International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Eutectic Mixtures: Bridging Physicochemical Fundamentals and Technological Applications

Vishal Wannur[1], Archana Patil[*2]

[1]Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research,Nehru Nagar-590010, Belagavi,Karnataka, India.
[2] Associate Professor, Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Nehru Nagar-590010, Belagavi, Karnataka, India.

Abstract

Eutectic mixtures are unique multi-component systems that melt at a temperature lower than their individual constituents, offering distinct advantages in various scientific and technological domains. This review explores the fundamental principles governing eutectic systems, with emphasis on phase behavior, thermodynamic interactions, and structural characteristics. The article highlights the pharmaceutical potential of eutectic mixtures in enhancing the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs, thereby improving oral and topical drug delivery. Applications in controlled drug release and dermal formulations are thoroughly discussed. Beyond pharmaceuticals, eutectic systems have found valuable applications in materials science, especially in alloy production, phase change materials, and eco-friendly solvents. Recent advances in deep eutectic solvents (DES) and natural deep eutectic solvents (NADES) showcase their promise as sustainable alternatives in green chemistry. The review also discusses characterization methods such as differential scanning calorimetry (DSC), Powder X-ray Diffraction (PXRD), and Fourier-transform infrared spectroscopy (FTIR), essential for analyzing eutectic behavior and interactions. Overall, eutectic mixtures represent a dynamic and versatile class of systems with broad implications for drug delivery, chemical processing, and materials innovation.

Keywords: Eutectic mixture, Deep Eutectic Mixture, Controlled Drug Release, X-Ray Powder Diffraction, Differential Scanning Calorimetry

1. INTRODUCTION:

Eutectic mixtures have garnered significant interest across diverse scientific disciplines due to their unique thermodynamic behaviour and versatility in practical applications. These systems, typically composed of two or more components, exhibit a eutectic point at which the mixture melts at a single, sharp temperature that is lower than the melting points of the individual constituents.[1] At this eutectic composition, a homogenous liquid phase is formed upon melting, followed by solidification into a finely dispersed microstructure. This phenomenon is primarily attributed to specific molecular interactions such as hydrogen bonding, van der Waals forces, and ionic interactions, which disrupt the regular lattice of pure components and lead to a depression in melting temperature.[2]

In the pharmaceutical domain, eutectic mixtures offer a promising strategy for improving the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients (APIs). They are particularly useful for enhancing the solubility and dissolution rate of poorly water-soluble drugs, thereby improving their oral bioavailability.[3] Additionally, eutectic systems are employed to design advanced drug delivery platforms, including transdermal, topical, and controlled-release formulations.[4] Their ability to form low-viscosity liquid phases also facilitates drug permeation through biological membranes, making them ideal candidates for dermal and mucosal applications. Moreover, eutectic systems often consist of biocompatible and pharmaceutically acceptable excipients, allowing for patient-friendly and cost-effective formulation strategies. The ability to design eutectic compositions with tunable physicochemical properties further enhances their utility across a spectrum of therapeutic areas.[5]

From a formulation science perspective, eutectic mixtures serve as effective carriers or solubilizers that can modulate drug stability, melting behavior, and mechanical strength of solid dosage forms. They provide a platform for developing solid dispersions or co-crystals without the need for complex processing techniques.[6] Eutectic behaviour can also be exploited to avoid crystallization issues during formulation, thereby promoting supersaturation and enhanced absorption. The intrinsic ability of eutectic systems to undergo phase transitions at lower energy inputs is especially advantageous in heat-sensitive drug delivery systems and green manufacturing approaches.[7]

Beyond their pharmaceutical relevance, eutectic mixtures are integral to materials science, where they are utilized in metallurgy, polymer science, and the development of green solvents.[8]

2. MECHANISM OF EUTECTIC MIXTURES:

Eutectic mixtures represent a unique class of multi-component systems characterized by a melting point depression relative to their individual constituents. The fundamental mechanism underlying eutectic behavior arises from the thermodynamic and molecular interactions between the components, which disrupt their pure crystalline lattices and enable a lower melting temperature at a specific composition known as the eutectic point.[9]

At the molecular level, when two or more components are combined, the presence of hetero-molecular interactionssuch as hydrogen bonding, van der Waals forces, ionic interactions, or dipole-dipole attractionsinterferes with the regular packing of molecules in the pure solid phases. This disruption reduces the lattice energy and weakens the overall crystal structure, leading to a reduction in melting temperature. Consequently, at the eutectic composition, the mixture forms a homogeneous liquid phase at a temperature lower than that of any pure component.[10]

Thermodynamically, the eutectic point is defined by the intersection of the liquidus lines in the binary (or multicomponent) phase diagram, representing the lowest temperature at which the liquid phase can coexist with two or more solid phases in equilibrium. Upon cooling from the melt, the eutectic mixture solidifies simultaneously into two or more intimately mixed solid phases, often producing a fine microstructure with enhanced surface area and altered physicochemical properties.[11]

