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Eutectic formulations in pharmaceutical development: a comprehensive review of modulation strategies

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Poorly soluble drugs pose significant challenges in terms of their pharmacokinetics and biopharmaceutical properties, reducing their therapeutic potential. Crystal engineering has emerged as a promising strategy to address this issue. This comprehensive review delves into the transformative potential of crystal engineering in designing eutectic multicomponent systems. Through the strategic exploitation of supramolecular synthons and non-covalent interactions, eutectic formulations demonstrate significantly improved solubilization, enhanced stability profiles, and augmented bioavailability. We explore the details of functional group interactions, molecular structural design, and crystal lattice dynamics to elucidate the underlying mechanisms governing eutectic formations. Our review provides a profound understanding of the interplay between crystal engineering and pharmacokinetics, paving the way for the rational design of eutectic formulations with optimized drug delivery and therapeutic outcomes.

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1. Introduction

Pharmaceutical industries continuously seek pioneering formulation strategies to improve drug delivery, bioavailability, and therapeutic efficacy. Eutectic formulations have appeared as promising advances, offering exclusive opportunities to modulate the basic physicochemical properties of active pharmaceutical ingredients (APIs) and excipients. By combining two or more components in a specific ratio, eutectic mixtures can exhibit improved solubility, stability, and dissolution rates, leading to enhanced drug performance and patient outcomes. For instance, commercially available Zantac® underlined the requirement of preformulation due to low stability.[1] Similarly, a polymorph of ritonavir, which was formulated as a capsule available in the market under the trade name Norvir®, was withdrawn due to solubility concerns and was re-formulated with an improved solubility range.[2–4] Reported studies of the combined formulation of isoniazid, rifampicin and pyrazinamide drugs were shown to have higher tuberculosis infection relapse rates than the parent drugs.[5] At this juncture, multicomponent crystal engineering technology is considered to be an effective and advanced choice for the formulation of eutectics to enhance their physiological properties or consistency.[6,7] Under the umbrella of multicomponent crystalline solids, cocrystallization is assigned as the supramolecular aggregation of two or more different chemical units in a crystalline lattice through the formation of non-covalent interactions.[8–20]

Multicomponent crystalline solids, such as cocrystals, eutectics, solvates, and solid solutions, are extensively studied in the pharmaceutical field due to their excellent ability to enhance physiochemical properties *via* cocrystallization techniques.[21–25] A critical distinction must be made between eutectics, cocrystals, and amorphous solid dispersions, as these systems are often discussed interchangeably in the literature, leading to conceptual ambiguities. Eutectics are physical mixtures of two or more components that, at a specific composition, exhibit a single sharp melting point that is lower than those of the individual constituents, without forming a new crystalline phase. In contrast, cocrystals represent true crystalline materials in which drug and coformer molecules are incorporated into the same lattice through defined supramolecular interactions such as hydrogen bonding or π–π stacking, thereby generating a new solid phase with distinct physicochemical properties. On the other hand, amorphous solid dispersions are non-crystalline systems in which the drug is molecularly dispersed within an inert polymeric carrier, with solubility enhancement arising primarily from the loss of long-range order and the increased free energy of the amorphous state. While all three strategies share the common goal of enhancing solubility and bioavailability, their mechanistic underpinnings, stability profiles, and regulatory implications are fundamentally different. Overlaps in reported solubility

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data and misinterpretation of thermal transitions have sometimes blurred these boundaries; however, advanced analytical techniques, such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and solid-state NMR spectroscopy, can help unambiguously distinguish between eutectic mixtures, cocrystals, and amorphous dispersions.

Herein, we highlight the significance of eutectics as multicomponent solids and the biopharmaceutical applications that are enabled by improving the pharmacokinetic properties of drugs. Like cocrystals,[26–28] the design of eutectic mixtures is a promising research area to enhance the fundamental applications of drugs.[10,15–19,29–32]In this scenario, the formulation of eutectics with tunable physiochemical properties provides a highly eye-catching environment in pharmaceutical industries.[10] A literature review revealed that the structure–property relationships of pharmaceutical drug-excipient eutectics play a crucial role in determining their performance. The formation of eutectic mixtures involves the intimate mixing of drug and excipient molecules, resulting in a homogeneous solid solution. In general, eutectic mixtures exhibit the unique property of having a lower melting point than their individual components due to intermolecular interactions, disruption of crystal structure, and increased entropy, which significantly influence the properties of eutectic systems, including their solubility, stability, and dissolution rate. Understanding the interplay between the structural features and properties of drug-excipient eutectics is essential for designing optimized formulations with enhanced bioavailability and therapeutic efficacy.[33–35] Crystal engineering technology plays a crucial role in understanding and manipulating these factors, enabling the design of eutectic mixtures with tailored melting points, solubility, and stability.[36–38] By optimizing intermolecular interactions, disrupting crystal structure, and influencing entropy, crystal engineering technology improves pharmaceutical applications by creating eutectic mixtures with optimized properties. A schematic representation of eutectic formation is shown in Fig. 1. It enhances the biopharmaceutical properties of poorly soluble drugs by dispersing them in hydrophilic carriers *via* particle size reduction.

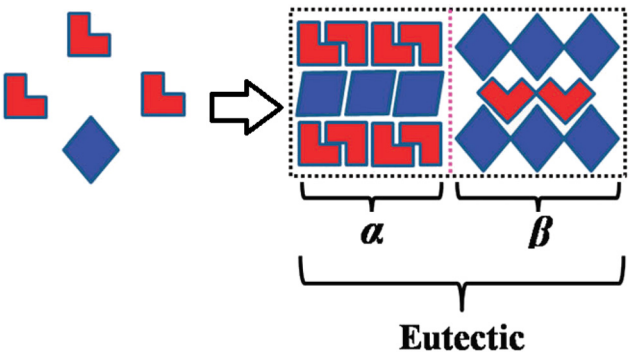

Fig. 1 Schematic illustration for the formation of eutectics *via* adoption of crystal structure of the parent constituents to form a heterogeneous lattice with incoherent interactions (denoted by the dotted lines).

Techniques such as ball-milling, grinding, fluid energy micronization and controlled precipitation can easily modify the solubility, dissolution rate, stability, permeability, and metabolism of drugs by optimizing drug properties.[39] The solvent method is considered to be the best tool to overcome preformulation issues for drugs containing a polar functional group. It has been established that dissolution and drug solubility are two key parameters that influence their *in vitro* and *in vivo* bio-pharmaceutical properties. Eutectic mixtures, like cocrystals, have high thermodynamic properties, including free-energy, enthalpy and entropy, which are attributed to non-covalent interactions such as hydrogen bonding, van der Waals forces, and π–π stacking between the drug and excipients.[9] These interactions make eutectic mixtures stable and useful for pharmaceuticals.[40–44] Furthermore, the benefits of eutectic mixtures can be particularly impactful when combined with the advantages of oral drug administration. Besides, the oral route of drug administration is found to be a more effective, common, non-invasive, and user-friendly path to improved patient compliance.[39,45] In this form, the drug is released and dissolved in gastrointestinal fluid before being absorbed. This is particularly relevant for drugs classified under BCS Class II and IV, according to the Biopharmaceutical Classification System (BCS), which exhibit low aqueous solubility and low permeability, respectively.[33–35,46] Details on this are further elaborated in section 4. Despite the potential of multicomponent approaches, including eutectic mixtures, to improve the properties of BCS Class II and IV drugs, there is a significant knowledge gap in this area.

Eutectic formulations can be developed into various dosage forms, including tablets, capsules, creams, and suppositories. Eutectic-based tablets offer a highly promising approach to enhance the bioavailability and solubility of poorly soluble drugs. By incorporating eutectic mixtures into tablet formulations, manufacturers can create solid dosage forms with improved dissolution rates and oral absorption.[47,48] However, very few studies have focused on utilizing mixtures of eutectics to enhance drug properties due to the complexity of understanding their occurrences, as well as a lack of research on the structural interactions between the drug and excipients. Moreover, eutectic mixtures in pharmaceuticals and materials sciences face challenges due to their physical and chemical stability, which can cause recrystallization, phase separation, or polymorphic transitions, affecting dissolution characteristics and therapeutic efficacy. Also, to achieve desired therapeutic outcomes, it is crucial to select appropriate co-formers and maintain precise control over their composition and processing conditions. Eutectic mixtures in industrial manufacturing require precise control over component ratios, mixing protocols, and thermal processing, but scaling up laboratory techniques can lead to variability in physicochemical properties. The regulatory acceptance of novel pharmaceutical drug eutectic formulations, which often incorporate innovative coformers or excipients, is hindered by the inadequate adaptation of existing evaluation frameworks, thereby causing delays in clinical translation and market entry.[49–51] In

addition, accurately predicting eutectic behaviour in complex multi-component systems is complex, requiring extensive empirical studies and computational tools, thereby increasing formulation development time and cost.

Therefore, this review aims to provide a comprehensive overview of eutectic formulation strategies in pharmaceutical development, highlighting their potential to modulate API behavior, improve drug delivery, and address specific therapeutic challenges. We will explore the fundamental principles of eutectic systems, discuss recent advances in eutectic formulation design, and examine the applications of eutectic mixtures in various drug development areas, including solubility enhancement, controlled release, and pediatric formulations. By elucidating the benefits and challenges of eutectic formulations, this review seeks to inspire further research and development in this exciting field, ultimately contributing to the creation of more effective and patient-friendly pharmaceutical products.

2. Pharmaceutical eutectic drug systems

As discussed in the Introduction, pharmaceutical eutectic systems are formed when two or more components interact through intermolecular forces, leading to a significant reduction in the melting point of the mixture compared to the individual constituents. Such systems improve physicochemical properties such as solubility, dissolution rate, and bioavailability, thereby addressing challenges associated with poorly water-soluble drugs. Eutectic formulations have been investigated for diverse administration routes, including transdermal, oral, buccal, percutaneous, and vaginal delivery, offering a versatile strategy to enhance therapeutic performance.

