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Article

Thymol–Menthol Deep Eutectic Solvents and Eutectogels as Pharmaceutical Crystallization Media

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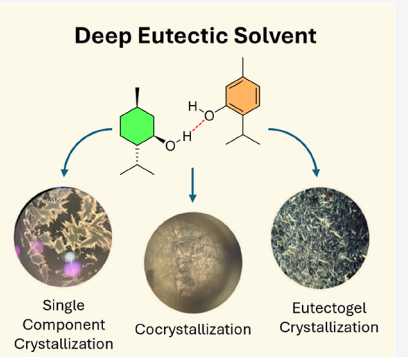
ABSTRACT: Deep eutectic solvents (DES) employing natural products represent a green alternative to conventional crystallization solvents in the pharmaceutical industry. In this work we report the use of the thymol–menthol DES as an effective crystallization solvent for a variety of active pharmaceutical ingredients and pharmaceutical cocrystals, namely aspirin, paracetamol, nicotinamide, benzamide, carbamazepine, mexiletine hydrochloride and ROY. While the involatile nature of thymol–menthol means that evaporative crystallization typically yielded the most thermodynamically stable forms, cooling crystallization yielded surprising metastable forms of the olanzapine precursor ROY depending on the composition of the DES. The 30:70 DES produced the triclinic YN form, the 70:30 composition formed monoclinic ON, while the thermodynamic Y form was obtained from a 50:50 DES mixture. Using L-menthol in the DES instead of racemic menthol resulted in dissolution rate differences in the case of ornidazole and offered the unusual property of chirality in a solvent medium. The DES was successfully used to form salicylic acid–nicotinamide and nevirapine–benzoic acid pharmaceutical cocrystals. It was also gelled by a small molecular bis(urea) gelator allowing supramolecular gel phase DES crystallization.



INTRODUCTION

Before a drug product can be marketed, pharmaceutical companies must consider the possible impact of the crystal form landscape relating to polymorphism, in which a drug substance can exhibit two or more different crystal packing arrangements of the same chemical composition.[1−4] Currently, more than 50% of active pharmaceutical ingredients (APIs) are known to exhibit polymorphism, and up to 90% of new chemical entities are classed as poorly soluble, limiting solvent based crystallization screening for solid forms.[5,6] Different polymorphic forms of an API exhibit varying pharmaceutical properties, such as solubility, stability, and bioavailability. Surveying the polymorphic landscape is critical to identify forms that are readily manufacturable and operate effectively on delivery. Often the most thermodynamically stable polymorph is the preferred form for solid formulations in order to mitigate any risk of potential issues that could arise in manufacturing and storage. However, metastable or amorphous forms may offer formulation, solubility and bioavailability advantages in some cases.[7] Moreover, new solid forms may represent intellectual property opportunities.[8] Regulatory agencies such as the United States Food and Drug Administration (FDA) require assurance on solid form stability within a drug product and the International Committee for Harmonization Q6A regulations that cover the USA, Europe and Japan recommend rigorous polymorphism screening as part of the drug development pipeline to ensure that the selected polymorph meets the necessary therapeutic, manufacturing and regulatory standards.[1,9,10] As a result there is very significant and growing interest in novel crystallization and solid form discovery methods that are both robust and continue to expand the number of known polymorphs and solvates even of very well studied systems such as the olanzapine precursor ROY, which now has 14 reported single-component polymorphs.[11] Recent methodological developments have been reviewed[12,13] and include the use of melt heteroseeding,[14] nanoconfinement,[15,16] microemulsion droplets,[17] structured ternary fluids,[18] supramolecular gels,[19] microgels[20] and the encapsulated nanodroplet crystallization (ENaCt) method.[21]

One area of pharmaceutical crystallization that is of fundamental importance is the use of solvent based cooling, slurry or drown out methods. Organic solvents comprise around half the mass used to manufacture active ingredients[22] but many solvents used in industry are derived from petroleum which has raised concerns about their sustainability, toxicity

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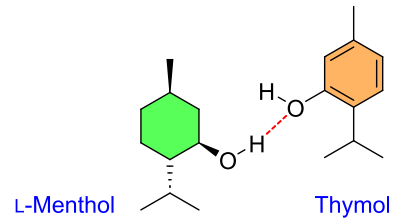
and nonbiodegradability.[23] This has led chemists to seek alternative, sustainable, cheap and green solvents. One class of solvent that has become of interest in this context is deep eutectic solvents (DES). DES are formed from a mixture of hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA), resulting in a melting point lower than that of the individual components[24−27] and hence DES remain in the liquid state at room temperature. While DES share some similar physical properties with ionic liquids, their chemical differences mean that they are distinct entities. Typically, DES are more easily synthesized, less toxic and have a lower environmental impact. DES were first introduced by Abbott and co-workers who focused on eutectic mixtures composed of urea and quaternary ammonium salts, particularly choline chloride and urea.[28] When choline chloride and urea are mixed in a 1:2 molar ratio the freezing point of the eutectic mixture is 12 °C, much lower than that of pure choline chloride and urea, which melt at 302 and 133 °C, respectively.[28] While many DES have ionic components, Type V DES[29] consist of nonionic molecular HBA and HBD such as terpene−terpene mixtures.[30] One of the most notable benefits of DES is their ability to dissolve many different compounds, making them helpful in extraction and separation processes. This property can be attributed to the tunable nature of DES where the choice of HBD and HBA can be adjusted to optimize solubility for a specific set of conditions.[31,32] Beyond their tunability, DES are considered low-cost, biodegradable and nontoxic alternatives to conventional organic solvents and ionic liquids.[33]

