolution testing is the most critical parameter for assessing the success of the technique. Studies often use USP Type II (paddle) apparatus. Key findings frequently include:

- **Rapid Release:** Many MHSD formulations achieve >80% drug release within 1 min to 15 min, compared to significantly slower release for pure drugs (1, 11, 22).
- **Cumulative Drug Release (%CDR):** Optimized formulations (e.g.,

Ketoprofen KSD1-KSD9) show improvements in %CDR ranging from 72.28% to 94.76% (6).

Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR is used to identify the drug and assess chemical compatibility. The absence of significant shifts in the characteristic peaks of the drug indicates that there is no strong chemical interaction (like covalent bonding) between the drug and the hydrotropic agents, ensuring the drug remains chemically stable (1, 3, 11).

Differential Scanning Calorimetry (DSC)

DSC analysis provides thermal data. The disappearance of the drug's endothermic melting peak in the solid dispersion thermogram confirms that the drug is molecularly dispersed or has converted to an amorphous state (3, 8, 11).

X-Ray Diffraction (XRD / PXRD)

XRD is the gold standard for characterizing crystallinity. A shift from sharp, intense peaks (crystalline) to a broad "halo" pattern or reduced peak intensity in the solid dispersion indicates the formation of an amorphous system, which is directly linked to enhanced solubility (3, 7, 11, 21).

Scanning Electron Microscopy (SEM)

SEM is used to visualize the surface morphology. It often reveals a change from the distinct crystalline shapes of the pure drug to a more homogenous, irregular, or porous matrix in the solid dispersion (8, 19, 21).

Other Parameters

- **Equilibrium Solubility:** Measured by the shake-flask method to determine the fold-increase in solubility (5, 11, 19).
- **Micromeritic Properties:** Evaluation of bulk density, tapped density, Carr's index, and angle of repose to ensure good flowability for tablet compression (3, 16, 23).
- **Drug Content and Yield:** Assessed to ensure uniformity and efficiency of the preparation process (9, 21).

CONCLUSION

The mixed hydrotropic solid dispersion technique is a powerful and versatile tool for overcoming the solubility challenges of BCS Class II and IV drugs. By leveraging the synergistic effects of multiple hydrotropic agents, researchers can achieve massive increases in drug solubility-sometimes exceeding 600-fold-while maintaining a favourable safety and stability profile. The integration of this technique with solid dispersion technology facilitates the transition of drugs to amorphous states, leading to rapid dissolution and potentially improved clinical outcomes. As the pharmaceutical industry continues to seek "greener" and more efficient formulation strategies, the MHSD approach stands out as a promising frontier in drug delivery science.

REFERENCES

1. Agrawal GP. Preparation of solid dispersions of ornidazole using mixed hydrotropic solubilization technique and their characterization. *Int J Green Pharm*. 2017;11(4): S732-S737. doi:10.22377/IJGP.V11I04.1349
2. Enhancement of solubility and dissolution rate of poorly water-soluble drug by hydrotropic solid dispersion. *Zenodo*. 2021. doi:10.5281/zenodo.15673357
3. adav NK, Shukla T. Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate. *J Drug Deliv Ther*. 2018;8(5):481-488. doi:10.22270/JDDT.V8I5.1911

4. Gawandar P, Biyani K. Application of mixed hydrotropy for the solubility enhancement of irbesartan. *Int J Biol Pharm Allied Sci*. 2021;10(12):2016-2027. doi:10.31032/ijbpas/2021/10.12.2016
5. Shukla S, Chauhan V, Kaushik R. Optimization and characterization of meloxicam orodispersible tablets using mixed hydrotropy for enhanced water solubility. *J Appl Pharm Sci Res*. 2023;6(1):41-49. doi:10.31069/japsr.v6i1.06
6. Patel D, Soni P, Kumar S. Enhancing Ketoprofen Solubility: A Strategic Approach Using Solid Dispersion and Response Surface Methodology. *Curr Drug Deliv*. 2024;21(11):1598-1612. doi:10.2174/0118744710311951241018054453
7. Gawandar P, Biyani K. Investigating the Effect of Mixed Hydrotropy Approach on Solubility Enhancement of Felodipine. *Int J Pharm Investig*. 2024;14(4):645-650. doi:10.5530/ijpi.14.4.143
8. Vaghela B, Patel J, Chaudhari S. Formulation and evaluation of mixed hydrotropic solid dispersion of hydrochlorthiazide. *J Emerg Technol Innov Res*. 2019;6(6):536-545.
9. Rathore KS, Gupta R, Singh S, et al. Solubility Enhancement of a Poorly Water-Soluble Drug Using Hydrotropy and Mixed Hydrotropy-Based Solid Dispersion Techniques. *J Pharm*. 2022;2022:7161660. doi:10.1155/2022/7161660
10. Kartheek N, Sravani T, Swathi B, et al. Development and evaluation of fast dissolving tablets of efavirenz by solubility enhancement technique. *Indo Am J Pharm Sci*. 2024;11(01):464-473.
11. Maheshwari RK, Singh S. Solubility enhancement studies on lurasidone hydrochloride using mixed hydrotropy. *Int J Pharm Pharm Sci*. 2015;7(4):114-118. doi:10.4103/2230-973X.153390
12. Kaur I, Singh J, Kaur S. Solubility-Permeability Interplay of Hydrotropic Solubilization of Piroxicam. *Drug Dev Ind Pharm*. 2024;50(5):542-552. doi:10.1080/03639045.2024.2349576
13. Kumar A, Saini S, Rana AC. Various techniques of bioavailability enhancement: a review. *J Drug Deliv Ther*. 2016;6(3):34-41. doi:10.22270/JDDT.V6I3.1228
14. Patel P, Suhagia B, Shah P. Lurasidone: A Review of analytical methods for Estimation in Pharmaceutical formulation. *Int J Pharm Res*. 2017;9(1):15-22.
15. Saini S, Dhiman S, Sharma S. In Vitro Studies on Binary Mixture of Skimmed Milk and Urea as Solid Dispersion Carrier for Aceclofenac. *J Adv Appl Sci Res*. 2022;3(2):1-9. doi:10.46947/joaasr442022446
16. .Jain P, Maheshwari RK. Improving the solubility of nevirapine using a hydrotropy and mixed hydrotropy based solid dispersion approach. *Polim Med*. 2017;47(1):33-40. doi:10.17219/PIM/77093
17. Sharma D, Maheshwari RK. Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of hydrotropic solid dispersion of aceclofenac. *Asian J Pharm*. 2010;4(3):219-223. doi:10.22377/AJP.V4I3.224
18. Pawar S, Harsulkar A, Dhawale S. Formulation and characterization of fast disintegrating tablet of gliclazide by hydrotropy technique. *Int Res J Pharm*. 2019;10(5):137-142. doi:10.7897/2230-8407.1005187
19. Maheshwari RK. Mixed hydrotropy: novel science of solubility enhancement. *Indian J Pharm Sci*. 2012;74(1):82-84. doi:10.4103/0250-474X.91585