2.1. Delivery routes

2.1.1. Transdermal delivery. Transdermal drug delivery (TDD) is a non-invasive route of drug delivery that permits a specific quantity of a drug to permeate through the epidermal layer of the skin by diffusion or other mechanisms and then pass into the bloodstream at a controlled rate.[49] Since the skin has a high surface area (1–2 m^2) and accounts for one-third of the blood circulation, this provides a larger active surface area for the TDD. This process reduces gastrointestinal deterioration, which, in turn, improves the bioavailability of the drug.[50] TDD also lowers the chances of infection, minimizes the risk of toxic side effects, exerts fewer traumas, and makes patients active for self-management.[51–53] However, limited drug suitability, skin irritations, contact dermatitis, inconsistent absorption, inability to deliver ionic drugs, dosage limitations, and failure to achieve elevated blood/plasma drug levels are some disadvantages of this delivery route.[54–56]

2.1.2. Oral delivery. Oral delivery is a method of administering medication, food, or other substances by mouth for local or systemic effects, most commonly used for drugs due to its convenience, non-invasiveness, and high patient compliance. It is the preferred route of drug delivery. However, the physiological environments of the gastrointestinal tract and physico–chemical conditions affect the bioavailability of the drug.[57] The development of oral delivery presents several challenges, which are mainly attributed to the physicochemical properties of drugs, including poor water solubility and membrane permeability. In addition, the absorption of drugs can be limited by their poor chemical and biological stability, as well as by physiological barriers, including pH, efflux transporters, and metabolic enzymes.[58]

2.1.3. Buccal delivery. Buccal drug delivery is a pharmaceutical method in which drugs are administered through the inner lining of the cheek (buccal mucosa) and absorbed directly into the bloodstream, bypassing first-pass metabolism in the liver.[59] This administration route is chosen for its ability to provide rapid drug absorption, high bioavailability, and patient convenience, making it suitable for drugs that degrade in the stomach or require a fast onset of action. Disadvantages of buccal drug delivery systems include low permeability through the buccal membrane, limited surface area for absorption, continuous saliva secretion leading to drug dilution and loss, patient restrictions on eating and drinking, unsuitability for higher doses of drug or drugs with disagreeable taste or odour, and likely unstable nature of the drugs at the buccal pH.[60,61]

2.1.4. Percutaneous delivery. Percutaneous drug delivery involves administering a drug through the skin, targeting either a localized area or achieving systemic absorption into the bloodstream. This delivery process is contingent upon the physicochemical characteristics of the drug, and optimal penetration requires drugs with a molecular weight below 500 Da and a melting point below 250 °C, modest lipophilicity, and restricted hydrogen bonding.[62] The dermal absorption of a drug is affected not only by the intrinsic properties of the drug but also by individual variations in skin and the conditions of exposure.[63]

2.1.5. Vaginal delivery. Vaginal drug delivery has garnered significant interest for poorly soluble drugs over the centuries due to its unique physiological and pharmacological advantages. It is important to note that the vagina is suitable for treating various vaginal diseases; therefore, it is the most suitable administration route for the treatment of these diseases. This route bypasses the first-pass metabolism, ensuring good blood flow, low systemic side effects, and the potential for sustained drug release.[64] However, novel technologies and smart polymeric materials are necessary to penetrate the vaginal mucosa and maintain its natural environment, necessitating novel technologies and smart polymeric materials.[65]

3. Permeation of the drugs across biological membranes

The permeation of a drug across biological membranes dictates its pharmacokinetic profile, influencing its Absorption,

Distribution, Metabolism, and Excretion (ADME).[66] Improving drug permeation across biological membranes requires optimizing the balance between lipophilicity (log *P*), solubility, and ionization state for passive diffusion. Among these factors, the lipophilicity, *i.e.* logarithm partition coefficient (log *P*), plays a crucial role in the permeation of a drug across biological membranes.[67] An ideal log *P* range of 1–3 is often cited; both very low and very high lipophilicity can impede oral permeation.[68] However, for drugs targeting the central nervous system (CNS), an optimal log *P* in the range of 2–4 may be preferred to facilitate crossing the blood-brain barrier.[69] A log *P* of 5 or less is often considered a guideline for good oral bioavailability, representing an acceptable upper limit for lipophilicity. Conversely, excessively high log *P* values can result in poor aqueous solubility, which impedes drug dissolution and target access.

There are some other approaches employed to enhance permeation, which include the incorporation of chemical permeation enhancers (CPEs), employing prodrugs, and adjusting the local pH to manage drug ionization.[70,71] Table 1 displays some common CPEs and their log *P* values. Permeation enhancers, including solvents such as ethanol (log *P* = −0.3), pyrrolidone (log *P* = −0.9), and sulfoxides (log *P* = −1.4), can be employed. At low concentrations, solvents such as pyrrolidone alter the stratum corneum's solubility. On the other hand, at higher concentrations, they form an internal phase, acting as a drug reservoir for sustained release.[66] Commonly used CPEs include the long-chain carboxylic acid, oleic acid (log *P* = 7.7), and surfactants such as sodium lauryl sulfate (log *P* = 1.6), limonene (log *P* = 4.6), and azone (log *P* = 6.3). Similarly, the use of prodrugs is also essential for overcoming solubility and permeability issues, with sophisticated design methods enhancing bioavailability, permeability, stability, and targeted drug delivery.[71] The permeability of a drug is also affected by its ionic state, with ionized species exhibiting poorer permeation than non-ionized species. Enhancing the proportion of non-ionized drug, achievable through adjustments in the pH of the drug delivery system, can lead to improved permeability.[72]

Table 1 Common chemical permeation enhancers and their log *P* values

Name of CPEs	Type	Molecular weight [Da]	log *P*
Ethanol	Solvent	46.1	−0.3
Pyrrolidone	Solvent	85.1	−0.9
Dimethyl sulfoxide	Solvent	78.1	−1.4
Decyl methyl sulfoxide	Solvent	204.4	3.8
Lauric acid	Fatty acid	200.3	4.6
Oleic acid	Fatty acid	282.5	7.7
Stearic acid	Fatty acid	284.5	8.2
Sodium lauryl sulfate	Anionic surfactant	288.4	1.6
Sodium octyl sulfate	Anionic surfactant	232.3	3.3
Sodium laureth sulfate	Anionic surfactant	332.4	5.4
Nonoxynol-9	Non-ionic surfactant	616.8	3.4
Limonene	Terpene	136.2	4.6
Nerolidol	Terpene	222.4	5.3

4. The role of BCS in enhancing eutectic bioavailability

BCS is a vital framework for understanding the biopharmaceutical properties of drugs, specifically their Absorption, Distribution, Metabolism, and Excretion (ADME) profiles, which are critical in determining their efficacy, safety, and pharmacokinetic behaviour in the human body. For instance, drugs with low solubility (BCS Class II) may exhibit poor absorption, while drugs with low permeability (BCS Class IV) may have limited distribution. Amidon and co-workers introduced the BCS and categorized drugs based on aqueous solubility and gastrointestinal permeability.[73] The BCS classification (Table 2) reveals that approximately 40% of oral drugs have poor aqueous solubility, with 30% classified as BCS Class II (low solubility, high permeability) and 10% as Class IV (low solubility, low permeability). By evaluating solubility and permeability, the BCS tool predicts *in vivo* performance of drugs by informing ADME studies and guiding their overall development. This enables researchers to optimize formulation and delivery strategies, ensuring effective drug absorption, distribution, and therapeutic outcomes. BCS also facilitates preclinical and clinical bioequivalence tests, monitoring drug development effectiveness.[74,75]

In particular, it helps to understand the development of solid eutectic mixtures by guiding the selection of suitable drug and carrier combinations to enhance their bioavailability and stability. Class II and Class IV drugs benefit from improved solubility, while Class III and Class IV drugs promote enhanced permeability. Moreover, solid formulations of eutectic mixtures stabilize both Class II and Class IV drugs

Table 2 BCS classification of drugs based on their solubility and permeability

BCS classification	Solubility	Permeability	ADME implication	Examples
Class I	High	High	Rapid absorption, extensive distribution, high bioavailability	Theophylline, metoprolol, propanolol, metoprolol, diltiazem
Class II	Low	High	Slow dissolution, variable absorption	Ibuprufen, ethenzamide, mefanimic acid, nisoldipine, nifedipine
Class III	High	Low	Limited absorption, restricted distribution	Acyclovir, enalaprilat, atenolol, ganciclovir
Class IV	Low	Low	Poor absorption, limited distribution, low bioavailability	Furosemide, famotidine, ritonavir, paclitaxel

against degradation. For instance, H-bonding between a drug and its carrier in a eutectic mixture can enhance solubility and permeability, potentially reclassifying a drug from BCS Class II to Class I. Moreover, π–π stacking interactions between a drug and its excipients can improve their stability and reduce metabolism, affecting the drug's ADME profile. These interactions are considered to ensure the compatibility of drug-excipient interactions. A notable example is the ibuprofen–menthol eutectic mixture, where H-bonding between the –COOH group of Ibuprofen and the –OH group of menthol enhances the solubility and permeability, improving bioavailability. By understanding the role of non-covalent interactions in ADME and BCS, researchers can design more effective drug formulations to optimize drug delivery and efficacy, accelerate new drug development, and reformulate poorly soluble drugs, ultimately enhancing therapeutic outcomes.[76] Therefore, the integration of BCS principles into eutectic formulation development streamlines the overall drug development process, reducing costs and accelerating the delivery of effective treatments to patients.

5. Pre-formulation of eutectics in the context of a crystal engineering approach

In 1961, Sekiguchi and Obi published the first study on the use of eutectic mixtures to increase solubility and bioavailability using urea and sulfathiazole.[42] When a tiny suspension of urea was exposed to the dissolution medium as a highly water-soluble carrier, it enhanced the solubility of the parent drug, *i.e.* sulfathiazole. The drug particles in this suspension had better wettability and smaller particle sizes, which sped up the dissolution process. The solubility of drugs was also improved by eutectic combinations of urea and chloramphenicol or acetaminophen.[39,45,47] In the past decades, the number of articles involving the utilization of eutectic mixtures to boost drug solubility has significantly increased. The following factors may contribute to the increased interest in eutectics for pharmaceutical formulation: (i) the preparation techniques are affordable, simple to produce, and easy to scale up; (ii) eutectics are not considered as new chemical entities or new crystal forms; and (iii) in eutectic systems, both of the components exist in crystalline form, which is highly stable in comparison to amorphous materials.[77] The use of crystal engineering concepts is crucial for the pre-formulation and control of organic solids and transforms their standard pharmaceutical studies into a better alternative combination of medication therapies. It deals with various crystalline solid phases that might be made up of one atom, molecule, or ion (referred to as single-component solids) or a mixture of more than one component (referred to as multicomponent solids). The formation of eutectic mixtures can also be influenced by a number of interaction parameters between drug and excipients, including the nature of intermolecular interactions and supramolecular synthons, functional group disposition, interaction strength, and packing efficiency.

The hydrogen bond is the most extensively utilized non-covalent interaction in crystal engineering within supramolecular chemistry. The nano structured self-assembly of molecules, both in solution and the solid state, makes use of strong and directed hydrogen-bond synthons. For instance, carboxylic acids and amides are two functional groups that are frequently used in crystal engineering to understand easily the concept of hydrogen bond synthons, which form architectures such as O–H···O and N–H···O, respectively.[78] However, a structural design of multicomponent crystalline solids with various functional groups is a significant problem, as it is impossible to foresee when a specific functional group (such as a hydroxyl, halogen, pyridine, ester, or amide) may disrupt the typical hydrogen bond pattern of a specific functional group. It is becoming more and more crucial to understand the factors that control the growth of different multicomponent solids, including cocrystals, solid solutions and eutectics, from both theoretical and practical perspectives. Statistical data retrieved from the Cambridge Structural Database (CSD) are considered a better tool for designing multicomponent solids.[79,80]

It is reported in the literature that the combination of the drug ornidazole and *para*-amino and *para*-hydroxy benzoic acids resulted in the formation of a cocrystal due to the strong inductive strength between the hydrogen bond donor and acceptor groups. Whereas, ornidazole with other coformers, such as *para*-methyl benzoic acid and *para*-iodo benzoic acid, favors eutectic formation due to insufficient inductive forces between the donor and acceptor,[14] as shown in Fig. 2a and b.

