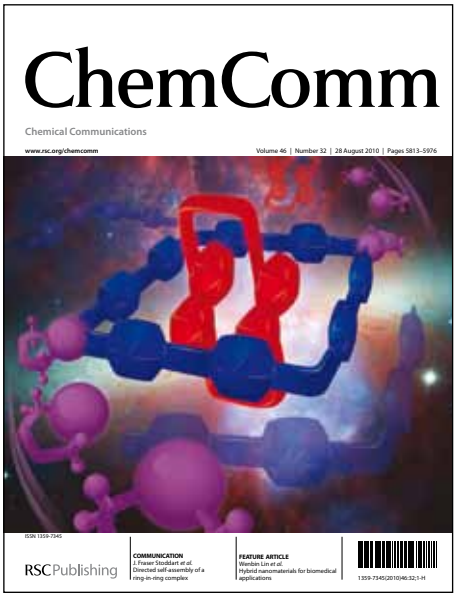
# ChemComm

## Accepted Manuscript




This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

# Eutectics as Improved Pharmaceutical Materials: Design, Properties and Characterization†

Suryanarayan Cherukuvada, and Ashwini Nangia*
School of Chemistry, University of Hyderabad, Prof. C. R. Rao Road, Central University PO, Gachibowli, Hyderabad 500 046, India
E-mail: ashwini.nangia@gmail.com

**Abstract**

Eutectics are a long known class of multi-component solids with important and useful applications in daily life. In comparison to other multi-component crystalline solids, such as salts, solid solutions, molecular complexes and cocrystals, eutectics are less studied in terms of molecular structure organization and bonding interactions. Classically, a eutectic is defined based on its low melting point compared to the individual components. In this article, we attempt to define eutectics not just based on thermal methods but from a structural organization view point, and discuss their microstructures and properties as organic materials vis-a-vis solid solutions and cocrystals. The X-ray crystal structure of a cocrystal is different from that of the individual components whereas the unit cell of a solid solution is similar to that of one of the components. Eutectics are closer to the latter species in that their crystalline arrangement is similar to the parent components but they are different with respect to the structural integrity. A solid solution possesses structural homogeneity throughout the structure (single phase) but a eutectic is a heterogeneous ensemble of individual components whose crystal structures are like discontinuous solid solutions (phase separated). Thus, a eutectic may be better defined as a conglomerate of solid solutions. A structural analysis of cocrystals, solid solutions, and eutectics has led to an understanding that materials with strong adhesive (hetero) interactions between the unlike components will lead to cocrystals whereas those having stronger cohesive (homo/self) interactions will more often give rise to solid solutions (for similar structures of components) and eutectics (for different structures of components). We demonstrate that the same crystal engineering principles which have been profitably utilized for cocrystal design in the past decade can now be applied to make eutectics as novel composite materials, illustrated by stable eutectics of the hygroscopic salt of the anti-tuberculosis drug ethambutol as a case study. A current gap in the characterization of eutectic microstrutcure may be fulfilled through pair distribution function (PDF) analysis of X-ray diffraction data, which could be a rapid signature technique to differentiate eutectics from their components.

Chemical Communications Accepted Manuscript

## Introduction

Eutectics find several applications in diverse fields of daily life.[1] From the traditional refrigeration and snow removal (sodium chloride–water eutectic) and anti-freeze (ethylene glycol–water eutectic) in vehicles[2] to the more recent energy storage devices,[3] and from conventional soldering materials (lead–tin alloy) to novel materials in ceramics and glass industry,[1] eutectics are present in day-to-day materials as well as in pharmaceutical formulations.[4] For example, a eutectic composition of the local anesthetic drugs Lidocaine and Prilocaine (trade name EMLA®) is used to enhance the transdermal permeation of Lidocaine.[5] These drugs when administered individually have a slower skin penetration because their melting points (Lidocaine, 68 °C; Prilocaine, 38 °C) are higher than the body temperature (37 °C); the 1:1 eutectic with a low melting point of 22 °C has faster skin permeation and rapid pharmacological action. The high thermodynamic functions of eutectics, such as free energy, enthalpy, and entropy,[6] can confer solubility and dissolution advantage to poor solubility drugs,[4b,c] similar to the more popular amorphous solids and solid dispersions (dispersion of one or more components in a solid matrix).[4a] Occasionally, solid dispersions of drugs exhibit a eutectic-like behavior and solubility improvement,[4a,7] e.g. Fenofibrate–Polyethylene glycol.[7e] On the down side, however, the low melting point of organic eutectics (usually below 100 °C) can pose stability issues.[8] Eutectics have often been confused with solid dispersions and vice-versa,[4a,7,8a,b] and therefore the problems associated with one of these materials were erroneously ascribed to the other category. The absence of a clear distinction between eutectics and solid dispersions in the literature mean that the time is right to revisit eutectics and appraise their structural details and potential benefits in pharmaceutical and materials fields. The scientific question posed in this article is if crystal engineering principles[9] can be adapted to design eutectic systems, understand their structural details, and correlate with their properties. We answer the above question in the affirmative by highlighting the importance, utility and potential of eutectics as novel pharmaceutical solids. The writing of this article was motivated by recent observations from our laboratory,[10,11] and those of others,[12] in which intended cocrystallization experiments resulted in eutectic compositions instead of the targeted cocrystals.