With the emergence of DES for pharmaceutical applications there have been a few reports of DES as pharmaceutical and protein crystallization media, although the area is in its early infancy.[34−36] The tunability of their physiochemical properties through changing the components and molar ratio potentially allows for the possibility of identifying DES that give rise to different polymorphs and morphologies of an API compared to those obtained using typical organic solvents,[37] and betaine DES for example, have been used as both solvents and reactants in the preparation of cocrystals.[38] Current focus is on volatile deep eutectic solvents (VODES), where one of the DES components is volatile at room temperature.[34,36] VODES have been used to control the morphology of Savolitinib causing a change from needles to stellates, without changing polymorphic form.[35] A VODES formed from phenol and paracetamol allows the evaporation of the volatile phenol component resulting in the crystallization of the paracetamol API.[34] Varying the molar ratio of the volatile component leads to different polymorphic forms. Nonvolatile DES have also been explored as media for cocrystal formation.[39]

A DES that we believe has particular promise as a crystallization medium is the thymol−menthol system (Scheme 1).[26] When mixed across a range of molar ratios thymol and menthol form a mixture that heavily deviates from ideality giving a Type V DES.[30,40] The nonideal behavior can be accounted for by strong hydrogen bonding between the two terpenoids. The thymol−menthol system is also regarded as a natural DES (NADES), because each component can be extracted sustainably from the environment.[24] Menthol is a monoterpene alcohol found in peppermint and is an important flavoring additive, particularly in tobacco products.[41] It is chiral in nature and is typically found as L-menthol, however racemic menthol can also give rise to DES allowing for the comparison of chiral and racemic solvent mixtures.[41] Like menthol, thymol

Scheme 1. Chemical Structures of Thymol and Menthol[a41]



[a]Menthol has three chiral centers and hence exists as a pair of enantiomers and as three other enantiomeric pairs of diastereoisomers isomenthol, neomenthol and isoneomenthol.[41]

is a monocyclic monoterpenoid found in the oil of common thyme (*Thymus vulgaris*) and is used as a food preservative and an antibacterial agent.[42] Thymol and menthol are both white crystalline solids at room temperature with melting points of 49.5 °C and 41−44 °C (L-menthol) respectively.[41,43] When they are mechanically mixed a thymol−menthol DES is formed.

The low viscosity of the thymol−menthol DES has prompted its application within spray towers for CO_2 capture.[44] Thymol−menthol DES gels (eutectogels) have also been used in drug delivery[45] and dye extraction.[30] However, the use of the DES as a crystallization solvent has not been previously explored to our knowledge. The thymol−menthol DES is particularly suitable in this context because of its low viscosity, in contrast to many DES systems where high viscosity presents practical challenges that could limit their effectiveness in crystallization applications. In the present work we undertake a wide-ranging study of both resolved and racemic thymol−menthol DES as a prototype pharmaceutical crystallization medium.

RESULTS AND DISCUSSION

A range of thymol−menthol DES compositions were prepared by grinding different masses of thymol and either racemic or L-menthol together in a pestle and mortar. It was evident that the eutectic mixture had formed as a clear, colorless liquid for compositions ranging from around 40−80% menthol by mass (Supporting Information, Figure S1) consistent with previous reports,[46] although liquid was evident across the full range of compositions. The DES were characterized by IR spectroscopy (Supporting Information Figure S2). The OH stretch shifts depending on the composition. The OH peak from pure menthol appears at a lower wavenumber, indicating stronger hydrogen bonding than that of pure thymol. This is consistent with previous work, which states that because menthol acts as a classical alcohol it can act as both a H-bond donor and acceptor in equal measure thereby promoting more efficient hydrogen bonding.[46] Conversely, the OH peak from thymol is shifted to a higher wavenumber, reflecting weaker hydrogen bonding.

Crystallization experiments were conducted initially using the thymol−racemic menthol DES using passive slow cooling. As an initial test of stability ^{1}H NMR spectroscopy was performed on the DES before and after heating at 140 °C for 10 min (Supporting Information Figure S3) which showed that there is no change in the DES composition on heating even at these elevated temperatures. Target substrates for crystallization were selected based on systems that have been extensively studied, with a range of chemical functionality, particularly

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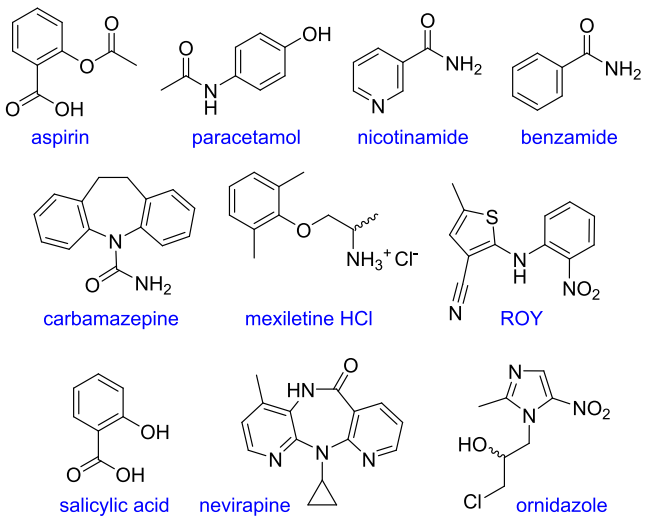
those with a variety of known solid forms. The compounds chosen were aspirin, paracetamol, nicotinamide, benzamide, carbamazepine, mexiletine hydrochloride and ROY, as well as salicylic acid, nevirapine and ornidazole for cocrystal and chiral discrimination tests (Scheme 2). Approximate solubilities were

Scheme 2. Target APIs Used for Crystallization Experiments



determined prior to crystallization by addition of increments of API in a fixed volume of DES until no further dissolution was observed (Supporting Information Table S1). The API was then dissolved in the DES with heating until the API-DES solutions were completely clear. The heated solution was then allowed to cool either under ambient conditions or gradually on a hot plate. If crystals formed, they were typically observed 1 day after cooling.