Similarly, using benzoic acid combined with its structural analogues 4-fluorobenzoic acid, pentafluorobenzoic acid, and benzamide as examples, Cherukuvada and Nangia reported the intriguing design in aspect of eutectics and their mutual interactions with solid solutions and cocrystals.[9] As hydrogen and fluorine are isomorphous in nature, benzoic acid and 4-fluorobenzoic acid form continuous solid solutions.[81] However, the combination of benzoic acid and penta-fluorobenzoic acid can form a cocrystal structure due to strong heteromolecular interactions, whereas the benzoic acid and benzamide system can form a eutectic mixture due to the absence of such hydrogen-bond interactions.[41,82–84] Ganduri and coworkers reported pyridoxine-based eutectics with an antitubercular drug, isoniazid, and vitamin B_3, *i.e.* nicotinic acid.[85] In this study, the authors discovered various multicomponent solids based on the role of supramolecular affinity of H-bonding due to the presence of functional groups and the pK_a differences. In order to formulate the best and/or most synergistic drug combination, this study confirms the necessity of comprehensive supramolecular compatibility. The authors claim that the pyridoxine–nicotinic acid (PY–NA) eutectic contains heteromeric hydroxyl···pyridine interactions that are not adequate to conquer the homomeric interactions present in individual NA, *i.e.* acid···pyridine, and in PY, *i.e.* hydroxyl···hydroxyl. In addition, the pyridine···acid heterodimer may not be competent to develop into a tetramer or for

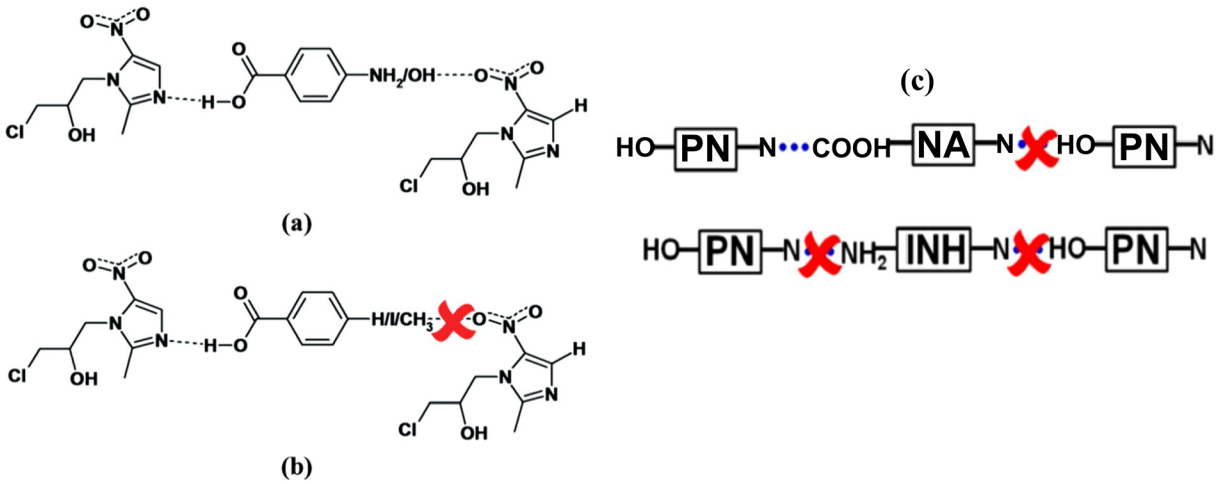

Fig. 2 (a) Formation of the ornidazole and *para*-amino/hydroxy benzoic acid cocrystal due to the strong acid-amide heterodimer hydrogen bond synthon and (b) formation of eutectics between ornidazole and *para*-methyl/iodo benzoic acid owing to the weak acid-imidazole heterodimer hydrogen bond synthon. Reproduced from ref. 14 with permission from RSC, Copyright © 2022. (c) The dominance of heteromeric interactions in PY–NA and equivalence of heteromeric as well as homomeric interactions for PY–INH. Reproduced from ref. 86 with permission from ACS Copyright © 2022.

the design of salt/cocrystal architectures due to the presence of weaker hydroxyl···pyridine interactions. Consequently, this leads to the formation of eutectics between them. However, author also reported here the details design in pyridoxine–isoniazid (PY–INH) multicomponent solids where both homomeric and heteromeric interactions *i.e.* hydroxyl···pyridine and hydrazide···pyridine are almost equivalent and no longer require energetic drive to manifest a structural design of cocrystal or salt. A plausible schematic representation of finite and random homomeric and heteromeric interactions is shown in Fig. 2c. According to the ΔpK_a rule of three, PY–NA multicomponent systems contain $\Delta pK_a \sim 3$, which indicates the possibility of salt formation due to the presence of pyridinium···carboxylate heterodimers.[87–90]

Therefore, in the context of crystal engineering, pre-formulation of eutectics involves the deliberate selection and combination of drugs and excipients to create crystalline solids with the desired properties. Within the crystal engineering principles, pre-formulation aims to design eutectic systems that exploit specific intermolecular interactions to form stable and bioavailable crystalline phases. The combination of individual drugs with excipients facilitates the formation of eutectic solids, driven by robust cohesive interactions that enable the arrangement of tetramers in a geometrically favorable manner. Moreover, the significance of H-bonding in binary systems is basically exemplified *via* the design of different multicomponent solids, such as salt/cocrystals, with potential physicochemical properties. However, ionic heteromers may lack sufficient energy to promote supramolecular growth within the structural framework of multicomponent solids. Notably, the recent literature discussed in this review has witnessed a surge in publications detailing the formulation of eutectic combinations involving drug–drug or drug–additive combinations and highlighting the growing interest in leveraging these systems to optimize biopharmaceutical properties and enhance therapeutic outcomes. Besides, the meticulous design of eutectics is more challenging as one has to identify molecules with an incompatible geometry and avoid the presence of strong heteromolecular synthons in the combination. Therefore, a proper understanding of their crystal structure and molecular association at the nanoscale level is still undeveloped.

6. Tailored physiochemical and biopharmaceutical performance of recently formulated eutectics

To develop a stable and advanced eutectic mixture, it is crucial to comprehend the altered physicochemical and biopharmaceutical properties of solid mixtures compared to individual drug entities. In sections 4 and 5, we emphasized the significance of drug selection, guided by BCS principles and non-covalent interactions, within the crystal engineering approach, as a critical factor in the pre-formulation of eutectics. Building on the foundational principles outlined in the preceding sections, recent advances in eutectic formulation have yielded tailored physiochemical and biopharmaceutical systems, offering enhanced therapeutic outcomes. This section delves into the latest developments in eutectic formulation, showcasing the optimized properties and improved performance of these advanced solid mixtures, and highlighting their potential to revolutionize drug delivery and treatment efficacy.

6.1. Glimepiride–arginine eutectic mixture (GAEM)

Park and co-workers established a eutectic mixture with a 1 : 1 molar ratio of glimepiride and arginine, yielding a eutectic temperature of 426.9 K.[91] The prepared GAEM led to

increased dissolution rates of poorly soluble glimepiride by enhancing its solubility and wettability. The existence of intermolecular H-bonding and hydrophobic interactions between glimepiride and L-arginine was revealed by quantifying the phase solubility of various stoichiometric mixtures as well as by solution-state ^{1}H NMR studies. In this case, degree of drug solubility with varying arginine molar fraction was increased significantly in case of distilled water than pH 6.8 phosphate buffers. However, a notable improvement in solubility was seen in phosphate buffer at pH 6.8 due to the formation of a eutectic mixture at a 1 : 1 molar ratio. The research group prepared Glimepiride-Arginin eutectic mixture (GAEM) using neat grinding physical method where dissolved glimepiride at 10 min (D_{10min}) enhanced remarkably with increasing molar composition of arginine which was explained owing to the increase in solubility and wettability (Fig. 3i) with tumble blending mixture of glimepiride and arginine at molar ratio of X_G = 0.5 shows lower dissolution than that of GAEM. The glimepiride dissolution rate improved due to increased solubility and wettability. This may be due to the fact that the pure glimepiride particles floated due to their hydrophobic properties, while the binary mixture resulted in a more hydrophilic glimepiride crystal surface. The Hot Stage Microscopy (HSM) studies of the diacerein (DIA) and 2,4-dihydroxy benzoic acid (DHA) eutectic mixture, shown in Fig. 3ii, revealed that the eutectic sample started melting at 190 °C and complete melting occurred at 230 °C.

In contrast, Park and co-workers observed that other comparable formulation techniques, such as solvent extraction (SE), melt quenching (QM), and supercritical antisolvent (SAS), failed to produce pure eutectic GAEM.[92] In that study, the authors analyzed and revealed the formation of a pure co-amorphous combination of glimepiride and arginine (GACA) with good content uniformity by using a 1 : 1 M ratio of the precursors using the SAS technique. The formation of GACA was further confirmed by PXRD, DSC and FTIR analyses. The authors also reported the enhancement of glimepiride solubility with increasing molar composition of L-arginine in the SAS-glimepiride arginine samples (SASGA). At a 1 : 1 molar ratio, the solubility of co-amorphous (SASGA) was surprisingly improved as compared to raw glimepiride and GAEM. The primary cause of this outcome is most likely the co-amorphous formation of SASGA. In addition, the formulation of co-amorphous SASGA has been reported to possess many advantageous pharmacokinetic properties, including diminished particle size, homogeneous drug distribution, enhanced solubility, increased dissolution rate and improved hypoglycemic effects compared to pure glimepiride. The rupture of the crystal lattice in the SASGA co-amorphous mixture was shown to enhance such favorable qualities. This breakage takes less energy input and can ultimately result in improved physiological properties of the mixture. In conclusion, it was observed that the preparation method can also play a significant role in the formation of different crystalline solids with remarkable physico–chemical properties.

6.2. Diacerein–fumaric acid eutectic mixture (DFEM)

In this study, the authors aimed to improve the physiochemical and mechanical characteristics of a BCS Class II drug known as diacerein *via* the formation of a eutectic mixture with an excipient, *i.e.* fumaric acid, *via* a liquid-assisted grinding method.[93] The prepared materials exhibited a lower melting point (237.97 °C) at 1 : 2 molar ratio of diacerein to fumaric acid. In comparison to the pure diacerein drug, DFEM exhibits an increase in kinetic solubility by over 3.15-fold within 1 h. As compared to the pure diacerein drug, this novel DFEM demonstrated superior plasticity and good tablet ability characteristics that are resulting instantaneously into tablets using compression techniques. The prepared eutectic exhibited 71.7% greater drug release in 1 h as compared to pure diacerein, which showed only 41.7% within the same time frame.