This melting point depression is governed by the Gibbs free energy minimization, where the system favours a liquid phase with lower free energy at the eutectic composition and temperature compared to

the pure solids. The Gibbs phase rule further explains the equilibrium state by defining the degrees of freedom within the system at this invariant point.[12]

In practical terms, the mechanism enables eutectic mixtures to achieve enhanced solubility, improved dissolution rates, and modified mechanical properties. For example, in pharmaceutical applications, the formation of a eutectic mixture can facilitate the generation of metastable or partially amorphous phases that dissolve more readily than their crystalline counterparts, thereby improving bioavailability.[13]

Overall, the mechanism of eutectic mixtures is a balance between molecular interactions and thermodynamic principles that result in a unique melting behaviour and phase equilibrium. This fundamental understanding enables the rational design and optimization of eutectic systems for diverse applications in drug delivery and material sciences.[14]

3. THERMODYNAMIC AND PHASE BEHAVIOR:

Eutectic mixtures are governed by fundamental thermodynamic principles that dictate the behavior of multi-component systems under varying temperature and composition conditions.[15] A eutectic system typically consists of two or more components that, when combined at a specific molar ratio known as the eutectic composition, exhibit a melting point significantly lower than the individual melting points of the pure components. This phenomenon results from the disruption of each component's crystal lattice due to the presence of the other, leading to an energetically favorable eutectic phase.[16]

The phase diagram of a binary eutectic system is typically characterized by two descending liquidus lines that meet at a singular point — the eutectic point — which corresponds to the lowest melting temperature achievable by the mixture. Upon cooling, the eutectic mixture undergoes a solidification process that yields a fine microstructure composed of intimately mixed solid phases. This characteristic melting behavior provides a thermodynamic advantage, especially for applications requiring low-melting formulations or rapid phase transitions.[17]

The formation and stability of eutectic mixtures are influenced by various molecular interactions, including hydrogen bonding, van der Waals forces, ionic interactions, and dipole-dipole forces.[18] These interactions affect the degree of miscibility between the components in both solid and liquid states, contributing to the depression of melting point and stabilization of the eutectic phase. The Gibbs phase rule is employed to analyze the number of phases present at equilibrium, and it plays a critical role in understanding the phase behavior of multicomponent systems.[19]

In pharmaceutical and materials science, thermodynamic modeling of eutectic behavior is increasingly supported by computational tools and software, allowing for the prediction of eutectic compositions and melting points with greater accuracy.[20] This predictive capability facilitates rational formulation design by narrowing down candidate mixtures before experimental validation. Moreover, eutectic systems can exhibit congruent or incongruent melting behavior depending on whether the melt recrystallizes to the original eutectic composition or a different phase assemblage.[21]

Understanding the thermodynamic behavior of eutectic systems is crucial in tailoring their performance in specific applications. For example, in drug delivery systems, controlling the eutectic composition allows for fine-tuning of drug release kinetics, dissolution rates, and phase transformation behaviors. In

materials engineering, eutectic systems provide essential information for the development of solder alloys, phase change materials, and low-temperature processing techniques.[22]

Overall, the thermodynamic and phase behavior of eutectic mixtures represents a foundational aspect in the design and development of advanced functional materials and pharmaceutical formulations. Insights into their phase diagrams, molecular interactions, and equilibrium dynamics enable the strategic utilization of eutectic systems across a broad range of scientific and industrial applications.[23]

4. TYPES OF EUTECTIC MIXTURES:

Eutectic mixtures can be broadly classified into several types based on their composition, origin, and intended application. Understanding these types aids in the strategic selection and formulation of eutectic systems for specific uses:

- Binary Eutectic Mixtures: These consist of two components and represent the simplest form of eutectic systems. The components are selected to achieve a specific eutectic composition and melting point. Examples include mixtures of menthol-camphor or ibuprofen-nicotinamide.[24]
- Ternary and Multicomponent Eutectic Mixtures: These involve three or more components and provide greater flexibility in tuning the melting behavior and functional properties. Multicomponent systems are often used in the formulation of deep eutectic solvents or in advanced material synthesis.
- Simple Eutectics vs. Deep Eutectic Solvents (DES): Simple eutectics involve physical mixing of solid components leading to a depressed melting point. In contrast, DES are formed through strong hydrogen bonding interactions and often involve a hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA), such as choline chloride and urea.[25]
- Natural Deep Eutectic Solvents (NADES): These are a subclass of DES derived from natural compounds like sugars, amino acids, and organic acids. NADES are biodegradable, non-toxic, and suitable for applications in pharmaceuticals, nutraceuticals, and cosmetics.
- Pharmaceutical Eutectics: These systems are designed to improve drug solubility, enhance bioavailability, and create novel dosage forms. Pharmaceutical eutectics often involve active pharmaceutical ingredients (APIs) combined with suitable coformers.
- Metallic Eutectics: Common in material science and metallurgy, metallic eutectics are used to produce alloys with desirable melting points and mechanical properties. Examples include tin-lead or silver-copper systems.[26]

These classifications highlight the versatility and broad utility of eutectic mixtures in both formulation development and material design.