Eutectics are basically multi-component crystalline solids closely related to solid solutions.[1,13] Both are well-documented in inorganic systems as alloys.[1,14] Several definitions of eutectics based on their composition and low melting behavior are known in the literature (Table 1). The word eutectic is derived from the Greek word *eutectos*, which means easily fused.[1] However, the structural organization of eutectics has not been studied in as much detail as solid solutions, which are defined based on the arrangement of a major (solvent) and a minor (solute) component in the crystal lattice.[1,14] Despite their

Chemical Communications Accepted Manuscript

long history, internal structural details of eutectic compositions are scarce, in contrast to the many X-ray crystal structure reports of solid solutions.[15] Similar to the famous lead–tin eutectic which is exhaustively studied as an inorganic example,[1,14] a molecular level understanding is necessary for organic eutectics and drug eutectic compositions.

Eutectics have been observed alongside solid solutions and the recently popularized cocrystals for organic systems and pharmaceuticals.[13,16] Moreover, cocrystals are reported to form solid solutions[17] as well as eutectics.[10] However, the exact reasons for their formation were not dissected at the molecular level. Eutectics were proposed as intermediates on way to certain cocrystals[12a,18] and solution eutectic constants were noted to be crucial for cocrystal formation and stabilization in solution.[19] Thus, cocrystals and solid solutions and eutectics are intimately related to each other but studies[20] to differentiate these multi-component crystalline solids have mainly focused on the binary compositions properties and their phase diagrams. We discuss structural inter-relationships of the above solids and propose modified definitions based on the internal organization of the components.

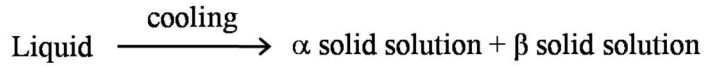
To strengthen the link between cocrystals and eutectics, a few literature examples are discussed. This is the first report on (i) the design aspects of eutectics, (ii) retro-engineering of a specific property (hygroscopic stability) in a eutectic, and (iii) the potential of eutectics as improved pharmaceutical solids. Stable eutectic compositions of the hygroscopic anti-tuberculosis drug ethambutol dihydrochloride (discussed at the end of this article) suggest a way forward for further explorations.

**Table 1** Literature definitions of Eutectic (including reactivity).

| | |
|---|---|
| Oxford Dictionary[21] | Relating to or denoting a mixture of substances (in fixed proportions) that melts and freezes at a single temperature that is lower than the melting points of the separate constituents or of any other mixture of them. |
| Encyclopaedia Britannica[22] | The one mixture of a set of substances able to dissolve in one another as liquids that, of all such mixtures, liquefies at the lowest temperature. |
| IUPAC Gold Book[23] | An isothermal, reversible reaction between two (or more) solid phases during the heating of a system, as a result of which a single liquid phase is produced. |
| Essentials of Materials Science and Engineering (2nd Edition)[1] | A three phase, invariant reaction in which one liquid phase solidifies to produce two solid phases. |
| Foundations of Materials | A phase transformation in which all the liquid phase |



Chemical Communications Accepted Manuscript

| | |
|---|---|
| Science and Engineering (4th Edition)[14] | transforms on cooling into two solid phases isothermally.   |

## Discussion

### Eutectic Microstructure

We begin the discussion with the structural integrity of solid solutions and eutectics in the better-studied inorganic systems. Inorganic alloys are classified as (i) solid solution alloys, and (ii) eutectic alloys.[1] Traditionally both these materials were prepared by the fusion of two or more solids in different ratios to give a product which was characterized by melting point and a solid–liquid phase diagram.[1,14] The typical phase diagram of a solid solution and a eutectic are exemplified by the copper–nickel solid solution alloy (Figure 1) and the lead–tin eutectic alloy (Figure 2). A solid solution, in general, exhibits a melting/freezing range and the temperature below which the material is a solid is called the solidus, and liquidus is the temperature above which it is a liquid (Figure 1a). Between solidus and liquidus, the solid and liquid phases coexist. On the other hand, a eutectic exhibits a characteristic lower melting point than its components (Figure 2a). Its melting point is sharp and not in a range, i.e. the solidus and liquidus temperature is at the same point.

A solid solution is made up of a major phase (solvent) and a second minor phase (solute). It is often formed by isomorphous crystals (i.e. crystal structures having the same space group and unit cell dimensions)[24] according to the Hume–Rothery rules[1,13,14] (similar crystal structure and valence, and similar size and electronegativity of metals). In contrast, non-isomorphous crystals can give rise to a eutectic. Such crystal structure–product structure correlations to give a solid solution or a eutectic system have been extensively studied for metal systems, but not explored so well for organic and pharmaceutical materials. This topic will be discussed in the subsequent sections. When the interacting materials have similar size and crystal structures, they can have unlimited solubility and accommodate well in the crystal lattice, either substitutionally or interstitially, without disturbing the parent lattice structure and thus form continuous solid solutions (from 1:99 to 99:1 ratios), as in the case of copper–nickel system (Figure 1b). When nickel (Ni, $Z = 28$) is added to copper (Cu, $Z = 29$), or vice-versa, both having a face-centered cubic (fcc) crystal structure, the elements mix in any amount and randomly distribute within the fcc crystal structure. They form a homogeneous phase or solid solution, designated as $\alpha$, throughout the lattice, wherein no interface exists between the copper and nickel atoms.