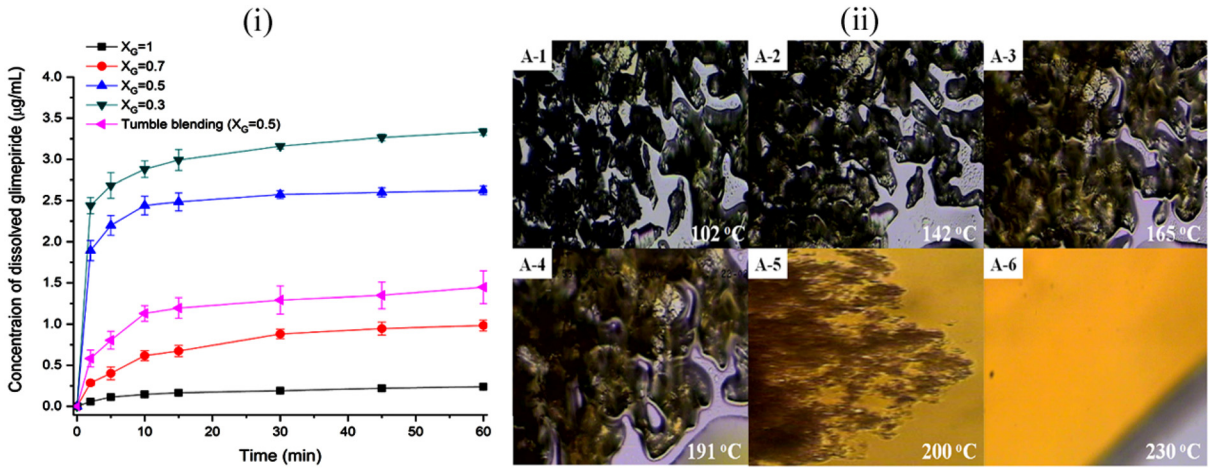

Fig. 3 (i) Powder dissolution profiles of the Glimepiride drug (X_G = 1) and GA binary mixtures at molar ratios of X_G = 0.7, 0.5 and 0.3 in pH 6.8 phosphate buffer solution at 37 °C. Reproduced from ref. 91 with permission from Elsevier, Copyright © 2022. (ii) HSM images of the DIA and DHA eutectic mixture show their melting behavior (A-1: before melting; A-2, A-3 and A-4: starting to melt; A-5: melting at 200 °C and A-6: fully melted). Reproduced from ref. 93 with permission from Elsevier Copyright © 2022.

According to the pharmacokinetic profile, DFEM gave 1.77 times more potential bioavailability than diacerein, which indicates the predominance of the non-covalent derivative in the eutectic form. Here, the authors successfully revealed the concept of crystal engineering to prepare the DFEM from the perspective of advanced material functionality.

Similarly, another multicomponent eutectic system of diacerein and 2,4-dihydroxy benzoic acid was reported with various compositions using an acetone-assisted grinding method.[94] The solubility and dissolution profile of the eutectic were revealed to be approximately 2.0- and 1.8-fold higher, respectively, at various buffer solutions, compared to the pure drug. The pharmacokinetic study demonstrated that the formed eutectic is quite stable in nature, with an approximately 2.1-fold superior bioavailability compared to diacerein. The eutectic solid form exhibited good flow and compressibility characteristics due to the plate-like nature of the uniformly distributed equi-dimensional particles in the mixture. This approach may also be employed commercially to generate directly compressible solid oral drugs in eutectic form.

6.3. Celecoxib–adipic acid/saccharin eutectic mixture

A selective cyclooxygenase-2 inhibitor, celecoxib (CEL), is used to treat various diseases such as inflammation, osteoarthritis, rheumatoid arthritis, and acute discomfort. However, the applicability of celecoxib is severely hindered due to its low solubility and dissolution rate. Binary compositions of celecoxib with adipic acid (ADI) and saccharin (SAC) coformers were used to prepare eutectic mixtures of CEL–ADI and CEL–SAC at molar ratios of 0.3 : 0.7 and 0.8 : 0.2, respectively.[95] The melting peaks observed in the phase diagram (Fig. 4a and b) were elucidated, and the estimated eutectic temperatures were 141.07 °C and 152.49 °C for CEL–ADI and CEL–SAC solid forms, respectively. Improved solubility in distilled water was demonstrated by the solid CEL–ADI and CEL–SAC eutectic forms. Intrinsic dissolution assay studies revealed that the suspended amount of celecoxib drug reached 2.78 mg cm^{-2} and 2.51 mg cm^{-2} for CEL–ADI and CEL–SAC eutectic mixtures, respectively, compared to the pure celecoxib drug, which shows a dissolution rate of only 2.32 mg cm^{-2}. The steeper slopes in the plot of dissolved drug amount (mg cm^{-2}) *versus*

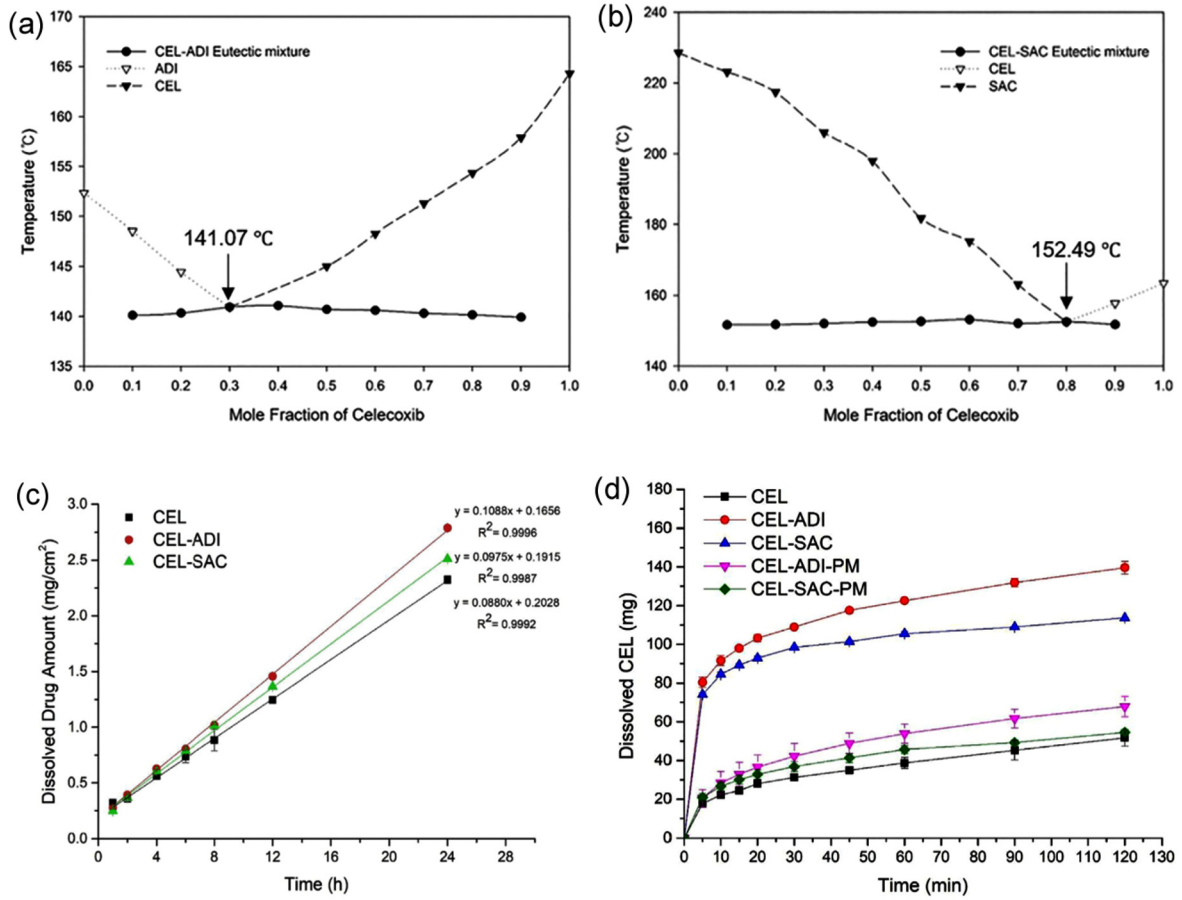

Fig. 4 (a) Phase diagrams of eutectic mixtures CEL–ADI and (b) CEL–SAC with variable mole fraction of CEL, ADI, and SAC based on melting point depression. (▽ and ▼) represent the variable liquidus state; (●) represents the solidus state. (c) Disk intrinsic dissolution rate profiles of raw CEL, CEL–ADI, and CEL–SAC, carried out in 0.5% SLS medium at 37 °C ± 0.5 °C for 24 h. Mean ± S.D. (n = 3). (d) Comparative powder dissolution rate in 0.5% SLS solution for 120 min for CEL, CEL–ADI, CEL–SAC, CELADI–PM, and CEL–SAC–PM. Reproduced from ref. 95 with permission from Elsevier Copyright © 2018.

time (Fig. 4c and d) for the pure CEL and the eutectics revealed the higher dissolution rate. Similarly, the powder dissolution of CEL–ADI–PM and CEL–SAC–PM, equivalent to 200 mg of CEL, showed a higher dissolution rate than raw CEL, with dissolved CEL levels 1.16–1.18 times higher at 5 min, which continues until 120 min.

6.4. Nimesulide–nicotinamide eutectic mixture (NNEM)

In this study, the authors revealed that the solubility of NNEM was 14-fold higher than that of the parent drug in the presence of distilled water.[96] A remarkable solubility enhancement of the eutectic was observed in different media such as pH 8.4 phosphate buffer, stimulated gastric fluid, and 0.1 N HCl. The reported dissolution profiles showed that the prepared eutectic released 43.49% of the drug within 1 h, whereas the pure drug showed only 24.30% drug release. Similar types of behavior were also noted when the prepared eutectic material was taken in tablet form. The dissolution efficiency of both powdered and tablet forms was found to be enhanced up to 4.7-fold and 4.9-fold as compared to the pure drug.

6.5. Febuxostat eutectics mixture

Jagiaand co-workers conducted cocrystallization studies to prepare three different eutectic systems of febuxostat (FXT) with coformers such as probenecid, adipic acid and α-ketoglutaric acid.[97] In contrast to the febuxostat, the solubility of the three eutectic systems decreased with varying pH values. For the FXT–probenecid, FXT–adipic acid, and FXT-α-ketoglutaric acid eutectic systems, the solubility of FXT was reduced from 46.53 μg mL^{-1} (pH 5.63) to 46.03 μg mL^{-1}, 28.53 μg mL^{-1}, and 18.88 μg mL^{-1}; from 770.58 μg mL^{-1} (pH 8.21) to 307.574 μg mL^{-1}, 116.63 μg mL^{-1}, and 113.40 μg mL^{-1}, and from 13165.97 μg mL^{-1} (pH 10.13) to 1409.737 μg mL^{-1}, 854.51 μg mL^{-1}, and 1218.99 μg mL^{-1}. The authors also carried out micro-environmental pH studies to understand the effect of the microenvironment on the solubility of these eutectic systems. The percent microspecies distribution of un-ionized micro-species between drug and coformers were predominated as each of the eutectic system with lower micro environmental pH than that of individual FXT drug. The system can prevent the protons from being transferred from the individual FXT drug molecules, resulting in enhanced solubility of all the eutectics.