5. EUTECTIC MIXTURES FORMATION

The formation of eutectic mixtures relies on selecting two or more compatible components that exhibit favorable intermolecular interactions, leading to a reduced melting point at a specific composition. Although eutectic mixtures differ from true cocrystals in crystal structure, many of the preparation

techniques overlap due to similar solid-state interaction principles.[27] The most commonly employed methods for eutectic mixture formation include:

Solvent Evaporation

In this method, the eutectic components are dissolved in a common volatile solvent and then allowed to evaporate slowly under controlled conditions (ambient or reduced pressure). As the solvent evaporates, the components co-precipitate in a fine crystalline form, potentially forming a eutectic system if the composition is near the eutectic point. This method is ideal for thermolabile substances and allows for fine control over morphology.[28]

Neat Grinding (Dry Grinding)

This solvent-free technique involves mechanically grinding the solid components together using a mortar and pestle or ball mill. The applied mechanical energy facilitates solid-state interactions that can lead to the formation of eutectic mixtures. It is a green and efficient method, often used for initial screening of eutectic behavior due to its simplicity and minimal solvent usage.[29]

Liquid-Assisted Grinding (LAG)

Similar to neat grinding, this method involves grinding the components in the presence of a small amount of solvent (just enough to wet the mixture). The added solvent can enhance molecular mobility and promote eutectic formation by facilitating intermolecular interactions. LAG often yields faster or more complete eutectic formation than neat grinding.[30]

Melt Crystallization

This method involves heating the mixture above the melting points of both components to create a homogeneous melt, followed by controlled cooling. If the cooling rate and composition are appropriate, a eutectic mixture will crystallize upon solidification. Melt crystallization is particularly useful for screening phase diagrams and evaluating thermal behavior.[31]

Sublimation

Sublimation is used when one or both components have sufficient vapor pressure to transition directly from solid to gas. Under controlled temperature and pressure, the vapors co-condense to form a fine solid that may exhibit eutectic behavior. This method is less common but useful for highly volatile compounds.[32]

These preparation methods help promote intimate mixing and specific interactions between the components, which are essential for achieving a stable eutectic mixture. Selection of method depends on the physicochemical properties of the components and the intended application of the eutectic system.

6. EUTECTIC MIXTURES IN ANTICANCER DRUG DEVELOPMENT:

Eutectic mixtures have become an innovative and valuable approach in the formulation of anticancer therapeutics, especially in overcoming the physicochemical limitations of hydrophobic drugs. A significant proportion of anticancer agents exhibit poor aqueous solubility, low bioavailability, and erratic absorption profiles, which compromise therapeutic efficacy.[33] Eutectic systems, formed by

combining two or more components that exhibit a reduced melting point at a specific composition, provide a favorable medium for solubilizing such drugs. For example, compounds like paclitaxel, tamoxifen, and curcumin have been successfully formulated with eutectic-forming agents such as menthol, fatty acids, and sugar alcohols to create low-melting, metastable systems that enhance dissolution kinetics and promote rapid drug release.[34]

Beyond solubility enhancement, eutectic mixtures offer additional benefits such as improved permeability across epithelial barriers, which is essential for drugs targeting solid tumors. This is particularly advantageous in transdermal and intranasal drug delivery approaches, where the eutectic phase helps disrupt the lipid structure of biological membranes, facilitating deeper penetration of anticancer molecules. Furthermore, eutectic mixtures can be tailored for localized or site-specific delivery, thereby minimizing systemic toxicity and reducing off-target effects, a critical consideration in chemotherapy.[35]

Recent advancements include the incorporation of eutectic systems into nanoparticle and solid dispersion platforms to further improve stability, drug loading, and release profiles.[36] Moreover, the use of deep eutectic solvents (DES) and natural deep eutectic solvents (NADES) is gaining traction as novel solubilizing vehicles or extraction media for phytochemicals with anticancer properties. These DES-based systems not only enhance the solubility and stability of bioactive molecules but also align with green chemistry principles, offering sustainable solutions in pharmaceutical processing.[37]

Eutectic-based formulations have also demonstrated potential in overcoming drug resistance mechanisms by improving intracellular uptake or co-delivering synergistic anticancer agents within a single matrix. This opens new avenues in combination therapy, where eutectic mixtures can serve as co-formulation platforms to deliver multiple agents simultaneously at optimal ratios.

Overall, eutectic mixtures represent a versatile and scalable strategy in the design of next-generation anticancer therapeutics. By enhancing solubility, bioavailability, permeability, and site-specific delivery, they address critical challenges in oncology drug development and hold promise for translating into clinically viable treatment options.[38]

7. CHARACTERIZATION OF EUTECTIC MIXTURES:

Comprehensive characterization of eutectic mixtures is essential to understand their structural, thermal, and physicochemical behavior. Various analytical techniques are employed to identify eutectic compositions, evaluate component interactions, and monitor physical changes during formulation or processing.[39] These tools enable scientists to confirm eutectic formation and assess the stability and performance of eutectic-based formulations.