Chemical Communications Accepted Manuscript

When the materials have atomic/molecular size/shape mismatch and asymmetry in the crystal structures, they have limited solubility and thus cannot fit beyond a threshold in the crystal lattice of each other, since this will cause strain and disorganization of the lattice structure. Such systems cannot form continuous solid solutions and instead tend to form eutectics exemplified by the lead–tin system.[1,14] When tin (Sn, $Z$ = 50, tetragonal) is added to lead (Pb, $Z$ = 82, cubic), or vice-versa, they form solid solution alloys just like copper–nickel system up to their solubility limits. Tin being smaller in size has higher solubility in lead (0 to 19%) whereas the larger lead has lower solubility in tin (0 to 2.5%). This means up to 19% tin can be accommodated in the lattice structure of lead to form a homogeneous solid solution represented as $\alpha$ (Figure 2), which retains the lattice structure of lead since it is the major component (81%). Similarly, 2.5% solid solution of lead in tin, represented as $\beta$, retains the crystal structure of tin, the latter being the major component (97.5%). When the percentage of either of the elements goes beyond their solubility, it leads to strain and disorganization of the solid solution lattice. To conciliate this, the solid solution ($\alpha$ or $\beta$) segregates and reorganizes into two different phases or solid solutions ($\alpha$+$\beta$, each of which is rich in a particular element and retains the parent lattice structure), which are bound together and constitute the eutectic phase (Figure 2b).[1,14] Thus, the distinction of components as solvent and solute is superficial in continuous solid solutions, since they can mix in any proportion. The components of eutectic solid solutions can be differentiated as solvent/solute because of limited solubility in one another. Therefore, a eutectic can be envisaged as an ensemble of many/different solid solutions which are discontinuous. The individual components retain their crystal structures as discontinuous solid solutions (containing only limited quantity of solute) and form the eutectic crystal lattice. A eutectic's microstructure may be more precisely defined as 'a conglomerate of solid solutions' or 'a conglomerate of lattice structures of different materials, elements or compounds'.

The eutectic microstructure consists of domains of solid solutions held together by weak inter-phase boundaries (the line between $\alpha$ and $\beta$ phases, Figure 2b & 2c) along which atoms can diffuse and redistribute in the solid solutions.[1,4a] The inherent strain in the solid solution domains (due to accommodating non-isomorphous solids), maximized by the imperfect atomic arrangements and poor inter-phase bonding[25] across the domain boundaries, lead to high thermodynamic functions such as free energy, enthalpy and entropy[6] of the eutectic phase, and hence the characteristic lower melting point relative to the components.[1] At 61.9% tin in lead or 38.1% lead in tin, the eutectic microstructure has the lowest melting point (183 °C) for the alloy compared to the pure elements (Sn = 232 °C, Pb = 327 °C) and also other mixed compositions (Figure 2a). Many eutectic systems adopt a lamellar or plate-like arrangement of component solid solution domains



Chemical Communications Accepted Manuscript

including the lead–tin system (Figure 2c & 2d).[1,14] The phase diagram (Figure 2a) shows that other compositions can exhibit solidus-liquidus melting behavior typical of solid solutions or lower melting point than the parent elements but these temperatures are higher than that of the eutectic composition. These compositions too can be composed of different amounts of solid solutions (as shown in Figure 2b) with varying degrees of domain organization and inter-phase interactions in the crystal lattice.

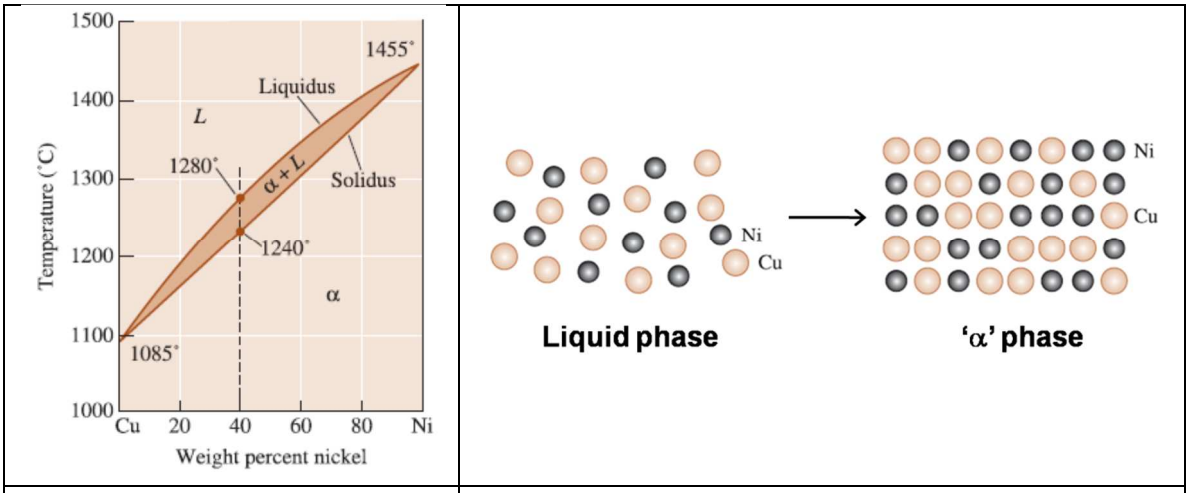



**Figure 1** (a) Phase diagram of copper–nickel solid solution alloy. The 40% copper solid solution of nickel exhibits a melting range of 1240-1280 °C. Below the solidus temperature (1240 °C), the alloy is a homogeneous solid phase designated as α and above the liquidus temperature (1280 °C) it is a liquid phase. (b) Liquid copper and liquid nickel are completely soluble in each other and occupy random lattice sites in the copper–nickel solid solution alloy. Adapted from Ref. 1.