6.6. Gliclazide–succinic acid eutectic system (GCZ–SUC)

GCZ–SUC eutectic mixtures were reported by Emamiand co-workers using liquid-assisted grinding and electrospray deposition methods.[98] Dissolution studies obtained at pH 1.2, shown in Fig. 5, revealed that eutectic mixtures were enhanced compared to the pure gliclazide drug. The eutectic mixture obtained from the electrospray deposition method (ESD-EM) exhibited distinctly higher surface area and lower particle size than the mixture obtained from the liquid-assisted grinding method. However, ESD-EM demonstrated a noticeably higher dissolving rate when proper excipients such as mannitol and pluronic F68 were used to break their agglomeration. Gliclazide has limited water wettability and a strong hydrophobic nature. Therefore, researchers have used surfactants in the Gliclazide dissolving medium to increase the wettability and to offer a selective medium for comparing the rates of dissolution of various solid forms of this drug. Furthermore, the prepared eutectic mixtures were reported as stable eutectic systems under accelerated conditions, *i.e.* 40 °C and 75% RH for 60 days, both in open and closed vials. Therefore, the stability data showed that eutectic mixtures can be a viable substitute method for unstable amorphous solid dispersions of drugs with low water solubility. It is important to note that although the raw GCZ dissolution was slow, ESD-EM and LAG-EM performed better due to reduced particle size, improved wettability, and fine crystal size in the EMs.

6.7. Curcumin–salicylic acid eutectic system

Curcumin has many pharmacological uses; however, its low bioavailability and poor water solubility limit its use in therapeutic

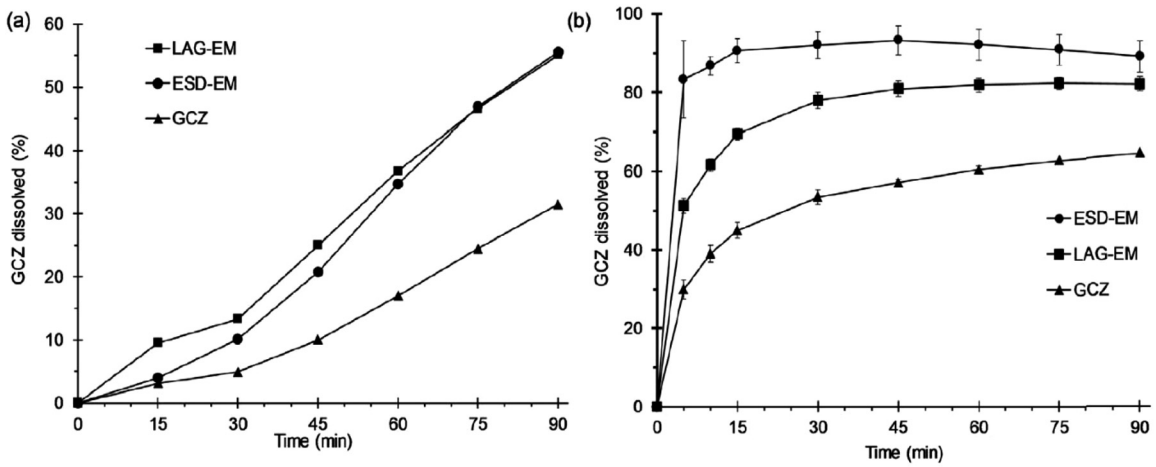

Fig. 5 Dissolution profiles of the raw GCZ and GCZ–SUC eutectic mixtures at pH 1.2 and 37 °C: (a) before formulation and (b) after formulation. Reproduced from ref. 98 with permission from Elsevier Copyright © 2018.

applications. Thus, attempts have been made in the literature to improve curcumin dissolution by formulating the multicomponent crystalline solids with highly soluble coformers. For instance, Dalvi and co-workers reported a twisted formulation of curcumin multicomponent solids using a crystal engineering approach wherein the authors prepared both eutectic and cocrystal formulations of curcumin using salicylic acid and hydroxyquinol conformer, respectively.[99] It was discovered that the curcumin–salicylic acid system formed a eutectic mixture at a curcumin mole fraction of 0.33, whereas the curcumin–hydroxyquinol system noticeably produced a cocrystal that contained a range of curcumin mole fractions of 0.33 and 0.5. The hydroxyl (–OH) group present at the *o*-position of salicylic acid and the ketone (–C═O) group of curcumin form a weaker intermolecular H-bonding interaction that results in the generation of eutectic mixtures. While the formation of strong H-bonding interactions between the hydroxyl (–OH) groups present in the hydroxyquinol and curcumin results in the formation of cocrystals *via* the utilization of melting and recrystallization techniques. In this study, the authors reported that both curcumin–hydroxyquinol cocrystals and pure curcumin drug exhibited slower rates of dissolution than the curcumin–salicylic acid eutectic mixture. The authors explained that this might be attributed to factors including the low aqueous solubility of salicylic acid compared to that of hydroxyquinol, as well as to the reduced requirement for lattice energy for the solubilization of the eutectic mixture.

6.8. Ibuprofen–poloxamer eutectic system

Dugarand co-workers reported that ibuprofen–poloxamer 407 eutectic mixture using melting *vs.* cooling followed by solid grinding.[100] The *in vitro* dissolution rate of the prepared eutectic mixture showed a significant enhancement in different pH media. The maximum solubility enhancement of the fused formulation in acidic media was reported at a fixed ratio of 10 : 75 of Ibuprofen and Poloxamer, respectively, which increased their solubility by 18-fold more effectively than pure Ibuprofen. Similarly, the most prominent effect of dissolution was also found at that particular ratio of combination drugs, with a 58.27% of cumulative drug release compared to the pure drug.

6.9. Nimesulide eutectic systems with PEG, urea and mannitol coformer

In this study, Abdelkadera and co-workers reported a eutectic mixture of Nimesulide drug (ND) with PEG, urea and mannitol coformer using the fused binary dispersion method.[101] The reported phase diagrams of the ND–PEG, ND–urea and ND–mannitol fused mixtures are shown in Fig. 6a–c. The authors reported that at different concentrations of PEG and urea, there were linear increases in the water solubility of the individual ND drug. However, mannitol did not show any significant effect on the aqueous solubility of pure ND. The solubility of ND was improved 2.3- and 1.6-fold, for the eutectic mixtures containing PEG and urea, respectively. The eutectic formulations exhibited superior solubility and dissolution rates, which can be attributed to the fast dissolution of ND solid dosages by taking simple and easily available excipients. In addition to that these findings would imply a plausible ND dose reduction due to efficient potentiation of the analgesic activity (1.6-fold to 2.3-fold) and that could lead to overcome the discrepancy arise due to increasing the size of the dose unit.

6.10. Eutectic compositions of curcumin with nicotinamide, ferulic acid, hydroquinone, *p*-hydroxybenzoic acid and tartaric acid

Cherukuvada and co-workers studied a bioactive curcumin drug (CUC) with pharmaceutically acceptable coformers such as nicotinamide (NIC), ferulic acid (FA), hydroquinone (HQ), *p*-hydroxybenzoic acid (*p*-HBA) and tartaric acid (TA) in a fixed stoichiometric ratio to formulate their eutectic mixtures.[102] Mechanochemical grinding of CUC and GRAS coformers resulted in binary eutectics with improved solubility and faster dissolution rates than pure CUC. In comparison to pure curcumin, the intrinsic dissolution rate (IDR) of all the binary eutectic compositions was shown to be 3 to 11 times faster, and the amounts of drug dissolved were 2 to 6 times higher. Moreover, CUR–NIC, CUR–FA, and CUR–HQ eutectics also exhibited better pharmaco-kinetics properties than their previously reported cocrystals.[102,103] The reported binary eutectic mixtures were found to be stable under ambient environmental conditions, *i.e.* 35 °C temperature with 40% RH, for more than 6 months.

6.11. Ritonavir–gelucire eutectic mixture

Sinha and co-workers demonstrated different multicomponent solid dispersions of Ritonavir, a BCS Class II drug that is used as an antiretroviral agent.[104] Here, the authors reported a eutectic mixture of Ritonavir and Gelucire drugs, which was formulated by using solvent evaporation and melting/cooling methods at a 1 : 4 fixed ratio of the used drugs. *In vitro* dissolution profiles performed in different media demonstrated improved dissolution rates in comparison to the pure drug. The outcome showed that the solvent evaporation method is a viable strategy for improving the bioavailability of solid oral dosages of ritonavir.

6.12. Eutectic mixture of caffeine with meloxicam, aceclofenac and flurbiprofen

Alshaikh and co-workers[105] examined the prospect of eutectic formulation of caffeine with different classes of non-steroidal anti-inflammatory drugs (NSAIDs). The authors selected various examples of NSAIDs, including meloxicam as an enolic acid class, aceclofenac as an alternative for acetic acid derivatives, and flurbiprofen was selected for the propionic acid sector, as coformers to formulate the eutectic mixtures. Here, the optimum eutectic composition was identified based on the type of coformer using Tamman's triangle method. For instance, the optimum temperatures for caffeine–meloxicam, caffeine–aceclofenac, and caffeine–flurbiprofen eutectic systems exhibited sharp endothermic peaks at 209 °C, 115 °C and 95 °C, respectively. The prepared eutectic systems showed significantly higher rates of dissolution that were 3.3, 1.4 and 1.7-fold superior to that of the unprocessed drug, respectively. The authors studied the dissolution profiles in different