- **Differential Scanning Calorimetry (DSC):** DSC is a primary technique used to determine the eutectic point by measuring the heat flow associated with phase transitions. It identifies characteristic endothermic peaks corresponding to the melting of individual components and the eutectic mixture. The onset temperature of the eutectic melting peak provides insight into the compatibility and thermodynamic behavior of the system. In addition to determining eutectic temperature, DSC helps in evaluating thermal stability and detecting polymorphic transitions.[40]

- **X-ray Powder Diffraction (XRPD):** XRPD is used to assess the crystallinity of the mixture and identify any changes in the crystal structure resulting from eutectic formation. The presence of sharp diffraction peaks indicates crystalline components, while a reduction in intensity or the appearance of new peaks may signal eutectic interactions or partial amorphization. XRPD thus assists in confirming the formation of a distinct eutectic phase and evaluating structural changes.[41]
- **Fourier Transform Infrared Spectroscopy (FTIR):** FTIR spectroscopy is applied to investigate the nature of molecular interactions between eutectic components. Shifts or changes in characteristic absorption bands (e.g., O-H, C=O, N-H stretches) can indicate hydrogen bonding, dipole-dipole interactions, or other non-covalent forces responsible for eutectic behavior. FTIR is particularly useful for elucidating the mechanisms of eutectic formation and understanding the interaction environment within the mixture.[42]
- **Scanning Electron Microscopy (SEM):** SEM provides detailed information about the surface morphology and microstructural arrangement of eutectic mixtures. It allows for visualization of the surface texture, particle distribution, and phase separation. Fine and homogenous microstructures typically reflect successful eutectic solidification, whereas irregular patterns may indicate phase segregation or incomplete mixing. SEM is crucial for correlating morphological features with functional performance, particularly in solid dosage forms.[43]

By combining data from these complementary techniques, researchers can develop a thorough understanding of eutectic mixtures' composition, structure, and behavior. This multi-faceted approach aids in optimizing formulation strategies, ensuring batch-to-batch consistency, and predicting performance in both pharmaceutical and materials science applications.

8. ADVANTAGES OF EUTECTIC MIXTURES IN ANTICANCER DRUGS

Enhanced Solubility of Poorly Water-Soluble Drugs

Many anticancer drugs (e.g., paclitaxel, docetaxel, tamoxifen) suffer from poor aqueous solubility. Eutectic mixtures reduce the melting point of the drug system, creating a metastable, partially amorphous phase that dissolves more readily in biological fluids.[44]

Improved Oral Bioavailability

By enhancing dissolution rates, eutectic systems facilitate greater absorption in the gastrointestinal tract, leading to improved systemic bioavailability of oral chemotherapeutic agents.[45]

Facilitated Drug Permeation and Transdermal Delivery

Eutectic mixtures (e.g., lidocaine-prilocaine) can disrupt skin lipid layers and increase membrane fluidity, making them effective in delivering anticancer agents transdermally or via mucosal routes, especially for localized tumors.[46]

Localized and Controlled Drug Release

The unique melting and solidification behavior of eutectic systems can be harnessed to design formulations that allow site-specific release, reducing systemic toxicity and side effects common with conventional chemotherapy.[47]

Combination Therapy Potential

Eutectic mixtures can co-formulate two or more anticancer agents, maintaining them in a stable, synergistic ratio. This facilitates combination therapy strategies in a single dosage form, enhancing efficacy and patient compliance.[48]

Green Solvent Alternatives

Deep eutectic solvents (DES) and natural deep eutectic solvents (NADES) are gaining attention as non-toxic, biodegradable media for formulating and extracting anticancer phytochemicals, aligning with sustainable pharmaceutical development.

Reduced Crystallization Risk

Due to their disrupted lattice structure, eutectic mixtures suppress crystallization of the drug during storage and processing, ensuring consistent performance and bioavailability.[49]

Thermally Stable Formulations for Sensitive Drugs

Eutectic systems allow processing at lower temperatures, which is beneficial for temperature-sensitive anticancer agents or biologics, preserving their stability and efficacy.

Versatility in Dosage Forms

Eutectic mixtures are compatible with various dosage forms including solid dispersions, topical gels, transdermal patches, and nanoformulations, making them adaptable for diverse therapeutic applications.[50]

9. PHARMACEUTICAL APPLICATIONS:

Solubility Limitation in APIs:

Many active pharmaceutical ingredients (APIs) exhibit poor aqueous solubility, resulting in limited dissolution rates and compromised oral bioavailability, which remains a critical formulation challenge.

Mechanistic Basis of Eutectic Enhancement:

Eutectic mixtures induce the formation of a metastable or partially amorphous phase by disrupting the crystalline lattice of individual drug molecules at the eutectic composition. This results in a significant depression of the melting point and increases the system's Gibbs free energy, thereby enhancing solubility and dissolution kinetics.[51]

Dissolution Rate Improvement:

The increased dissolution rate facilitated by eutectic formation directly correlates with enhanced drug absorption, especially relevant for Biopharmaceutics Classification System (BCS) Class II drugs, where dissolution is the rate-limiting step for bioavailability.