Chemical Communications Accepted Manuscript

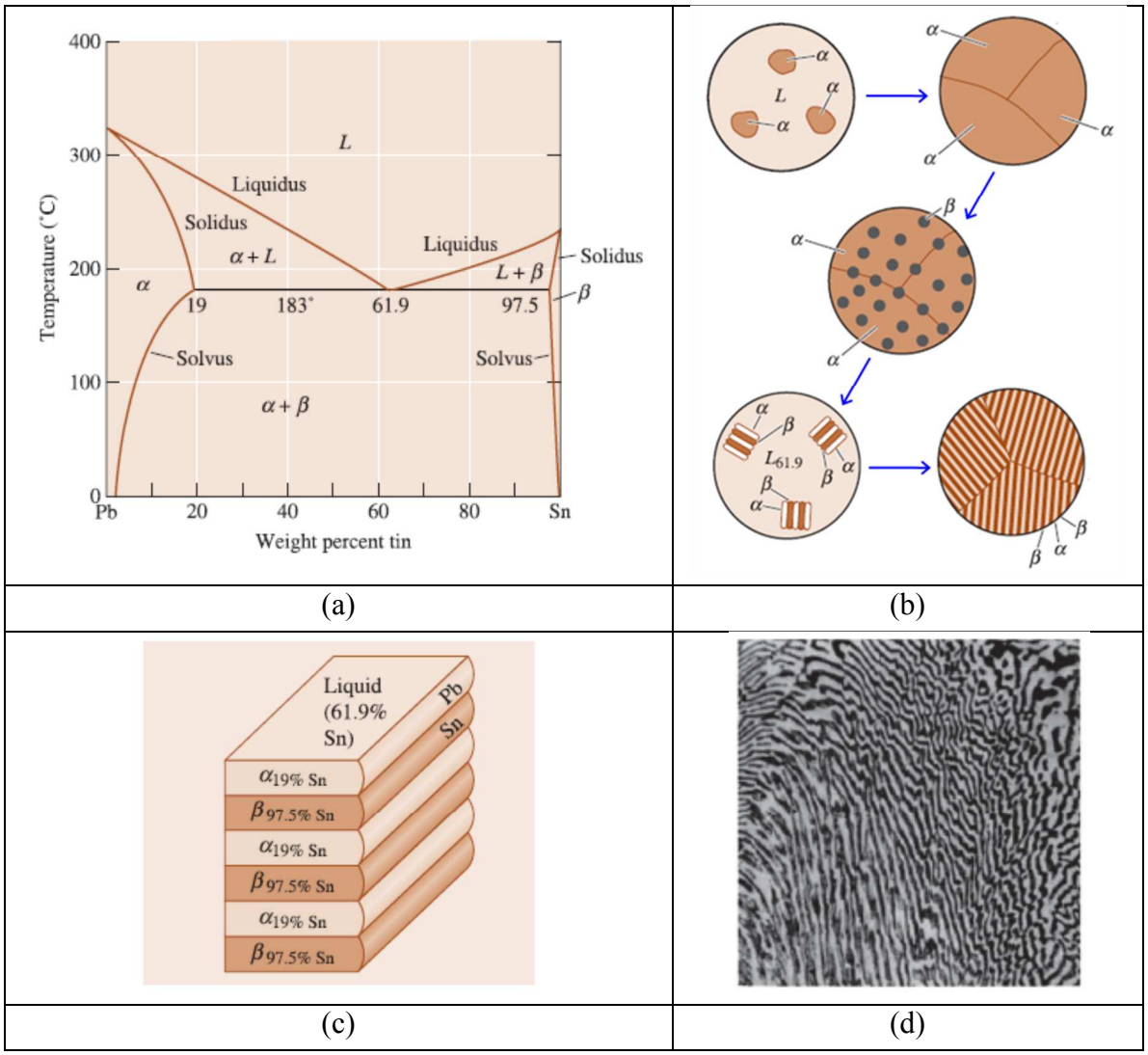



**Figure 2** (a) Phase diagram of lead–tin eutectic alloy. The 61.9:38.1 tin–lead composition exhibits the characteristic lower melting point (183 °C) than the parent materials (tin = 232 °C, lead = 327 °C) and also other compositions. (b) The microstructure of lead–tin eutectic alloy to show solidification and growth of solid solutions. (c) Lamellar arrangement of lead-rich $\alpha$ and tin-rich $\beta$ solid solutions in lead–tin eutectic alloy. Lead atoms from the liquid preferentially diffuse to the $\alpha$ plates, and tin atoms to the $\beta$ plates. (d) Photomicrograph of lead–tin eutectic microconstituent. Adapted from Ref. 1.