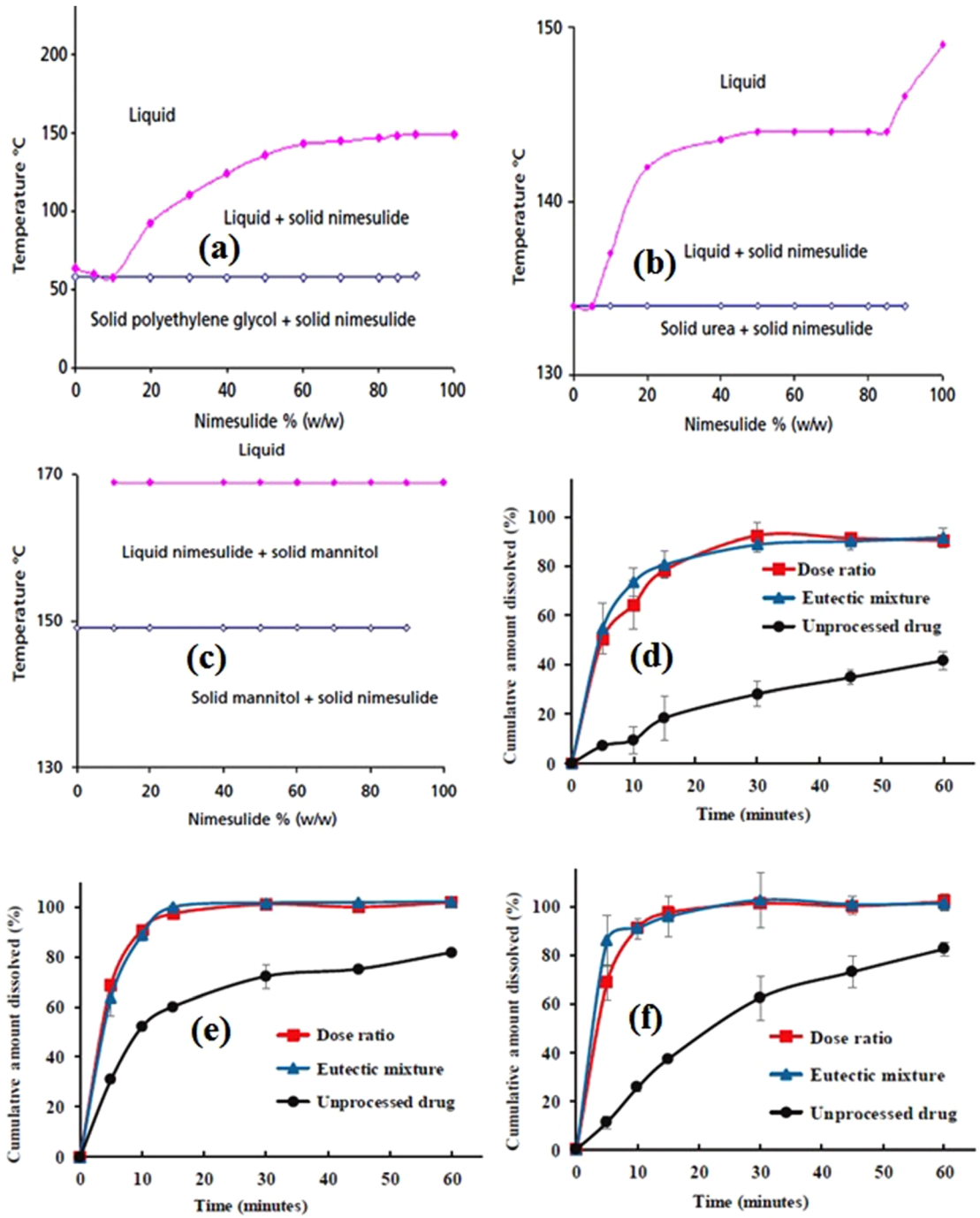

Fig. 6 (a) Phase diagram of the ND–PEG mixture. (b) Phase diagram of the ND–urea mixture. (c) Phase diagram of the ND–mannitol mixture. Reproduced from ref. 101 with permission from Wiley-Blackwell Copyright © 2022. (d) *In vivo* dissolution rate profiles of meloxicam. (e) *In vivo* dissolution rate profiles of aceclofenac and (f) *in vivo* dissolution rate profiles of flurbiprofen. Reproduced from ref. 105 with permission from Elsevier Copyright © 2022.

media, for example, phosphate buffer with pH 7.2 media for flurbiprofen, pH 6.8 media for aceclofenac, and pH 7.5 media for meloxicam. Pharmacodynamic studies[105] revealed that the improved dissolution rate was reflected in increases in the effect of the anti-inflammatory drug after oral administration to rats (Fig. 6d–f).

6.13. Levetiracetam eutectic systems with ibuprofen, naproxen, ketoprofen and flurbiprofen

Machado and co-workers formulated binary solid mixtures of levetiracetam with NAIDs derived from various propionic acids using a neat ball milling mechanochemical methodology.[106]

The formulated eutectic mixtures were found to be an effective route to improved drug pharmacokinetic parameters. An increase in the dissolution rate was observed in the presence of phosphate buffer, pH 7.4, for all the binary eutectic mixtures, as compared to pure NSAIDs.

6.14. Eutectic mixtures of etodolac with propranolol hydrochloride and paracetamol

Thipparaboina and co-workers reported two different drug–drug eutectics, *i.e.* etodolac–propranolol hydrochloride (EPHC) and etodolac–paracetamol (EP), with improved material properties such as hardness, dissolution, and reduction of inflammatory mediators.[16] These eutectics remarkably improved by 6–9 fold the drug efficiency within 1 min, which signifies a faster dissolving capacity of the mixture compared to that of the pure etodolac drug. Furthermore, dissolution studies revealed that etodolac in its pure form released about 50% of the drug within 5 min, whereas the EPHC and EP eutectics released around 80% and 99% of the etodolac, respectively, in that limited time frame. Cytotoxicity studies of the mixtures were also conducted on human PC-3 cancer cells, and the reported IC_{50} values were found to be 86.7, 887.7 and 185.6 micrograms for propanolol hydrochloride, etodolac, and the EPHC eutectic mixture, respectively. The dose and median effects of these systems are shown in Fig. 7A and B, which indicates the types of potential combinations that could help in formulating improved solid binary dispersions with a lower risk of adverse effects.

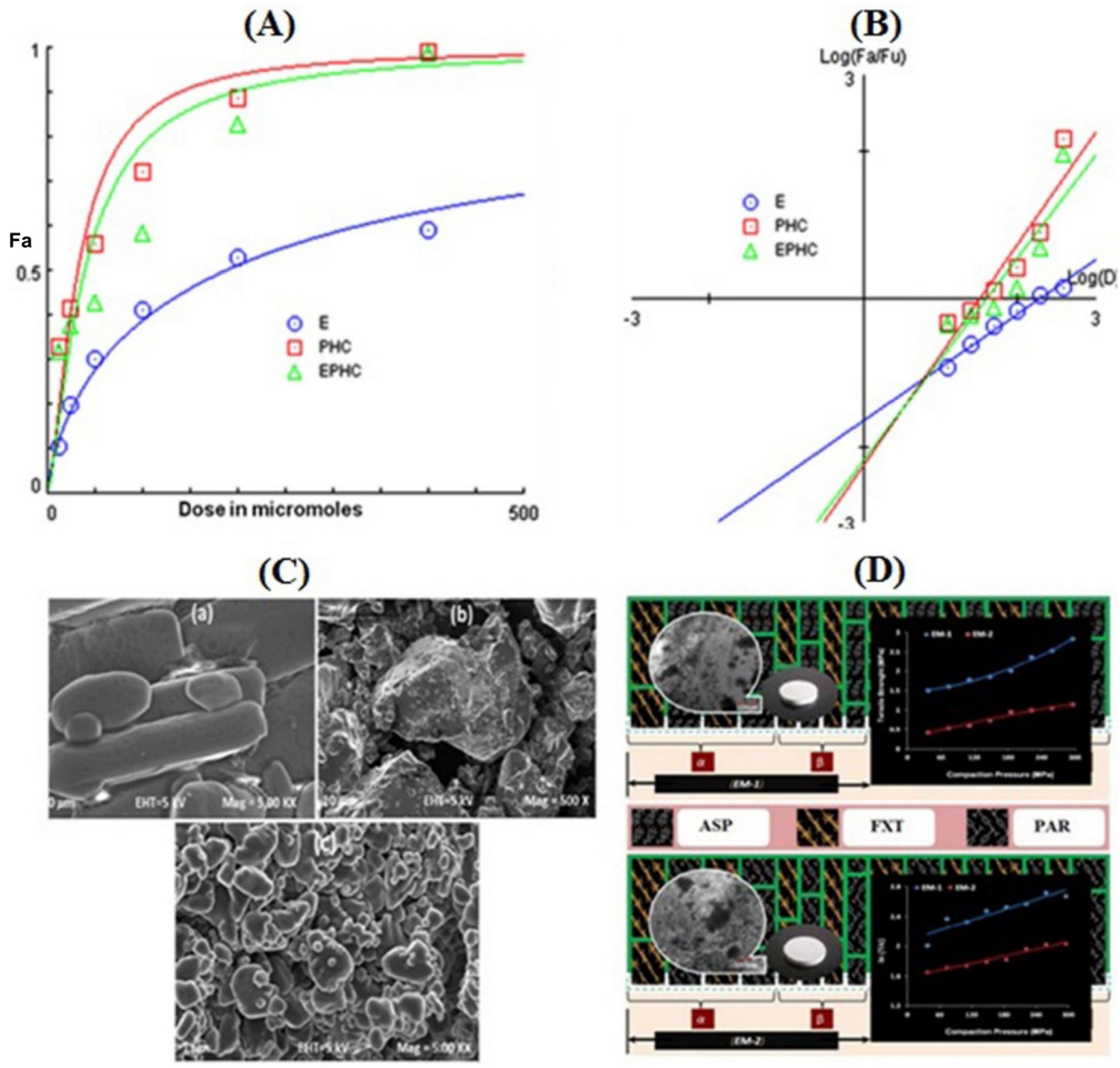

Fig. 7 (A) Dose effect and (B) median effect of the etodolac (E), propanolol hydrochloride (PHC) and EPHC eutectic. Reproduced from ref. 16 with permission from Elsevier Copyright © 2022. (C) SEM micrographs of (a) Zidovudine, (b) Lamivudine and (c) Zidovudine-lamivudine binary eutectics. Reproduced from ref. 108 with permission from Elsevier Copyright © 2022. (D) Solid-state engineering of FXT–ASP (EM-1) and FXT–PAR (EM-2) for tablet processing. Reproduced from ref. 109 with permission from ACS Copyright © 2022.

6.15. Lidocaine–NSAID eutectics

Marei and co-workers reported drug–drug combinations of eutectics to enhance transdermal delivery of NASAIDs.[107] The main objective of this work was to explore lidocaine drug formulation as a eutectic form with a variety of NSAIDs, *i.e.* ketoprofen, flurbiprofen, aceclofenac, meloxicam and tenoxicam. The optimum composition of the eutectic formation of lidocaine depended on the characteristics of the NSAIDs. For instance, NSAIDs with lower melting points required a smaller composition of lidocaine to form the eutectic mixture. The transdermal flux exhibits a strong correlation with the lower melting point of eutectics, which is associated with improved drug permeation rates through the skin.

6.16. Zidovudine–lamivudine binary eutectic

Ngilirabanga and co-workers reported a 1 : 1 mixture of zidovudine and lamivudine eutectic with enhanced solubility and improved dissolution rate.[108] The thermal analyses confirmed the formation of a eutectic with a lower melting profile. SEM analysis verified the particle size aggregates with a round morphology of the eutectic mixture (Fig. 7C). DSC analysis indicated the presence of an endothermic peak at 109 °C, whereas the TGA curve confirmed the absence of volatility of the prepared sample. To understand the physiochemical properties of prepared binary eutectic mixture, the authors also performed the measurement of solubility and dissolution rate profile of the eutectic mixture for pharmaceutical development in different pH media. The study suggested that the formulation of a solid dispersion on both the drugs could improve their bioavailability and potentially reduce patients' compliance with their treatment course.

6.17. Febuxostat–paracetamol (FXT–PAR) and febuxostat–aspirin (FXT–ASP) eutectic mixtures

Yadavand co-workers recently reported the formation of FXT–PAR and FXT–ASP eutectics at a fixed ratio of 1 : 3 and 1 : 2.5, respectively.[109] In these studies, authors conducted molecular-level studies of both eutectics to understand their structural integrity (Fig. 7D). Drug–drug eutectics are generally expected to offer an intermediate and alternative structural arrangement that influences their physio–chemical and mechanical properties due to the contribution of different chemical interactions and good entropy of fusion between the components. Therefore, this study was conducted to determine the intrinsic deformational character of the second component *i.e.* PAR and ASP which may affect the overall tableting behavior of eutectics with a very common solid shape FXT. This work also increased the potential for controlling the bulk deformation of pharmaceutical materials. Furthermore, the authors discovered that the supramolecular characteristics of the individual components were responsible for the improved physical properties of the eutectic surface rather than their molecular structure.