Aspirin. Aspirin exists as three known polymorphs with the most stable being form I, commonly used commercially.[47] Because of the similarity in crystal structures, form I and form II are readily found intergrown. Additionally, form III can be formed using high pressures or from the melt but converts to form I within a day, limiting this form's pharmaceutical applications.[47] Aspirin was recrystallized in seven different compositions of the thymol−menthol DES at a constant concentration of 0.67 g mL^{-1}. In all compositions, plank-shaped crystals were observed (Figure 1), and SC-XRD confirmed these crystals were form I, by unit cell parameters. IR spectroscopy was used to rule out the degradation of aspirin to salicylic acid. Degradation often occurs when aspirin is in solution, especially at elevated temperatures. Overall, the crystallization behavior remained consistent across compositions, with no significant changes in crystal morphology, polymorphic form or nucleation times. The formation of the thermodynamically stable form I is unsurprising given that form II requires the presence of a seed such as aspirin anhydride[48] while form III occurs at high pressures. However, this experiment establishes that the two-component DES can act as a crystallization solvent for APIs.

Paracetamol. Paracetamol has three known polymorphic forms where form I is the stable phase and forms II and III are metastable.[49] Despite form I being less soluble and typically showing poor compactability, which can result in low quality tablets, it is more economically feasible to formulate because of its higher yields and softer production conditions compared to the metastable forms of paracetamol. Paracetamol was recrystallized in seven different compositions of the thymol−menthol DES at a constant concentration of 0.25 g mL^{-1}. In each composition, irregular or plate crystals were observed (Supporting Information Figure S4). SC-XRD confirmed that all paracetamol crystals were in the commercially distributed form I by unit cell parameters. IR spectroscopy also confirmed the presence of paracetamol and that no side reactions with the DES had occurred. Overall, the morphology, size and nucleation times were roughly constant and independent of the thymol−menthol DES composition used.

Nicotinamide. Nicotinamide is a bioactive form of vitamin B_3 that can be used to treat vitamin B_3 deficiencies such as Pellagra. Nicotinamide has nine known polymorphs, identified mainly through melt crystallization.[50] Typically, only forms α and β can be produced using solution crystallization, while all nine polymorphs are observed in melts. Nicotinamide was recrystallized in the 50:50 thymol−menthol DES at varying concentrations. Upon cooling, a white gel-like suspension formed. Optical microscopy revealed a mesh of small needle crystals (Supporting Information Figure S5). As supersaturation increased, the gel-like suspension became more viscous, possibly due to nucleation dominating over crystal growth, which led to the formation of many smaller crystals. PXRD analysis confirmed that all nicotinamide crystals were in form α.[51] Despite observed changes in viscosity of the suspension produced, the degree of supersaturation of the DES did not result in any change in polymorphic form.

Benzamide. Benzamide is used as an intermediate for the synthesis of a variety of pharmaceuticals and is also one of the first molecular compounds reported to exhibit polymorphism.[52] Currently, four polymorphs have been identified, each accessible depending on the crystallization conditions used.[53,54] These include solution crystallization, melt cooling and mechanochemistry. The thermodynamic form I is well characterized, while the metastable forms are more challenging to obtain, particularly form III, which crystallizes concomitantly with form I, making characterization of this particular polymorph difficult. Benzamide was recrystallized from the

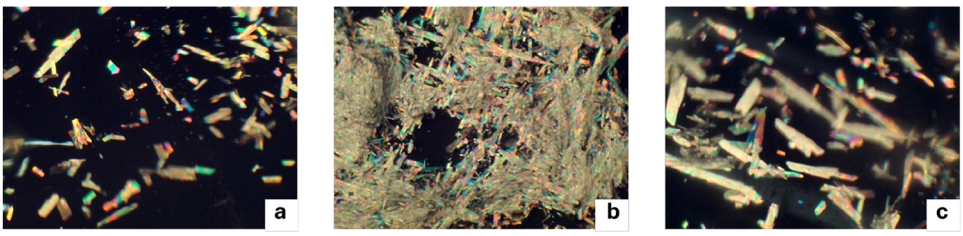


Figure 1. Form I aspirin crystals, recrystallized from different compositions of the thymol−menthol DES. (a) 30:70, (b) 50:50, and (c) 70:30.

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50:50 thymol−menthol DES at varying concentrations, forming tabular crystals. The diffractogram of the resulting material (Figure 2), shows peaks that match forms I and some

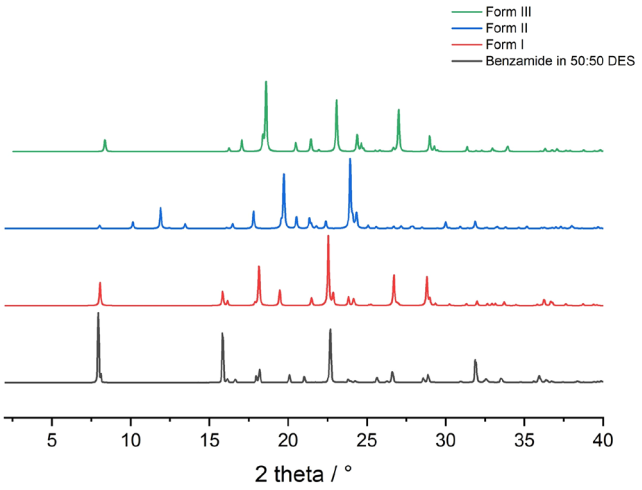

Figure 2. Diffractogram of benzamide, recrystallized from the 50:50 thymol−menthol DES compared to the calculated diffractograms of known polymorphs of benzamide.

additional peaks that may arise from forms II or III. This result may indicate some concomitant crystallization. Since the different experiments result in the same powder pattern, it is unlikely that degree of supersaturation is the reason for a polymorphic mixture.

Carbamazepine. Carbamazepine is an anticonvulsant drug used to treat epilepsy and is known to crystallize in anhydrous forms I, III, IV, V, and VI, a dihydrate form and a range of inclusion structures (form II).[13] Among the anhydrous forms, form III is the most common commercially, as it can be crystallized from solution under ambient conditions. However, in crystallization experiments, especially from the melt, it is common for forms I, III, IV, and VI to crystallize concomitantly. Carbamazepine was recrystallized in three DES compositions (30:70, 50:50, and 70:30) at varying concentrations, producing a variety of morphologies (Figure 3). As the proportion of thymol used for each composition increased, the morphology became more diverse. From the 30:70 composition crystals appear to be exclusively of block morphology, in contrast to the 70:30 composition where six different morphologies can be seen including spherulites, needles and hexagonal plates. PXRD analysis shown in Figure 4 revealed variations in the powder patterns across the different compositions. The 70:30 composition showed dominant peaks at angles 4.9°, 8.6°, and 13.1° which are assigned to form II. This form typically contains solvent molecules, which in this case is likely to be thymol and/or menthol.