Representative Eutectic Systems:

- *Ibuprofen–Menthol:* Formation of eutectic mixtures leads to improved wettability and reduction in particle agglomeration, yielding faster dissolution and enhanced bioavailability.

- *Ibuprofen–Camphor:* Demonstrates analogous melting point depression and solubility enhancement.
- *Lidocaine–Prilocaine:* Widely utilized in topical formulations, eutectic systems form a liquid phase at skin temperature that increases drug permeation and accelerates onset of pharmacological action.[52]

Controlled Drug Release Potential:

Modulation of eutectic composition allows fine-tuning of drug release kinetics, enabling sustained or controlled release profiles beneficial for transdermal and other advanced drug delivery systems.

Clinical and Therapeutic Impact:

By enhancing solubility and bioavailability, eutectic systems improve the pharmacokinetic profile of drugs, thereby optimizing therapeutic efficacy and patient compliance.[53]

10. RECENT ADVANCEMENTS IN EUTECTIC MIXTURES:

In recent years, eutectic mixtures have emerged as a pivotal area of research due to their versatile applications and environmentally sustainable nature. A major breakthrough in this domain is the development of deep eutectic solvents (DES) and natural deep eutectic solvents (NADES), which have revolutionized the way solvents are designed and used. DES are typically formed by mixing a hydrogen bond acceptor (such as choline chloride) with a hydrogen bond donor (such as urea, glycerol, or organic acids) in specific molar ratios.[54] This results in a eutectic system with a melting point significantly lower than that of the individual components, often yielding a stable liquid at room temperature. These solvents exhibit unique properties such as low vapor pressure, high thermal stability, tunable polarity, and excellent solvation ability for a wide range of chemical species, making them attractive alternatives to traditional volatile organic solvents and ionic liquids.

NADES, a subset of DES, are composed entirely of naturally occurring metabolites such as sugars, amino acids, organic acids, and choline derivatives. Their biodegradability, low toxicity, and biocompatibility render NADES highly suitable for applications in pharmaceuticals, cosmetics, food processing, and extraction of bioactive compounds from natural sources.[55] Recent studies demonstrate that NADES can improve the solubility and stability of poorly water-soluble drugs, thus enhancing their bioavailability. Moreover, their mild preparation methods and ability to preserve the activity of sensitive biomolecules have catalyzed interest in their use for drug delivery and enzymatic catalysis.

Beyond pharmaceutical applications, eutectic mixtures are gaining momentum in green chemistry, where they facilitate environmentally benign synthesis routes, reduce hazardous waste, and improve reaction efficiencies. Researchers have developed tailored DES and NADES formulations to optimize viscosity, polarity, and hydrogen bonding networks, enabling precise control over chemical reactivity and selectivity. This has significant implications for catalysis, metal processing, electrochemistry, and biomass valorization.

Despite these advancements, challenges remain in scaling up the production of DES and NADES, ensuring long-term stability, and gaining regulatory approval for widespread industrial use. However, ongoing research is focused on overcoming these hurdles through high-throughput screening,

computational modeling, and rigorous toxicological assessments. The promising attributes of eutectic mixtures, combined with their sustainable profiles, underscore their potential to transform diverse scientific and industrial fields, positioning them at the forefront of next-generation solvent technologies.[56]

11. CHALLENGES AND FUTURE PERSPECTIVES:

Challenges

Despite the growing interest and promising applications of eutectic mixtures in pharmaceutical and material sciences, several significant challenges remain. A foremost issue is the physical and chemical stability of eutectic systems. Due to their often metastable or semi-amorphous nature, these mixtures can undergo recrystallization, phase separation, or polymorphic transitions during storage, which may adversely affect their dissolution characteristics, bioavailability, and overall therapeutic efficacy. This instability can limit shelf-life and complicate formulation development.

Another critical challenge is the scalability and reproducibility of eutectic mixtures in industrial manufacturing. Precise control over component ratios, mixing protocols, and thermal processing is essential to maintain the eutectic composition and ensure batch-to-batch consistency. However, scaling up laboratory techniques such as melt-quenching or solvent evaporation often leads to variability in physicochemical properties, posing a barrier to commercial production.

Regulatory acceptance remains an additional hurdle, particularly for novel eutectic formulations involving innovative excipients like deep eutectic solvents (DES) or natural deep eutectic solvents (NADES). These systems require thorough toxicological and safety evaluations, and existing regulatory frameworks are not yet fully adapted to accommodate these new materials, delaying clinical translation and market entry.[57]

From a scientific perspective, the complexity of predicting eutectic behavior including melting points, phase stability, and miscibility arises from intricate molecular interactions within multi-component systems. Although computational tools and thermodynamic models have advanced, their predictive accuracy is still limited, necessitating extensive empirical studies that increase formulation development time and cost.