6.18. Resveratrol binary eutectics with nicotinamide

Zhou and co-workers applied cocrystallization technology to form a eutectic mixture of resveratrol drug with nicotinamide.[110] DSC analysis confirmed the presence of an endothermic peak at 105 °C. Hot melt extrusion methods were employed to formulate an amorphous solid dispersion (ASD), which helps to prevent the heat sensitivity that previously led to the degradation of the individual resveratrol drug. However, the authors used a hydroxyl-propylmethyl cellulose acetate succinate (HPMCAS) polymer to formulate the polymer matrix of resveratrol. At the lowest extrusion temperature, *i.e.* 213 °C, resveratrol suffered 7.36% degradation. Therefore, they introduced nicotinamide drug into a resveratrol (RES)-hydroxypropyl methylcellulose acetate succinate (HPMCAS) polymer matrix to reduce the required hot-melt extrusion temperature from 215 °C to 155 °C. This effectively prevented the thermal degradation of resveratrol without adversely affecting the non-sink dissolution. This study recommended the use of the binary eutectic formulation to prevent thermal degradation of heat-sensitive drugs such as resveratrol through the extrusion of ASD.

6.19. Nevirapine–paracetamol eutectic mixture (NPEM)

Sathisaran and Dalvi[111] prepared a binary solid dispersion of Nevirapine and Paracetamol in eutectic form at a fixed 1 : 3 ratio using the solid-state grinding method and characterized the product by using various experimental methods such as DSC, PXRD, FESEM and vibrational analysis. The prepared NPEM exhibited a melting point of 158.8 °C in DSC thermograms, which is lower than the melting points of the individual drugs. The binary phase diagram and PXRD pattern of the formulated eutectic mixture are shown in Fig. 8A and B. Vibrational spectroscopy analysis revealed no significant peak change of nevirapine and paracetamol drugs after the formation of the binary mixture, as shown in Fig. 8C. In order to investigate the dissolution profile of the nevirapine multicomponent mixture, the authors conducted a slurry experiment in the presence of deionized water with 0.1% (w/v) SDS at 37 °C and stirred the mixture at 200 rpm. The powder dissolution profiles showed a 3.07-fold improved dissolution rate of the mixture compared to that of pure nevirapine and other prepared multi-component solids, such as the nevirapine–trimeric acid cocrystal. Therefore, these studies emphasized that such drug–drug eutectic compositions can impart a synergistic effect in pharmaceutical applications rather than other multi-component solids, based on the nature of the drug and the excipients.

6.20. Curcumin (CUC) binary eutectics with succinic acid (SA), paracetamol (PAR), carbamazepine (CBZ), ethyl paraben (ETP), glycine (GLY), tyrosine (TYR), *N*-acetyl D,L-tryptophan (*N*-ATP) and biotin (BIO) coformers

As we discussed earlier, the potential use of curcumin (CUC) has been limited in the literature due to its poor solubility and bioavailability. In this regard, Dalvi and co-workers reported[112] various binary eutectic mixtures, including CUC–SA, CUC–PAR, CUC–CBZ, CUC–ETP, CUC–GLY, CUC–TYR and CUC–BIO. To identify the nature and compositions of the binary eutectics, the authors also developed different binary phase dia-

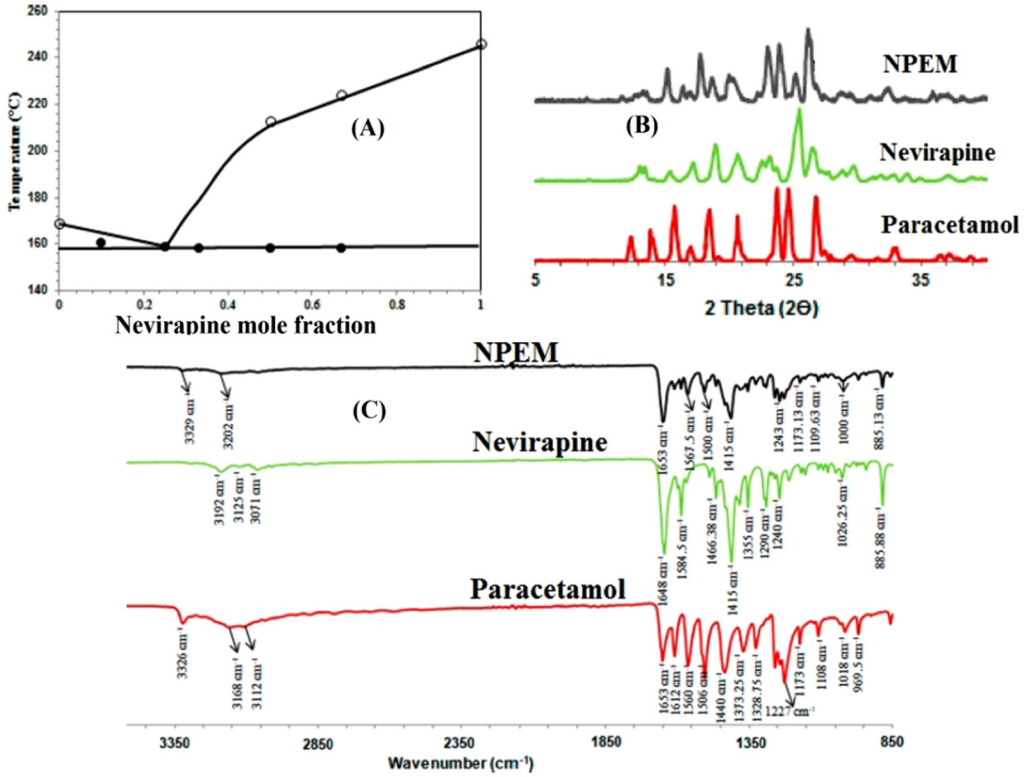

Fig. 8 (A) Binary phase diagram of the NPEM (solid temperature represented by solid circles and liquid temperatures indicated by open circles). (B) Overlay of the PXRD patterns. (C) Overlay of the FT-IR spectra of paracetamol, nevirapine and NPEM. Reproduced from ref. 111 with permission from ACS Copyright © 2022.

grams for the mixtures, and the prepared eutectics were characterized further by using different analytical methodologies. The powder dissolution rates of the eutectics were found to be improved compared to pure CUC in the presence of ethanol-water media. In these studies, the authors evaluated the concept of eutectic formulations in terms of their molecular symmetry and intermolecular interactions. It was established that control of the cohesive interactions present in the binary mixture can lead to the formation of a eutectic phase over other multi-component solids. In addition, the authors determined the apparent CUC (CUC form I) solubilities of the eutectics, except for the CUC–ETP mixture, and the data were compared to those of the individual CUC drug in the presence of ethanol-water mixture media. The order followed by the prepared eutectics was CUC–TYR < CUC–PAR < CUC–SA < Pure CUC < CUC–BIO < CUC–CBZ < CUC–*N*-ATP < CUC–ETP < CUC–GLY. Furthermore, the powder dissolution studies showed that an excellent amount of CUC was released with time from the binary mixtures. In comparison to other binary eutectic mixtures, the CUC–SA eutectic exhibited five times higher dissolution rate than the pure CUC.

It is surprising to note that, number of research papers has been increasing in the literature as an application of eutectic mixtures to tailor their physio–chemical and bio-pharmaceutical properties. Interestingly, in recent years, different kinds of organic additives such as xanthine derivatives, hydroxy–benzoic acid and its derivatives, and vitamins have also been used as hydrophilic carriers to formulate binary active pharmaceutical drug mixtures. A list of a few more recent examples, together with their improved pharmaceutical properties, is presented in Table 3.

The examples presented in this section demonstrate the successful tailoring of physiochemical and biopharmaceutical properties of formulated eutectics, realizing the potential envisioned in sections 4 and 5. Recent advances highlight the growing role of computational tools, predictive modeling, and machine learning (ML) in the rational design of eutectic formulations. Traditional experimental approaches are often labor-intensive and limited in scope, whereas data-driven methods enable rapid screening and mechanistic insights. For instance, a recent study introduced ML classifiers to reliably distinguish eutectic from non-eutectic mixtures and employed regressors to predict viscosity with notable accuracy (MAE ≈ 2.2 mPa s), with SHAP analysis providing interpretability of structural descriptors.[128] Similarly, quantum–chemical techniques integrated with ML have been used to predict eutectic points, including melting temperatures and fusion enthalpies, across a wide chemical space, demonstrating adaptability to complex pharmaceutical mixtures.[129] Additionally, mechano-synthesis combined with computational modelling, such as Monte Carlo simulations and dispersion-corrected DFT calculations, has been applied to pyrene and anthracene eutectic composites, enabling prediction

Table 3 Recent eutectic mixtures and their enhanced solubility/dissolution

Sl. no.	Binary eutectics	Likely BCS outcome (as eutectic mixture)	Improvement in dissolution rate[a]	Ref.
1	Diacerein-2,4-dihydroxybenzoic acid	Class II	2.5-fold	93
2	Nimesulide–nicotinamide	Class II	4.7-fold	94
3	Hesperitin–theophylline	Class I	3.0-fold	113
	Hesperitin–gallic acid	Class I	3.5-fold	
	Hesperitin–theobromine	Class II	2.5-fold	
	Hesperitin–adenine	Class II	1.5-fold	
4	α-Eprosartan-*p*-hydroxy benzoic acid	Class I	6.1-fold	114
	α-Eprosartan–nicotinamide	Class I	2.4-fold	
5	Felodipine–malonic acid	Class I	2.0-fold	115
	Felodipine–nicotinamide	Class I	2.5-fold	
6	Irbesartan–syringic acid	Class I	2.0-fold	116
	Irbesartan–nicotinic acid	Class I	1.6-fold	
	Irbesartan–ascorbic acid	Class I	1.5-fold	
7	Lovastatin–benzoic acid	Class I	5.0-fold	77
	Lovastatin–salicylic acid	Class I	~4.0-fold	
	Lovastatin–cinnamic acid	Class II	~4.0-fold	
8	Efavirenz–tenofovir disoproxil fumarate	Class III	2.5-fold	117
9	Diacerein–fumaric acid	Class I	3.5-fold	118
10	Hydrochlorothiazide–atenolol	Class IV	10-fold	119
11	Fenofibric–syringic acid	Class III	3.6-fold	120
12	Glimepiride–arginine	Class II	—	121
13	Myristic acid–palmitic acid	Class II	n.a.	122
	Myristic acid–tetradecanol	Class II	n.a.	
14	Griseofulvin–saccharin	Class I	n.a.	123
	Griseofulvin–isomalt	Class III	n.a.	
	Griseofulvin–maltitol	Class I	n.a.	
15	Celecoxib–tapentadol	Class I	~2.0-fold	124
	Celecoxib–milnacipran	Class III	~2.0-fold	
16	Kojic acid–Panthenol	Class III	n.a.	125
	Kojic acid–urea	Class III	n.a.	
	Kojic acid–nicotinamide	Class III	n.a.	
	Kojic acid–salicylic acid	Class III	n.a.	
17	Curcumin–salicylic acid	Class III	1.7-fold	126
18	Rivaroxaban–caffeic acid	Class II	1.5-fold	127
	Rivaroxaban–coumaric acid	Class II	1.4-fold	

[a] w.r.t. the first component. n.a.: not applicable.

of mixing energies, binding modes, and interaction parameters, and highlighting the influence of molecular shape and synthon compatibility on eutectic formation.[130] Furthermore, computational frameworks that combine thermodynamic modelling with ML have been developed to predict eutectic temperatures in combinatorial mixtures, offering a pathway for high-throughput screening and optimization of candidate formulations.[131] Collectively, these approaches indicate that predictive modelling and AI-driven frameworks will play a pivotal role in overcoming experimental bottlenecks and accelerating the development of multi-drug eutectic systems.