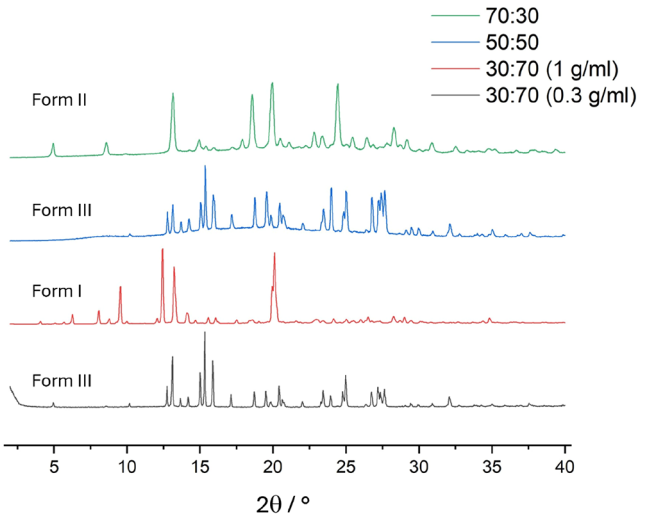

Figure 4. Diffractograms of carbamazepine recrystallized from the thymol−menthol DES at different compositions.

In contrast, both 50:50 and 30:70 compositions (0.3 g/mL) produce form III. The 50:50 sample has some amorphous content while in the 30:70 composition sample additional small peaks at 5.0° and 10.2° suggest a small amount of another form, possibly form I. Increasing the concentration from 0.3 g mL^{-1} to 1.0 g mL^{-1} in the 30:70 DES composition gave rise to pure form I (Figure 4) which is metastable to form III and is typically formed at high temperature, especially from melt crystallization.[13]

Mexiletine Hydrochloride. Mexiletine hydrochloride, an antiarrhythmic drug used to treat irregular heartbeat, has three anhydrous forms that are mutually enantiotropic as well as a variety of isostructural solvate families.[55,56] Mexiletine hydrochloride was crystallized in three DES compositions (30:70, 50:50, and 70:30) at varying supersaturations, resulting in long, colorless needles (Supporting Information Figure S6). These needles intermeshed to form a gel-like material. The diffractogram of this material exhibits sharp peaks superimposed on a broad halo indicating considerable amorphous content. Although some peaks in the diffractogram align with known polymorphs, additional peaks suggest a mixture of polymorphs, possibly arising from solvate forms (Figure 5). Mexiletine hydrochloride is a prolific solvate former and the poorly crystalline polymorphic mixture consistently obtained from the DES may arise from the lack of conventional small solvent molecules in the medium.

ROY. The olanzapine precursor 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile also known as ROY exhibits extensive polymorphism. It has 14 known pure conformational forms that display red, orange or yellow colors depending on the dihedral angle between the nitrophenyl and

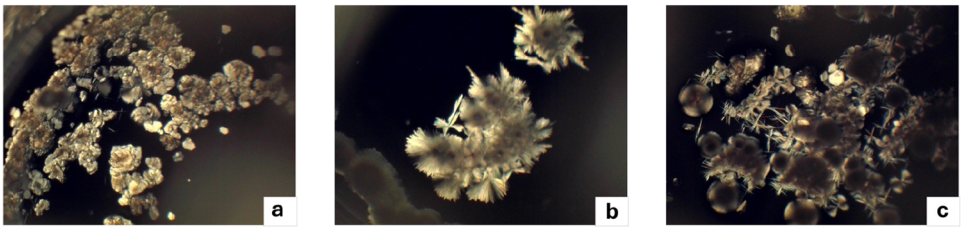

Figure 3. Carbamazepine crystallized in different compositions of the thymol−menthol DES. (a) 30:70, (b) 50:50, and (c) 70:30.

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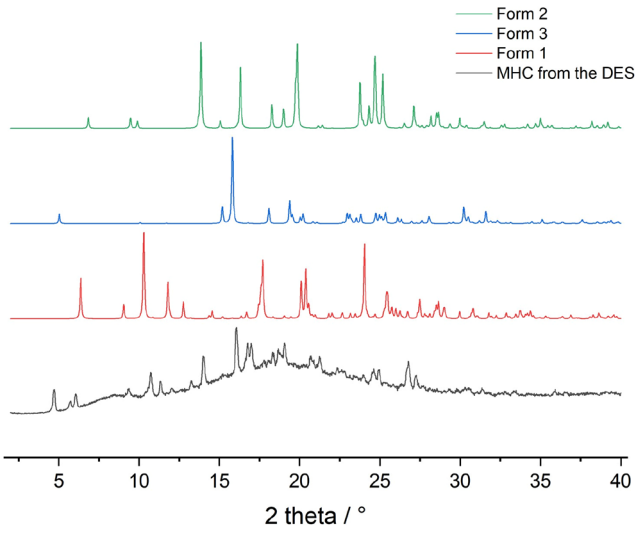

Figure 5. Diffractogram of mexiletine hydrochloride recrystallized from thymol−menthol DES compared to powder patterns of its known single-component polymorphs.

thiophene rings.[11,57] While the most thermodynamically stable yellow (Y) form and ON, R, OP, YN, ORP can be obtained through solution crystallization, other forms require melt crystallization, vapor deposition, polymorphic conversion, heteroseeding and ENaCt high throughput methods.[11,58] ROY was crystallized twice each in three DES compositions at different concentrations. Remarkably, the crystals proved to be of distinctly different colors depending on the DES composition, as seen in Figure 6 indicating a strong and