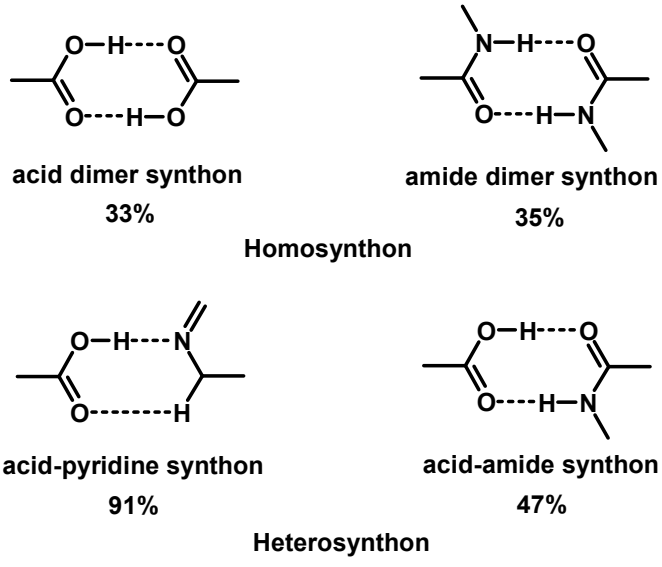
**Cocrystals, Solid solutions and Eutectics**

Cocrystals are the subject of intense studies in the past decade as promising novel materials in pharmaceutical development.[16,26] A cocrystal is a multi-component crystalline solid which was defined by Shan and Zaworotko[26c] as "*a multiple component crystal in which all components are solids under ambient conditions when in their pure form. These components co-exist as a stoichiometric ratio of a target molecule or ion and*



Chemical Communications Accepted Manuscript

*a neutral molecular cocrystal coformer(s)*". Jones et al.[27] elaborated cocrystal as "*a crystalline complex of two or more neutral molecular constituents bound together in the lattice through noncovalent interactions, often including hydrogen bonding*." A more inclusive and broader definition of cocrystals and salts[26h] emerged after a recent Indo-US discussion meeting. The supramolecular synthon and molecular recognition principles of crystal engineering are the lynchpin for cocrystal design (Scheme 1).[9] Desiraju coined the term supramolecular synthon and defined them as "*structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions*."[28] Depending on the type of functional groups involved in the hydrogen bonds which lead to the supramolecular assembly, synthons were categorized by Walsh et al.[29] as homosynthon (self-complementary moieties, such as carboxylic acid and carboxamide dimer), and heterosynthon (two different functional groups associate as in acid–pyridine and acid–amide) (Scheme 1). A quantitative understanding of the supramolecular behavior of a given functional group is facilitated by the Cambridge Structural Database (CSD), a repository of over half a million small-molecule X-ray crystal structures.[15] The current version of the CSD contains over 250 000 crystal structures of organic compounds, which provide information about "how often" a given supramolecular synthon occurs in the CSD, statistics that are integrated into the cocrystal design strategy (Scheme 1). For example, if a molecule contains a carboxylic acid group one can choose a partner molecule, popularly called as cocrystal former or simply coformer,[16,30] with complementary functionality such as acid, amide or pyridyl group to make a cocrystal, and the preference order based on CSD frequency is pyridine > amide > acid (Scheme 1).




**Scheme 1** A few supramolecular synthons with their probability of occurrence (%) in the CSD.[26f,31]



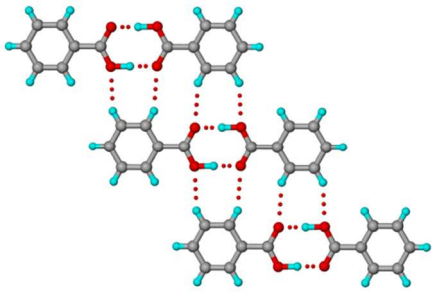
Chemical Communications Accepted Manuscript

However, not all molecules having complementary functional groups can be partnered to make cocrystals. Apart from giving a cocrystal, the cocrystallization product can be a solid solution, a eutectic, or even a simple physical mixture of unreacted compounds.[32] A solid solution occurs between materials that are isomorphous (having same space group and unit cell dimensions and/or almost same type and position of atoms or functional groups),[24] or isostructural (having same structure but not necessarily the same unit cell dimensions).[33] Thus, solid solutions are sustained by strong cohesive interactions and retain the lattice structure of the parent (major) component as the inclusion of the second (minor) component happens substitutionally or interstitially in the parent crystal lattice.[1,13,14,17,33b,c,d,e] In case of a eutectic, the adhesive (heteromolecular) interactions are relatively weaker as they are formed between non-isomorphous materials (having size/ shape mismatch between the components), the structure lacks a unique lattice arrangement distinct from the individual components and retains the cohesive interactions in its solid solutions. In comparison, a cocrystal is formed when the adhesive interactions can overcome the size/shape mismatch features of the components, and the resultant crystal packing is distinct from the parent components. Thus, the X-ray diffraction pattern and spectroscopic signature peaks of a cocrystal, with its unique crystalline arrangement mediated by hydrogen bonds and intermolecular interactions, is different from that of the individual components. In contrast, solid solutions and eutectics exhibit close similarity to the patterns of the pure constituents.