Future Perspectives

To overcome these challenges, several promising avenues of research and technological advancement are being pursued. The adoption of high-throughput screening and combinatorial formulation strategies can accelerate the identification of eutectic compositions with optimized solubility, stability, and bioavailability profiles. These approaches enable rapid, systematic exploration of diverse component combinations and processing conditions.

Advances in computational modeling and machine learning hold considerable potential to enhance the rational design of eutectic mixtures. By integrating molecular dynamics simulations, thermodynamic phase prediction, and big data analytics, researchers can more accurately forecast eutectic points, miscibility windows, and stability parameters. This predictive capability will reduce reliance on trial-and-error experimentation, streamlining development.[58]

Further progress in analytical and characterization techniques—such as solid-state nuclear magnetic resonance (NMR), synchrotron X-ray diffraction, and atomic force microscopy—will deepen molecular-level understanding of eutectic interactions and microstructural organization. These insights are critical for improving formulation robustness and ensuring reproducible performance.

From a translational standpoint, comprehensive clinical evaluation and regulatory harmonization are essential. Well-designed pharmacokinetic and pharmacodynamic studies will validate the therapeutic benefits of eutectic-based formulations, while collaboration with regulatory agencies will facilitate the establishment of clear guidelines for approval and commercialization.

Finally, the future of eutectic mixtures aligns closely with sustainable and green chemistry principles. The development and application of biodegradable, non-toxic, and naturally derived eutectic components support environmentally friendly pharmaceutical manufacturing and materials processing. This focus on sustainability is likely to drive continued innovation and adoption in the coming years.[59]

CONCLUSION:

Eutectic mixtures represent a compelling and versatile strategy in the rational design of pharmaceutical formulations and functional materials. Their characteristic melting point depression, arising from specific intermolecular interactions and favorable thermodynamic properties, enables the development of systems that enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble active pharmaceutical ingredients (APIs). The integration of eutectic technology into anticancer drug delivery platforms, in particular, offers notable improvements in membrane permeability, controlled release, and combination therapy potential.

The recent evolution of deep eutectic solvents (DES) and natural deep eutectic solvents (NADES) as green, biocompatible, and tunable solvents aligns with the global movement toward sustainable pharmaceutical manufacturing and environmentally responsible chemistry. These solvents provide unique physicochemical environments for solubilizing hydrophobic drugs and stabilizing bioactive compounds, expanding their application beyond conventional solvents and excipients.

Despite these advances, the practical implementation of eutectic systems is hindered by challenges in physical stability, scalability, regulatory compliance, and predictive design. Addressing these limitations requires a multidisciplinary approach involving advanced computational modeling for eutectic point prediction, high-resolution analytical techniques for structural elucidation, and robust in vivo validation to confirm therapeutic efficacy and safety.

Continued exploration and systematic optimization of eutectic mixtures will likely yield next-generation formulation strategies that meet the growing demands for efficient, patient-friendly, and sustainable therapeutics across a range of clinical and industrial applications.

DECLARATION OF COMPETING INTEREST

The authors confirm that there are no known competing financial interests or personal relationships that could have influenced the findings presented in this paper.

ACKNOWLEDGEMENTS

The authors are thankful to Mr. Rahul Koli, Ph.D. Research Scholar, Department of Pharmaceutical Quality Assurance, KLE College of Pharmacy, Belagavi. The authors gratefully acknowledge the Principal of KLE College of Pharmacy, Belagavi, The Authors are also thankful to Department of Pharmaceutics for their assistance.

REFERENCES:

1. Rawla P. Epidemiology of prostate cancer. World journal of oncology. 2019 Apr 20;10(2):63.
2. Tucci M, Zichi C, Buttigliero C, Vignani F, Scagliotti GV, Di Maio M. Enzalutamide-resistant castration-resistant prostate cancer: challenges and solutions. OncoTargets and therapy. 2018 Oct 24:7353-68.
3. Scher HI, Fizazi K, Saad F, et al. Increased survival with Enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197. doi:10.1056/NEJMoa1207506. https://pubmed.ncbi.nlm.nih.gov/22894553/
4. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787–790. doi:10.1126/science.1168175. https://pubmed.ncbi.nlm.nih.gov/19423871/
5. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424–433. doi:10.1056/NEJMoa1405095. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715745/
6. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381:121–131. doi:10.1056/NEJMoa1903835. https://pubmed.ncbi.nlm.nih.gov/31141632/
7. Clegg NJ, Wongvipat J, Joseph JD, et al. AR mutations and resistance to Enzalutamide. *Cancer Discov*. 2012;2(9):805–816. doi:10.1158/2159-8290.CD-12-0060. https://pubmed.ncbi.nlm.nih.gov/22993403/
8. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to Enzalutamide in prostate cancer. *N Engl J Med*. 2014;371(11):1028–1038. doi:10.1056/NEJMoa1315815. https://pubmed.ncbi.nlm.nih.gov/25184630/
9. U.S. Food and Drug Administration. *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*. 2017. https://www.fda.gov/media/70963/download
10. Serajuddin, A.T.M. (2007). Salt formation to improve drug solubility. *Advanced Drug Delivery Reviews*, 59(7), 603–616.
11. Yu, L. (2001). Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Advanced Drug Delivery Reviews*, 48(1), 27–42.
12. Qiao, N., Li, M., Schlindwein, W., Malek, N., Davies, A., &Trappitt, G. (2011). Pharmaceutical co-crystals: an overview. *International Journal of Pharmaceutics*, 419(1-2), 1–11.
13. Bazzo, G.C., Pezzini, B.R., &Stulzer, H.K. (2020). Eutectic mixtures as an approach to enhance solubility, dissolution rate and oral bioavailability of poorly water-soluble drugs. *International Journal of Pharmaceutics*, 588, 119741