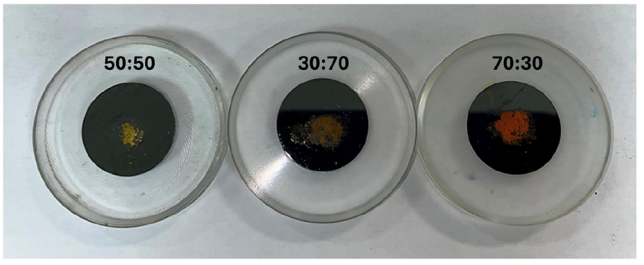

Figure 6. Different ROY polymorphs Y, YN, and ON from different compositions of the thymol−menthol DES.

directed polymorph selectivity according to DES composition (Figure 7). The 50:50 composition yielded the monoclinic Y form which is the most thermodynamically stable form at room temperature. Surprisingly, the 30:70 DES produced the less stable triclinic YN form in addition to some amorphous material. Metastable YN is normally obtained through rapid solution crystallization or from a supercooled melt.[59] Forming the triclinic YN form through solution crystallization from the DES may offer a simpler approach using standard experimental setups. The 70:30 composition formed exclusively monoclinic ON, a metastable polymorph typically formed concomitantly alongside YN, Y04 and RO5.[60] The sensitivity of ROY to DES composition implies a dependence of the nucleation process and inhibition of the nucleation and growth of the stable form to the speciation and microenvironment of the hydrogen bonded clusters within the DES.

Quaternary Compositions−Cocrystallization in Thymol−Menthol. Pharmaceutical cocrystals are crystalline

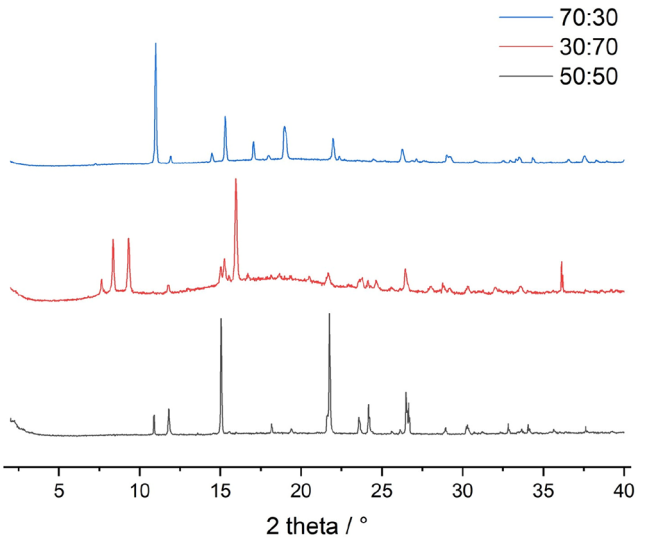

Figure 7. Diffractograms of ROY form Y (50:50), YN (30:70), and ON (70:30) in different compositions of the DES.

solids that involve two or more components bonded together through noncovalent interaction, where one component is an API and the other is a pharmaceutically acceptable molecule.[61−63] Cocrystals can enhance the physical and chemical stability of the API involved, delay its degradation and prolong usability. Cocrystals can be challenging to prepare by solution methods because the two components may have different solubilities causing the less soluble conformer to crystallize first. As a result, melt and mechanochemical methods are often employed. Formation of cocrystals in a DES solvent necessarily involves crystallization of a quaternary mixture comprising the two coformers and the two solvent components. Since impurities can inhibit crystallization processes it is not clear whether such a complex mixture is likely to crystallize at all. To study cocrystallization within the thymol−menthol DES we selected two known pharmaceutical cocrystal systems with a variety of functional groups, namely salicylic acid-nicotinamide[64] and nevirapine-benzoic acid.[65] Salicylic acid−benzamide was discovered by a cocrystal screening approach with cooling crystallization resulting in a mixture of cocrystals and starting components. The pure cocrystal was obtained by seeded solution crystallization using melt-grown material. Nevirapine, a type of HIV-1 treatment, has a strong bitter taste when in its neat form. However, when in a cocrystal with benzoic acid the drug's bitter taste is effectively masked.[65]

Salicylic acid and nicotinamide were mixed in a 1:1 molar ratio before being dissolved in the thymol−menthol DES. Passive slow cooling crystallization of the mixture was performed in different compositions of the DES at different concentrations. In all compositions, the known cocrystal of the two components was successfully formed and identified by its characteristic PXRD pattern corresponding to the pattern calculated from the single crystal data in the Cambridge Structural Database (CSD)[66] with refcode SODDOF.[64] While this phase formed across all DES compositions, the resulting crystal morphology varied considerably (Figure 8). In the 50:50 DES, long needles were produced, whereas spherulites formed in the 30:70 and 70:30 compositions. In addition, both the 30:70 and 70:30 compositions produced a diffractogram that was broad with considerable amorphous content while the

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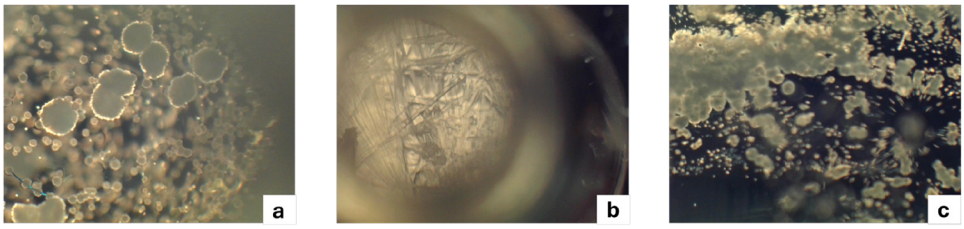

Figure 8. Crystal images of salicylic acid-nicotinamide cocrystals in different thymol−menthol DES compositions (a) 30:70, (b) 50:50, and (c) 70:30.

samples obtained from the 50:50 eutectic mixture proved to be more crystalline (Supporting Information Figure S8). This suggests the possibility of face-specific interactions of the DES with the growing crystal or an influence of DES liquid microenvironment on nucleation rate. The variability of the morphology implies surface media interactions during growth, possibly as interactions with different DES components dominate at different compositions. However, solubility does change with DES composition and so the changes in morphology may arise from differences in supersaturation.