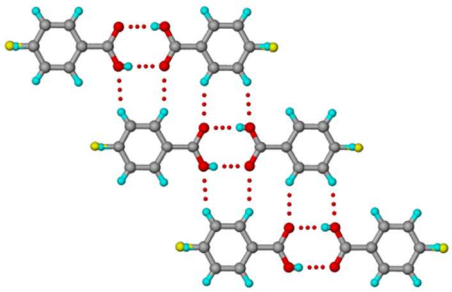
We illustrate the structural boundary between cocrystal and eutectic through two systems. Benzoic acid combines with structural analogues 4-fluorobenzoic acid, pentafluorobenzoic acid, and benzamide to form a solid solution,[34] a cocrystal,[35] and a eutectic,[6b] respectively. Since 4-fluorobenzoic acid and benzoic acid are isomorphous (hydrogen in para position is replaced by isosteric fluorine), they form continuous solid solutions (Figure 3a).[34] In case of benzoic acid–pentafluorobenzoic acid, the cocrystal structure is formed due to the crucial stabilization from auxiliary C–H···F interactions to the primary carboxylic acid synthon (Figure 3b).[35] The integrity of benzoic acid–benzamide system has been studied with different interpretations.[6b,36] In 2008, Singh et al.[6b] reported that benzamide and benzoic acid form a eutectic system. A year later, Brittain[36a] claimed the formation of a cocrystal between benzamide and benzoic acid based on minor changes in spectroscopic and diffraction patterns compared to the parent compounds. The conclusions were tentative in the absence of X-ray crystal structure. In 2011, Seaton et al.[36b] concluded that in the absence of secondary/auxiliary interactions, which can extend the finite structural motif of amide···acid heterodimer, the benzamide–benzoic acid product is a eutectic. These three graded systems suggest that weak adhesive

Chemical Communications Accepted Manuscript

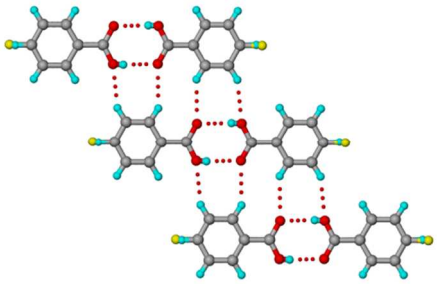
interactions are the key to determining the classification of benzamide−benzoic acid structure.



Benzoic acid

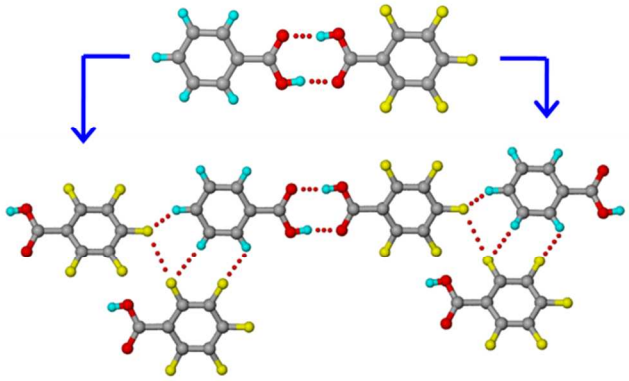


Benzoic acid–4-fluorobenzoic acid 0.268:0.732 solid solution

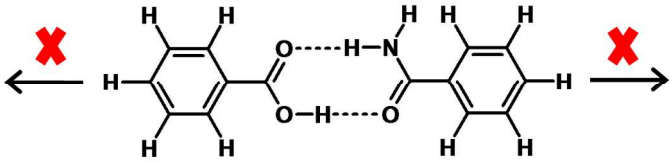


Benzoic acid–4-fluorobenzoic acid 0.557:0.443 solid solution

(a)



(b)




(c)

**Figure 3** (a) Benzoic acid–4-fluorobenzoic acid solid solutions (CSD Refcodes: SATHOK & SATJAY) retain the same zigzag tape motif of carboxylic acid dimer and C–H···O interactions, present in the parent benzoic acid structure (CSD Refcode: BENZAC12). (b) Growth of the benzoic acid–pentafluorobenzoic acid dimer in the cocrystal structure (CSD Refcode: UKOKIO01) is sustained by C–H···F and F···F interactions. (c) The absence of such auxiliary interactions in benzoic acid−benzamide system means that instead of a cocrystal the product is a eutectic. The powder X-ray diffraction patterns of the compounds are shown in Figures S1-S3, Supplementary Information.

In the second illustration, curcumin combines with isomeric dihydroxybenzenes to give different products. It forms a cocrystal with resorcinol[37] (1,3-dihydroxybenzene) but a eutectic with hydroquinone[11] (1,4-isomer) (Figure 4). In the crystal structure of curcumin (1,3-diferuloylmethane),[38] linear tapes of O−H···O bonded molecules are connected through C–H···O interactions involving the carbonyl groups (Figure 4). When



Chemical Communications Accepted Manuscript

curcumin is combined with resorcinol, the strong O–$H_{resor}$···O=$C_{cur}$ adhesive interactions replace the C–H···O=$C_{cur}$ and O–H···O–$H_{resor}$ cohesive bonds, consistent with the oft-quoted Etter's rule of the best donor−best acceptor pairing of hydrogen bonds.[39] The strong heteromolecular interactions together with conformation change of resorcinol OH groups give good molecular packing in the cocrystal structure. However, the higher symmetry of p-substituted hydroquinone together with lower symmetry of the β-keto-enol structure in curcumin gives shape mismatch for efficient packing as compared to resorcinol (Figure 4), and therefore the product is a eutectic. The PXRD plots and DSC thermograms of compounds are shown in Figures S4-S7, Supplementary Information.