14. Craig, D.Q.M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
15. Lu, J., & Rohani, S. (2009). Preparation and characterization of carbamazepine–nicotinamide cocrystal. *Organic Process Research & Development*, 13(6), 1269–1275.
16. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. Journal of pharmacological and toxicological methods. 2000 Jul 1;44(1):235-49.
17. Dugar, R.P., Gajera, B.Y., & Dave, R.H. (2016). Fusion method for solubility and dissolution rate enhancement of ibuprofen using block copolymer poloxamer 407. *AAPS PharmSciTech*, 17, 1428–1440.
18. Pezzini, B.R., Silva, M.A.S., & Ferraz, H.G. (2020). Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. *Journal of Pharmaceutical Sciences*, 109(9), 2738–2748.
19. Amidon, G.L., Lennernäs, H., Shah, V.P., &Crison, J.R. (1995). A theoretical basis for a biopharmaceutic drug classification. *Pharmaceutical Research*, 12(3), 413–420.
20. Liao, J.H., Wu, P.C., & Bai, Y.H. (2005). Eutectic mixture of choline chloride/urea as a green solvent in synthesis of a coordination polymer: [Zn(O3PCH2CO2)]·NH4. *Inorganic Chemistry Communications*, 8(4), 390–392.
21. Pereira PF, Andrade CT. Optimized pH-responsive film based on a eutectic mixture-plasticized chitosan. Carbohydrate Polymers. 2017 Jun 1;165:238-46.
22. Tiwari, R.V., & Tiwari, R. (2016). Drug Delivery Systems: An Overview. In Dos Santos, D. (Ed.), Handbook of Pharmaceutical Manufacturing Formulations. CRC Press.
23. Serajuddin, A.T.M. (2007). Salt formation to improve drug solubility. Advanced Drug Delivery Reviews, 59(7), 603–616. https://doi.org/10.1016/j.addr.2007.05.010
24. Rawla, P. (2019). Epidemiology of prostate cancer. World Journal of Oncology, 10(2), 63–89. https://doi.org/10.14740/wjon1191
25. Dai, W., Zhang, D., Duan, C., Jia, L., & Li, Y. (2020). Strategies to improve the solubility and bioavailability of poorly water-soluble drugs: From basic research to industrial applications. Advanced Drug Delivery Reviews, 152, 2–40. https://doi.org/10.1016/j.addr.2019.11.009
26. Shah, B., Khunt, D., Misra, M. (2016). Enhancement of oral bioavailability of poorly soluble drugs through solid-state modifications. Journal of Drug Delivery Science and Technology, 31, 47–59. https://doi.org/10.1016/j.jddst.2015.12.009
27. Thakral, S., Thakral, N. K., & Majumdar, D. K. (2018). Eutectic systems in pharmaceutical applications: A review. Drug Discovery Today, 23(4), 760–770. https://doi.org/10.1016/j.drudis.2018.01.007
28. Alhalaweh, A., & Velaga, S. P. (2010). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Expert Opinion on Drug Delivery, 7(8), 1019–1030. https://doi.org/10.1517/17425247.2010.498476
29. Kalepu, S., & Nekkanti, V. (2015). Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharmaceutica Sinica B, 5(5), 442–453. https://doi.org/10.1016/j.apsb.2015.07.003
30. https://go.drugbank.com/drugs/DB08899
31. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 15951529, Enzalutamide. Retrieved May 22, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Enzalutamide.