By applying BCS principles and crystal engineering approaches to drug selection and eutectic design, researchers have achieved enhanced solubility, permeability, and stability, leading to improved bioavailability and therapeutic outcomes. These advancements validate the strategic framework outlined earlier, showcasing the power of rational eutectic formulation to overcome drug development challenges and enhance clinical performance. Despite significant advances in the design of eutectic solid mixtures using crystal engineering principles and supramolecular synthons, several challenges and limitations persist. Predicting supramolecular synthon formation and stability between a suitable drug and excipients, controlling polymorphism and solvate formation, and scaling up such formulation from laboratory to industrial scale remain significant hurdles. Furthermore, ensuring reproducibility and batch-to-batch consistency, integrating multiple APIs or excipients into a single eutectic system, together with our limited understanding of the complex intermolecular interactions, hinders progress. Specific supramolecular synthon-related limitations include sensitivity to moisture and pH for hydrogen bonding, restricted control over stacking geometry for π–π interactions, and limited donor–acceptor pair availability for halogen bonding. Addressing these challenges will require developing predictive models for supramolecular synthon formation, investigating novel supramolecular synthons, and designing modular eutectic systems.

7. Impact of eutectics formulation on modulation preclinical research

Eutectic formulations have emerged as powerful tools in preclinical research, enabling precise modulation of drug delivery

and therapeutic performance. By generating homogeneous solid mixtures with optimized physicochemical properties, eutectics improve the solubility and bioavailability of poorly water-soluble drugs, thereby strengthening pharmacokinetic and pharmacodynamic evaluations. This accelerates the identification of suitable candidates and dosing regimens, ultimately enhancing the translation from bench to clinic. Beyond enhancing solubility, eutectic formulations also support personalized medicine by allowing flexible dosage adjustments tailored to patient-specific needs. Recent preclinical studies provide concrete evidence of these advantages: for example, eutectic mixtures processed *via* hot-melt extrusion (HME) have been incorporated into oral dispersions, transdermal films, implantable devices, and mucosal inserts, demonstrating controlled release, improved systemic exposure, and strong biocompatibility profiles.[132] Importantly, HME ensures dose uniformity, reproducibility, and scalability, addressing manufacturability and regulatory translation challenges. Similarly, mechanochemical screening of trimethoprim (TMP)-based eutectic solid systems with GRAS-listed coformers revealed enhanced dissolution performance; notably, a TMP-paracetamol eutectic improved intrinsic dissolution, while eutectics with curcumin and ciprofloxacin significantly boosted the antibacterial activity against Gram-positive and Gram-negative strains.[133] Preformulation studies further guide the selection of drug-excipient ratios, optimizing solubility (0.1 μg mL^{-1}–1 mg mL^{-1}), particle size (0.2–200 μm), and permeability (1–1000 × 10^{-6} cm s^{-1}), thereby strengthening ADME profiling during preclinical assessment. Moreover, the defined thermal behaviour and miscibility of eutectics improve the formulatability by minimizing batch variability, enhancing reproducibility, and simplifying scale-up. Collectively, these findings demonstrate that eutectic formulations not only improve therapeutic efficacy but also offer a commercially viable and regulatory-compliant pathway for pharmaceutical development.

From a manufacturability standpoint, eutectic systems offer clear advantages as they can be processed using conventional industrial methods such as milling, granulation, and compression, without the need for specialized equipment. Their reproducible melting behavior supports scalability, ensuring smooth transition from laboratory development to pilot and commercial production. Importantly, eutectics can overcome dose-loading limitations commonly associated with solubilized formulations (>500 mg), enabling higher drug loading through excipient-assisted stabilization.[134] By optimizing dosage regimens of lead candidates, researchers can fine-tune therapeutic outcomes based on pharmacokinetic and biopharmaceutical properties.[77,135] From a regulatory perspective, eutectics occupy a unique position between pharmaceutical co-crystals and amorphous solid dispersions. While regulatory agencies such as the US FDA and EMA already provide guidelines for co-crystals, similar frameworks are being extended to eutectic formulations. These require comprehensive documentation of solid-state characterization, thermal stability, dissolution performance, and safety data. Case studies, for example, paracetamol-based eutectic systems, demonstrate that with robust preclinical and stability evidence, such formulations can satisfy regulatory expectations for new solid-state forms of active pharmaceutical ingredients. Collectively, these findings highlight that eutectic formulations not only enhance solubility, dissolution, and bioavailability in preclinical models but also meet the industrial requirements of manufacturability and scalability, while aligning with evolving regulatory standards. This convergence of scientific innovation with industrial feasibility underscores the transformative potential of eutectic solid mixtures in modern pharmaceutical development.

Despite significant progress in the design of eutectic solid mixtures using crystal engineering principles and supramolecular synthons, several critical challenges remain. Chemical interaction challenges can complicate formulation, as unintended interactions between APIs and coformers may alter the physicochemical properties, potentially reduce therapeutic efficacy, or induce instability. Formulation issues are equally prominent, since developing finished dosage forms typically involves multiple unit operations such as granulation, compression, or coating, where process variables may disrupt the delicate balance of eutectic interactions, leading to batch-to-batch variability and reduced reproducibility. Stability concerns remain a central obstacle; minor variations in humidity, temperature, or pH can induce phase separation, undesired polymorphic transitions, or dissolution inconsistencies, which have been noted as primary causes of product recalls in the pharmaceutical industry. On an industrial scale, additional challenges such as scalability and regulatory ambiguities persist, as eutectics often occupy a gray zone between co-crystals and amorphous solid dispersions, making regulatory pathways less straightforward.[136] These considerations underscore the urgent need for predictive computational models, standardized manufacturing protocols, and clearer regulatory frameworks to bridge the gap between laboratory innovation and industrial translation, ultimately ensuring stable, reproducible, and clinically viable eutectic formulations.

8. Conclusions

This review provides a comprehensive understanding of the relationship between crystal engineering and pharmacokinetics, enabling the rational design of eutectic formulations with optimized drug delivery. The authors believe that pharmaceutical eutectics have emerged as a promising strategy for modulating physicochemical and biopharmaceutical properties of active pharmaceutical ingredients. Simple eutectic mixtures have also been shown to be promising systems for improving drug solubility. The recent advances in eutectic formulation design, particularly through crystal engineering principles and supramolecular synthons, have enabled enhanced solubility, bioavailability, and stability of poorly soluble drugs. However, further research is necessary to overcome challenges in preclinical development, scalability, and regulatory approval. Future investigations should focus on developing predictive models and computational tools, elucidating crystal structures and molecular associations at nanoscale levels, and exploring novel coformers and supramole-

cular synthons. Furthermore, investigating eutectic-based combination therapies and multifunctional drug delivery systems, and scaling up eutectic manufacturing processes while ensuring their reproducibility and batch-to-batch consistency, also need to be focused on in the future. In addition, accurately predicting eutectic behaviour in complex multi-component systems requires extensive empirical studies and computational tools, thereby increasing formulation development time and cost. Further studies are also needed to assess the chemical stability, dosage forms, and anti-inflammatory, anticarcinogenic, and other efficacies of eutectic formulations *in vitro* and *in vivo*. By addressing these challenges and advancing eutectic formulation design, researchers can unlock the full potential of pharmaceutical eutectics, leading to improved therapeutic outcomes, enhanced patient care, and innovative solutions for unmet medical needs.

Conflicts of interest

The authors declare that there are no conflict of interests, including any financial, personal or other relationships with other people or organizations that can influence this work.

Abbreviations

APIs	Active pharmaceutical ingredients
BCS	Biopharmaceutical classification system
ADME	Absorption, distribution, metabolism, and excretion
CSD	Cambridge structural database
PY–NA	Pyridoxine–nicotinic acid
PY–INH	Pyridoxine–isoniazid
GAEM	Glimepiride–arginine eutectic mixture
SE	Solvent extraction
QM	Melt quenching
SAS	Supercritical antisolvent
GACA	Glimepiride and arginine mixture
PXRD	Powder X-ray diffraction
FTIR	Fourier transform infrared
GA	Glimepiride arginine
DFEM	Diacerein–fumaric acid eutectic mixture
HSM	Hot stage microscopy
CEL	Celecoxib
ADI	Adipic acid
SAC	Saccharin
NMR	Nuclear magnetic resonance
NNEM	Nimesulide–nicotinamide eutectic mixture
FXT	Febuxostat
GCZ–SUC	Gliclazide–succinic acid eutectic system
ESD-EM	Electrospray deposition method
ND	Nimesulide drug
PEG	Polyethylene glycol
CUC	Curcumin drug
NIC	Nicotinamide
FA	Ferulic acid
HQ	Hydroquinone
p-HBA	*p*-Hydroxybenzoic acid
TA	Tartaric acid
GRAS	Generally recognized as safe
IDR	Intrinsic dissolution rate
NSAIDs	Non-steroidal anti-inflammatory drugs
EP	Etodolac–paracetamol
EPHC	Etodolac–propranolol hydrochloride
IC_{50}	Half maximum inhibitory concentration
PHC	Propanolol hydrochloride
TGA	Thermogravimetric analysis
SEM	Scanning electron microscopy
FXT–PAR	Febuxostat–paracetamol
FXT–ASP	Febuxostat–aspirin
ASD	Amorphous solid dispersion
HPMCAS	Hydroxyl-propylmethyl cellulose acetate succinate
NPEM	Nevirapine–paracetamol eutectic mixture
FESEM	Field emission scanning electron microscopy
DSC	Differential scanning calorimetry
SDS	Sodium dodecyl sulphate
SA	Succinic acid
PAR	Paracetamol
CBZ	Carbamazepine
ETP	Ethyl paraben
GLY	Glycine
TYR	Tyrosine
N-ATP	*N*-Acetyl D,L-tryptophan
BIO	Biotin
AUC	Area under curve
MA–PA–TD	Myristic acid/palmitic acid/tetradecanol
GSF	Griseofulvin
FaSSIF	Fasted state simulated intestinal Fluid
MAE	Mean absolute error
SHAP	SHapley Additive exPlanations

Data availability

The authors declare that no primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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