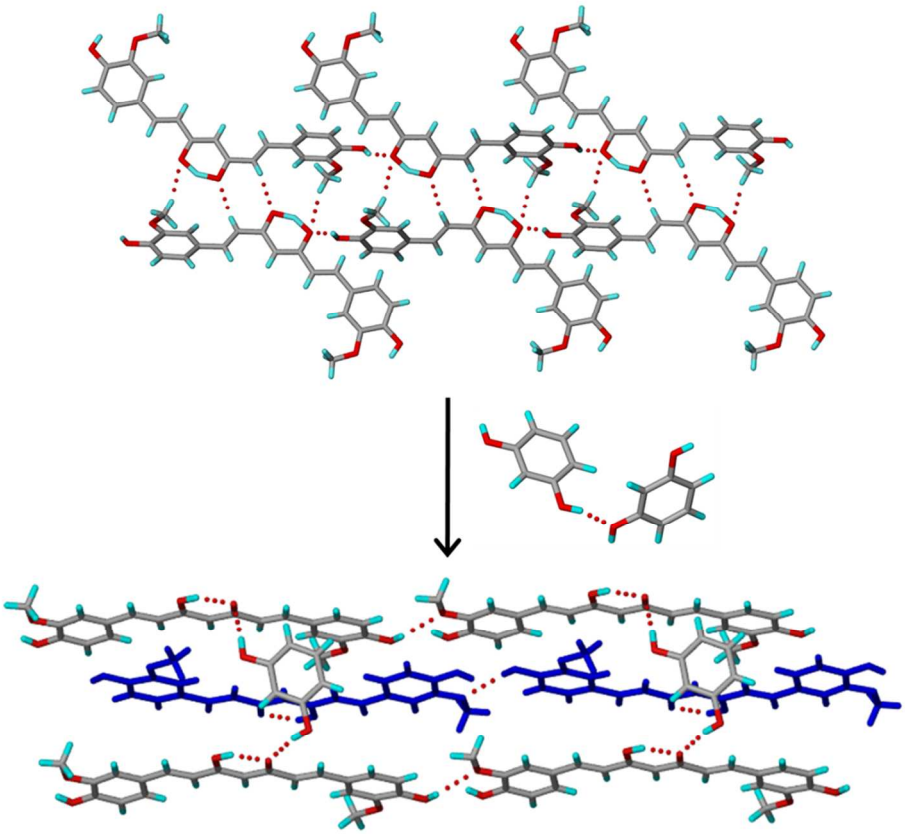


**Figure 4** Curcumin–Resorcinol cocrystal structure (CSD Refcode: AXOGIE) is sustained by the dominance of strong O–$H_{resor}$···O=$C_{cur}$ adhesive interactions over the cohesive C–H···O=C and O–H···O–H bonds in Curcumin (CSD Refcode: BINMEQ02) and Resorcinol (CSD Refcode: RESORA03) respectively. In the cocrystal, anti-parallel tapes of curcumin (shown in CPK and blue colors) lie at a distance of 3.44 Å and resorcinol molecules connect alternate curcumin tapes.

These examples suggest that the formation of cocrystal or eutectic is difficult to anticipate from knowledge of the molecular components. Eutectics tend to form when the simplistic functional group complementarity recognition model fails to give cocrystals



Chemical Communications Accepted Manuscript

due to subtle structural factors, which became apparent only post facto in the curcumin study. To our understanding there are no ground rules or structural guides as to the point at which the cohesive interactions dominate over the adhesive ones (to give a eutectic) and vice-versa (to give a cocrystal). The lack of detailed structural information on the micro/nano-structure of eutectics (single crystal X-ray structure is not possible because they are phase separated solids) is the single-most factor that makes analysis of eutectics circumstantial in the absence of molecular packing details. The take home lesson from our preliminary analysis is that cocrystal and eutectic products result from a fine balance between interactions (adhesive or cohesive) and size/ shape (geometric fit) of the molecular components. Very strong adhesive interactions give a cocrystal product irrespective of size/shape/symmetry factors. When the cohesive interactions are strong but auxiliary interactions are weak to nil, then the result is a solid solution (shape similarity) or a eutectic (mismatched shape). To cite an example, sulfamethazine (4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide) and sulfamerazine (4-amino-*N*-(4-methylpyrimidin-2-yl)benzenesulfonamide) have the same hydrogen bonding groups but sulfamethazine is more symmetric (with two meta-dimethyl groups) whereas sulfamerazine has a slightly awkward shape (with a single meta-methyl group). This slight difference is sufficient to result in the formation of a cocrystal between sulfamethazine and 4-aminobenzoic acid whereas sulfamerazine with the same coformer gave a eutectic.[12b] The above trends are summarized in Table 2.