32. Stuurman FE, Nuijen B, Beijnen JH, Schellens JH. Oral anticancer drugs: mechanisms of low bioavailability and strategies for improvement. Clinical pharmacokinetics. 2013 Jun;52:399-414.
33. Erdogan B, Kostek O, Bekirhacioglu M. Enzalutamide in prostate cancer, a review on Enzalutamide and cancer. Eurasian j med oncol. 2018;2(3):121-9.
34. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. Cold Spring Harbor perspectives in medicine. 2018 Dec 1;8(12):a030361.
35. Varma MM, Pandi JK. Dissolution, solubility, XRD, and DSC studies on flurbiprofen-nicotinamide solid dispersions. Drug development and industrial pharmacy. 2005 Jan 1;31(4-5):417-23.
36. Shilei L, Neng Z, Guohui F. Eutectic mixtures of capric acid and lauric acid applied in building wallboards for heat energy storage. Energy and buildings. 2006 Jun 1;38(6):708-11.
37. El Achkar T, Greige-Gerges H, Fourmentin S. Basics and properties of deep eutectic solvents: a review. Environmental chemistry letters. 2021 Aug;19:3397-408.
38. Cherukuvada S, Nangia A. Eutectics as improved pharmaceutical materials: design, properties and characterization. Chemical Communications. 2014;50(8):906-23.
39. Patel RD, Raval MK, Pethani TM, Sheth NR. Influence of eutectic mixture as a multi-component system in the improvement of physicomechanical and pharmacokinetic properties of diacerein. Advanced Powder Technology. 2020 Apr 1;31(4):1441-56.
40. Yong CS, Oh YK, Jung SH, Rhee JD, Kim HD, Kim CK, Choi HG. Preparation of ibuprofen-loaded liquid suppository using eutectic mixture system with menthol. European Journal of Pharmaceutical Sciences. 2004 Dec 1;23(4-5):347-53.
41. Hong SH, Dinh L, Abuzar SM, Lee ES, Hwang SJ. Synthesis of celecoxib-eutectic mixture particles via supercritical CO2 process and celecoxib immediate release tablet formulation by quality by design approach. Pharmaceutics. 2022 Jul 26;14(8):1549.
42. Palanisamy V, Kale DP, Chormale JH, Bansal AK, Sanphui P. Improved tableting properties of ascorbic acid via eutectic compositions with sugars. Journal of Molecular Structure. 2024 Feb 5;1297:136969.
43. Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery–a review. Pharmaceutical science & technology today. 2000 Apr 1;3(4):138-45.
44. *Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications*.
45. *A review on advancement of cocrystallization approach and a brief on screening, formulation and characterization of the same*.
46. *Recent Advances in Co-Former Screening and Formation Prediction of Multicomponent Solid Forms of Low Molecular Weight Drugs*.
47. *Cocrystals by Design: A Rational Co-former Selection Approach for Tackling the API Problems*.
48. Shaligram PS, George CP, Sharma H, Mahadik KR, Patil S, Vanka K, Arulmozhi S, Gonnade RG. Rivaroxaban eutectics with improved solubility, dissolution rates, bioavailability and stability. CrystEngComm. 2023;25(22):3253-63.
49. Prajapati JD, Chhalotiya KU, Prajapati DM. Quantification of newer anticancer drug Enzalutamide by stability indicating RP-LC method and UV-visible spectroscopic method in bulk and synthetic mixture. J Mol Oncol Res. 2017; 1 (2): 65-85. 66 J Mol Oncol Res. 2017 Volume 1 Issue. 2017;2:3.

50. Zamir GK, Shwetal SP, Prashant KD, Praveen OP. Validated UV spectroscopic methods for determination of Enzalutamide in pure and pharmaceutical dosage form. Analytical Chemistry. 2016;16:111.
51. Anjaneyulu Reddy B, Radhakrishnanand P, IrshadAlam M, Kiran R. A Validated Stability Indicating Rp-Hplc Method Development For Anti Cancer Drug EnzalutamideIn Bulk And Pharmaceuticals.
52. Sitamahalakshmi DS, Bharath P, Ramachandran D, Ramamurty DS. Development and Validation of Stability Indicating RP-HPLC Method for Quantitative Estimation of Enzalutamide in Enzalutamide Capsules Dosage Form. International Journal of Pharmaceutical Investigation. 2023 Apr 1;13(2).
53. Gaudêncio SP, Pedrosa R, Vasconcelos V, editors. Selected Papers from XVI MaNaPro and XI ECMNP. MDPI; 2021 Sep 3.
54. Gupta, M. K., & Jain, A. (2012). Formulation and evaluation of eutectic solid dispersions of poorly soluble drugs. *Drug Development and Industrial Pharmacy*, 38(6), 714–723.
55. Shah, N., et al. (2021). Investigation of eutectic systems for enhanced oral delivery of BCS class II drugs. *Pharmaceutics*, 13(1), 1–18.
56. Suryanarayanan, R. (2001). Determination of the glass transition temperature of amorphous solids: Analytical techniques and challenges. *AAPS PharmSciTech*, 2(1), 9–16.
57. Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2), 131–144.
58. Zhang Y, Chen S, Fan F, Xu N, Meng XL, Zhang Y, Lin JM. Neurotoxicity mechanism of aconitine in HT22 cells studied by microfluidic chip-mass spectrometry. Journal of Pharmaceutical Analysis. 2023 Jan 1;13(1):88-98.
59. Sharma A, Chauhan R, Kumar R, Mankotia P, Verma R, Sharma V. A rapid and non-destructive ATR-FTIR spectroscopy method supported by chemometrics for discriminating between facial creams and the classification into herbal and non-herbal brands. SpectrochimicaActa Part A: Molecular and Biomolecular Spectroscopy. 2021 Sep 5;258:119803.