Nevirapine and benzoic acid were combined in a 1:1 molar ratio in the 50:50 DES, and both cooling crystallization and slurrying over 24 h were undertaken. Cooling crystallization produced microcrystalline material crystal that could not be easily characterized. However, slurrying two coformers together in the DES over 3 days under ambient conditions produced the known cocrystal refcode RUTRAC (Supporting Information Figure S9).[65] This cocrystal was originally formed via liquid-assisted grinding in chloroform, so its formation from slurrying in the DES offers a potentially more sustainable crystallization route.

Nonracemic Menthol DES. In addition to the use of racemic menthol, DES were prepared using resolved L−menthol and the racemic and nonracemic media were used for crystallization of chiral substrates. Initially racemic ascorbic acid (vitamin C) and serine were used as test cases because of their pharmaceutical importance and their ability to exhibit polymorphism. However, these two compounds were both insoluble in both types of DES, likely because of its relatively nonpolar nature. As a result, our attention focused on racemic ornidazole, a highly soluble antibiotic with an aromatic imidazole core that may undergo π-stacking with thymol. Ornidazole exhibits an unusual $Z' = 3$ structure as a racemate and forms a hydrate and a cocrystal.[67] Ornidazole proved to be highly soluble in both the racemic and nonracemic DES (50:50 compositions) with an equilibrium solubility under ambient conditions of 40 mg mL^{-1}. However, surprisingly, ornidazole appears to dissolve more rapidly in the chiral DES. To quantify this difference the time taken for 20 mg of ornidazole to dissolve with stirring in 500 μL of each DES was recorded in triplicate. This gave average dissolution rates of 0.86 ± 0.14 mg min^{-1} for the chiral DES compared to 0.70 ± 0.10 mg min^{-1} in the racemic DES (see Supporting Information Table S2). All experiments used the same batch of ornidazole to ensure consistency in particle size distribution. Since ornidazole is racemic this result, although statistically of low significance, may arise from speciation differences such as different degrees or modes of DES aggregation in the two DES rather than enantiomer-specific ornidazole L-menthol interactions.

Upon passive cooling of saturated ornidazole solutions in the chiral and racemic DES crystal growth proved to be much faster within the chiral medium. XRPD showed that the solids obtained from the racemic DES are much less crystalline than those grown in the chiral DES (Figure 9). Crystallinity improved using a 70:30 racemic DES medium. However, both types of DES give rise to same polymorph of racemic ornidazole in each case, CSD refcode NETRUZ01.[67]

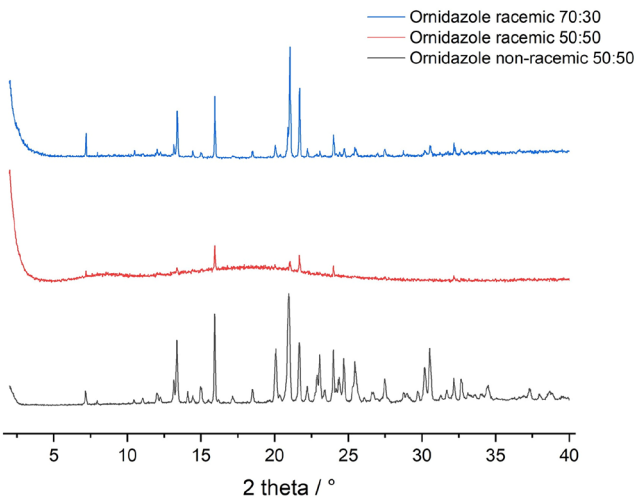

Figure 9. Diffractogram of ornidazole crystallized in racemic and nonracemic DES.

Evaporative Crystallization. The volatile deep eutectic solvent method (VODES) involves the use of evaporative crystallization from a DES in which the volatile component(s) of the DES are evaporated, leading to spontaneous crystallization of the remaining solute. This method has been used by Potticary et al. in which evaporation of phenol from a two component DES comprising phenol and paracetamol as an API resulted in the crystallization of the elusive metastable paracetamol form II at room temperature.[34] In the present case the thymol−menthol mixture is substantially less volatile than phenol, however the crystallization of a range of API DES solutions was undertaken using high temperature evaporation over an extended period. Aspirin, paracetamol, benzamide, nicotinamide and carbamazepine all formed crystalline material after evaporation of the 50:50 racemic DES to dryness at 90 °C for 24 h. In each case the most thermodynamically stable form of the APIs was observed, which was the form used in preparing the solutions. It is likely that the high temperature of the evaporation of the DES favors the crystallization of the thermodynamic forms rather than the metastable polymorphs. In addition, the DES involatility also results in slow evaporation and hence lower and slowly changing supersaturation levels, also favoring the thermodynamically most stable form.

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Eutectogel Crystallization. Over the past 15 years low molecular weight supramolecular small molecule gels (LMWG) of organic solvents (organogels) have been increasingly studied as pharmaceutical crystallization media. The gels limit convection, allow versatile and tunable solvent choice, can give high quality crystals and offer a chemically tunable functional fiber surface. LMWG crystallization media have given rise to novel polymorph selectivity and the reversibility of supramolecular gel formation allows facile crystal recovery.[19,56,68−71] Gels of DES with polymer gelators have recently become topical and while the gels have been loaded with nanocrystals as a means of altering their properties[45,72,73] they do not seem to have been used as pharmaceutical crystallization media. There have also been reports of LMWGs based on DES[74] including hydrophobic dibenzene sorbitol gels of DES comprising menthol or thymol and carboxylic acids but no applications have been reported to date.[73] In order to produce a LMWG of the Type V thymol−menthol DES we used the previously reported bis(urea) gelator methyl(2S)-2-[6-[[(1S)-2-methoxy-1-methyl-2-oxo-ethyl]carbamoylamino]hexyl carbamoylamino]propanoate (M2MP) gelator (Figure 10).[75] The bis(urea) motif gives