20. Mahajan N, Maheshwari RK. Formulation optimization of mouth dissolving tablets of meloxicam using mixed hydrotropic solubilization technique. *J Sci Innov Res*. 2015;4(2):81-86. doi:10.31254/jsir.2015.4206
21. Soni P, Kumar S. Design and characterization of glimepiride hydrotropic solid dispersion to enhance the solubility and dissolution. *J Adv Pharm Res*. 2024;12(2):68-78. doi:10.18231/j.joapr.2024.12.2.68.78
22. Sahoo SK, Mallick AA, Barik BB, Senapati PC. Formulation, characterization and in-vitro evaluation of fast dissolving tablets containing gliclazide hydrotropic solid dispersions. *Curr Drug Deliv*. 2017;14(8):1160-1168. doi:10.2174/1872211311666170427100213
23. Saha N, Singh S. Solubility enhancement of candesartan cilexetil by using different hydrotropic agents. *Int J Pharm Sci Res*. 2018;9(6):2354-2362.
24. Hameed SS, Al-Shawi AF. The development of ternary and quaternary solid dispersion based hydrotropic blends of atorvastatin calcium. *Zanco J Med Sci*. 2024;28(1):361-370. doi:10.15218/zjms.2024.010
25. Soni P, Kumar S. Solubility enhancement technique of cinnarizine by mixed hydrotropy. *Zenodo*. 2024. doi:10.5281/zenodo.14050663
26. Ali J, Al-Sawahli MM, Al-Wahaibi N, et al. Curcumin-loaded hydrotropic solid dispersion topical gel development and evaluation: A greener approach towards transdermal delivery of drugs. *Curr Drug Deliv*. 2023;20(8):1140-1152. doi:10.2174/2213346110666221020121020
27. Maheshwari RK, Nasare M. Solubility enhancement methods with importance of hydrotropy. *J Drug Deliv Ther*. 2012;2(6):134-138. doi:10.22270/JDDT.V2I6.329
28. Soni P, Kumar S. Solubility enhancement of miconazole by formulation of hydrotropic solid dispersions. *J Drug Deliv Ther*. 2017;7(3):121-125. doi:10.22270/JDDT.V7I3.1459
29. Vishwakarma AK, Maheshwari RK. Formulation development and evaluation of controlled release tablets of lamotrigine using mixed solvency concept. *Asian J Pharm*. 2014;8(1):42-48.
30. Vora P, Badhan AC. Improving solubility and dissolution of meloxicam by solid dispersion using hydroxypropyl methylcellulose 2910 3 cps and nicotinamide. *J Basic Clin Physiol Pharmacol*. 2020;31(1):20190249. doi:10.1515/JBCPP-2019-0249
31. Soni P, Kumar S. Formulation and evaluation of ibuprofen tablets using hydrotropic solid dispersion technique. *Zenodo*. 2024. doi:10.5281/zenodo.15111440
32. Sharma D, Kumar S. Solid dispersion – a technology for solubility enhancement of poorly soluble drugs. *Zenodo*. 2025. doi:10.5281/zenodo.16994038
33. Vasconcelos T, Sarmento B, Costa P. Solid dispersion as strategy to improve oral bioavailability of poor water-soluble drugs. *Drug Discov Today*. 2007;12(23-24):1068-1075.
34. Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D. A review on the recent advances in hot-melt extrusion for pharmaceutical applications. *Int J Pharm*. 2012;436(1-2):242-255.
35. Balasubramanian S, Iyer A. Hydrotropic solubilization: an emerging approach. *Int J Pharm Pharm Sci*. 2015;7(10):1-6.
36. Crowley MM, Zhang F, Repka MA, et al. pharmaceutical applications of hot-melt extrusion: part I. *Drug Dev Ind Pharm*. 2007;33(9):909-926.

37. Maheshwari RK. A review on: novel solubility enhancement technique hydrotropy. *Int J Pharm Res*. 2014;6(2):1-5.

HOW TO CITE: Athmika Haika, Neema George, Krishna Haridas, Shabnam Shibu, Aswathy Mohan, Divyamol A.K, Gayathri P.M, Praveena V.A, Mixed Hydrotropic Solid Dispersion Technique - A Green Solubilization Pathway: A Comprehensive Review on Solubility Enhancement Strategies, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 526-533, https://doi.org/10.5281/zenodo.21788980