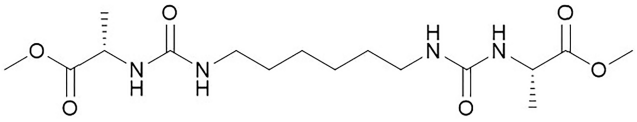

Figure 10. Structure of the bis(urea) M2MP gelator.

rise to versatile gels from urea−urea hydrogen bonding that have been used previously as crystallization media.[19,71] Given that hydrogen bonding is a crucial aspects of the formation of the DES it was of interest to see whether they type of gelator could form a gel of a type V DES or whether the presence of the gelator would inhibit the DES behavior.

The M2MP gelator was dissolved, using heat, in three different DES systems: the thymol−menthol DES used throughout this work (50:50) and in addition related DES based on thymol−camphor and menthol−camphor.[76,77] Gel formation was initially assessed through the simple inversion test and gels were formed in each medium. The critical gelation concentration (CGC) was 5%, 4% and 2% w/v for the three DES. These values are relatively high compared to some organogels with can gel at significantly less than 1% gelator but are not extreme.[78]

These new hydrophobic supramolecular eutectogels were characterized by frequency sweep and stress sweep rheometry. The frequency sweep rheology plot for the menthol-camphor eutectogel at 2% w/v is shown in Figure 11. The gel is relatively weak, however $G' > G''$ indicates that a viscoelastic solid material has been produced, albeit not at the typical order of magnitude difference of a true gel.[79] Stress sweeps demonstrated that all gels have a constant G' at low stress, but after yielding, G'' is greater than G', showing the material transitions to liquid-like state, where it can flow. Table 1 shows the mean storage modulus (G') and the loss modulus (G'') at a selected point in the linear viscoelastic region (LVR) from the frequency sweep plots (averaged over three experiments) for each eutectogel.

Eutectogel phase crystallization was explored as an alternative to crystallization from the liquid DES to see if the crystallization outcomes would differ from those from solution.

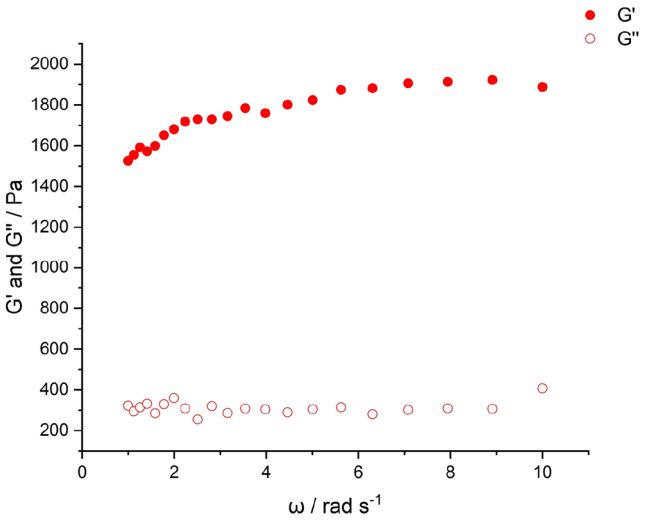

Figure 11. Frequency sweep rheology of the menthol-camphor eutectogel showing the storage modulus (G') and the loss modulus (G'') against angular frequency.

Table 1. Rheological Properties of the Eutectogels, Including Mean G' and G'' in the LVR of the Frequency Sweeps, Their Ratio, and Yield Stress from the Stress Sweeps[a]

eutectogel	G' (Pa)	G'' (Pa)	G'/G''	yield stress
thymol−menthol	2650	821	3.23	501
thymol−camphor	501	103	2.59	63
menthol−camphor	2232	422	5.29	445

[a]Errors are around 10% although some variation was noted from sample-to-sample.

Five APIs (aspirin, paracetamol, benzamide, carbamazepine and nicotinamide) were crystallized within the three DES systems based on their ability to crystallize in the thymol−menthol system. The resulting crystals, still suspended in the gel, were then analyzed using PXRD. However, in most cases, the powder patterns were difficult to interpret due to the presence of the gel matrix itself. In order to isolate the API crystals the gels were decomposed using tetrabutylammonium acetate, a strong competitor that disrupts urea−urea hydrogen bonding.[80] In the cases of the DES, adding acetate successfully broke down the gel fibers resulting in deposition of solid gelator and API crystals together at the bottom of the DES solution where they could be isolated by filtration. The presence of the solid gelator, however, made analysis of the crystallization outcome challenging.

Crystallization of aspirin crystals from the eutectogel crystallizations produced aspirin in form I from both the thymol−menthol DES and menthol-camphor DES, which was the same form from DES solution. While some additional peaks were noted in the material arising from the thymol-camphor gel the sample is also likely to be form I with interference from the gelator (Supporting Information Figure S10). Paracetamol crystals from gel crystallization experiments yielded the thermodynamic form I in both the thymol−camphor and the menthol-camphor DES. The analysis of the thymol−menthol eutectogel product was complicated by the interference from the presence of the crystalline gelator. Benzamide, carbamazepine and nicotinamide all crystallized in each of the three different DES. Carbamazepine and

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nicotinamide formed form III and form α respectively in all eutectogels, similarly to the solution DES experiments. On the other hand, benzamide interfered with the gelling of the gelator causing a semigel like liquid to form. This medium formed benzamide as form I, the same as solution crystallization.

EXPERIMENTAL SECTION

Materials and Instrumentation. The chemicals were purchased commercially and used as received without further purification. The M2MP gelator was prepared according to the published method.[75] ^{1}H NMR spectra were measured in DMSO-d_6 solvent under ambient conditions, on a Bruker Avance III-HD-400 spectrometer, with an operating frequency of 399.95 MHz. Infrared spectra were recorded between 4000 and 550 cm^{-1} using a PerkinElmer 100 FT-IR spectrometer with a uATR attachment. Unless otherwise specified, powder X-ray diffraction (XRPD) patterns were collected at room temperature using a Bruker AXS D8 Advance GX003410 diffractometer with a Lynxeye Soller PSD detector, using Cu Kα radiation at a wavelength of 1.5406 Å and collecting from $2° \leq 2\theta \leq 40°$ under ambient conditions with a scan time of 20 min. To obtain powders for PXRD, crystals suspended in solution were lightly ground and air-dried on a PXRD slide overnight. Gelled samples were left to air-dry for 2−3 days to ensure evaporation of residual DES. Thermomicroscopy analysis was performed using a polarized microscope (BX53, Olympus) coupled with the LTS420 hot stage (Linkam). Samples were heated from room temperature up to 350 °C at a heating rate of 10 °C/min.

DES Preparation. Different compositions of the thymol−menthol DES were prepared by grinding up varying molar quantities of thymol and menthol using a mortar and pestle, indicated below in Table 2.[46]

Table 2. Masses of Thymol and Menthol Used for Each DES Composition

molar ratio of thymol−menthol	mass of thymol (g)	mass of menthol (g)
50:50	7.511	7.813
40:60	6.090	9.376
33:66	4.957	10.313
30:70	4.507	10.938
60:40	9.013	6.250
66:33	9.915	5.157
70:30	10.515	4.688

The liquid formed was sonicated at 40 °C for 10 min to ensure a homogeneous mixture. FT-IR of 50:50 thymol−menthol DES (ν_{max}/cm^{-1}) 3342br, 2954s, 2918s, 2865m, 1452m, 1417m, 1288s, 803s. Menthol−camphor and thymol−camphor DES were also prepared in a 50:50 molar ratio. FT-IR of the menthol−camphor DES (ν_{max}/cm^{-1}) 3401br, 2953s, 2915s, 2867m, 1742s, 1456m, 1044s. FT-IR of the thymol-camphor DES (ν_{max}/cm^{-1}) 3408br, 2963m, 2870w, 1726s.

Crystallization Procedure. API crystallizations were carried out primarily in the 50:50 thymol−menthol DES composition using passive/slow cooling. A small mass of the API was placed in a vial along with a known volume of DES. The mixture was stirred for 30 min to ensure a saturated solution had formed. Any remaining, undissolved API was then heated using a heat gun or hot plate to achieve full dissolution. After cooling, the solution was left to stand for several days, resulting in the formation of crystals suspended in solution. For cocrystallization, two methods were undertaken either (1) passive/slow cooling of two APIs at a particular molar ratio following a similar approach to single API crystallization or (2) slurrying of partially undissolved API mixtures in the DES over a 72 h period.

Dissolution Test for Ornidazole. Ornidazole (20 mg) was stirred in 500 μL of racemic and chiral DES (50:50) at 500 rpm until fully dissolved. The time taken for complete dissolution was recorded in triplicate and the average time taken for dissolution to occur calculated.

VODES Method. Each API (0.10 g) was mixed with 0.6 mL of 50:50 thymol−menthol DES. The mixture was then stirred and heated at varying temperatures over 24 h until the DES was completely removed through evaporation.

Gel Crystallization Procedure. Gel crystallizations experiments were conducted by dissolving API and M2MP gelator (at a concentration that exceeds critical gelation concentration) in a set volume of DES. The two components were then fully dissolved, ensuring a homogeneous solution. The hot solution was then left to stand and cool at room temperature, allowing gelation and crystallization to occur simultaneously.

Rheology. Rheology experiments were performed using a TA Instruments AR2000 rheometer with a parallel plate set up using a 25 mm rough plate on 1 mL of eutectogel. All experiments were carried out at 25 °C. Frequency Sweeps were carried out from 1−10 rad/s at a constant stress of 1 Pa. Stress sweeps were performed from 1 to 1000 Pa at a constant frequency of 1 Hz. Each test was performed three times on each eutectogel and the results averaged.

CONCLUSIONS

This work has demonstrated that the thymol−menthol NADES is highly effective as a green crystallization solvent and provides a sustainable alternative to conventional organic solvents for pharmaceutical crystallization. This DES is effective for both single-component and cocrystallization of a range of APIs. Notably, this DES offers potential for polymorph selectivity in some cases, particularly ROY in which the polymorph obtained proved to be dependent on the DES composition with the highly metastable YN form arising from menthol-rich DES while the thymol rich medium gave the metastable ON form usually obtained as a concomitant mixture. The 50:50 DES mixture gave the thermodynamic Y form. Thus, the use of DES may offer additional routes to explore the polymorphic profile of API molecules. The chirality of the thymol−menthol DES offers interesting scope for enantioselective crystallization and in this case notable dissolution rate differences of ornidazole were observed in the chiral and racemic DES. Evaporative crystallization of this relatively involatile DES proved possible and led to the thermodynamic forms of the APIs studied, likely because of the high temperature required to evaporate the (VO)DES and the slow evaporation rate. It proved possible to prepare several NADES eutectogels with a common bis(urea) gelator and to carry out quaternary gel phase crystallization on APIs. However, a key limitation of this method with this particular combination of components is the difficulty in separating the crystals from the gel or precipitated gelator, hindering preventing characterization of the resulting solid forms. Despite this challenge this approach offers a way to extended the search for novel polymorphs. This work demonstrates that a range of APIs can be successfully crystallized in a controlled way from DES media offering a green and versatile alternative to traditional solvent methods.

ASSOCIATED CONTENT

Data Availability Statement

Underlying electronic data for this work comprising XRPD, IR, NMR and rheometry files can be obtained from doi: 10.15128/r22n49t171v.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.5c01081.

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Photographs of the DES, DES FTIR spectra, ^{1}H NMR spectra, PXRD patterns and additional photographs of crystallization outcomes (PDF)

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Notes

The authors declare no competing financial interest.

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