**Table 2** Comparison of cocrystals, solid solutions and eutectics.

| Solid | Nature of Components | Nature of Interactions | Lattice Structure | Examples |
|---|---|---|---|---|
| Cocrystal | Can be similar or dissimilar | Predominantly adhesive | Different from components | Benzoic acid–Pentafluorobenzoic acid[35] Curcumin–Resorcinol[37] |
| Solid solution | Isomorphous | Cohesive | Similar to components | Benzoic acid–4-Fluorobenzoic acid[34] sym-Triiodophenol–Triiodoresorcinol[33c] |
| Eutectic | Can be similar or dissimilar | Predominantly cohesive | Similar to components (ensemble of solid solutions) | Benzoic acid–Benzamide[6b,36b] Curcumin–Hydroquinone[11] |

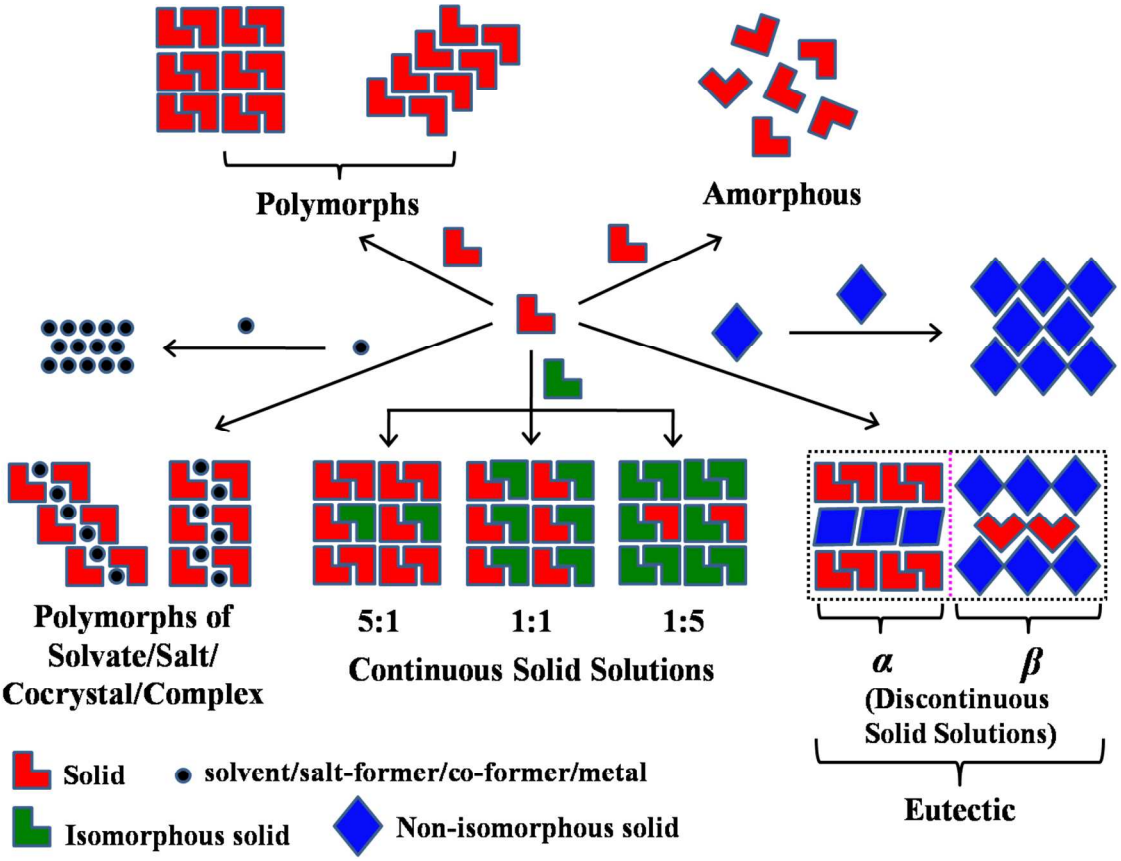
**Classification of Solid Materials**

Our present understanding of various solid-state materials is depicted in Scheme 2. A solid is categorized as a single- component or a multi-component system. Elemental and molecular solids are single-component entities (e.g. metals, benzoic acid, benzamide,



Chemical Communications Accepted Manuscript

etc.). Multi-component solids contain two different chemical species, e.g. different metal atoms as in alloys and intermetallic compounds, ions or molecules of different compositions as in coordination compounds, salts, cocrystals, etc. Both elemental and compound solids can exist in crystalline and/or amorphous states (e.g. carbon[40] and steel[41]). Again solids of the same chemical composition can exhibit different structures in the crystalline state, referred to as allotropism and polymorphism for elemental and molecular species, respectively.[42] For example, carbon exists in three categories of allotropic forms, diamond, graphite, and fullerene.[42a] Glycine,[43] a biomolecule, and calcium carbonate,[44] a biomineral, exist in polymorphic forms. The discussion and examples of different solid-state forms are only illustrative of the diversity and by no means exhaustive. For the sake of brevity, we limit the subsequent discussions to the crystalline states of alloys, ionic and molecular solids.




**Scheme 2** Schematic representation of different solid-state forms. Salts and cocrystals have distinct crystal structures and can be polymorphic. Solid solutions and eutectics adopt the crystal structures of their parent components but the former are homogeneous throughout the crystal lattice whereas the latter are heterogeneous with incoherent interactions (dotted magenta line).

Chemical Communications Accepted Manuscript

An alloy is a multi-component crystalline solid made up of different atoms of which at least one is a metal atom, e.g. steel. A multi-component crystalline solid formed by oppositely charged ions/molecular ions is a salt; sodium chloride (common salt) is different from cytosinium 4-aminosalicylate[45a] (a molecular salt).[45] A coordination complex is one formed by coordination bonding between a metal center and an anion or a molecule. A stoichiometric multi-component molecular crystal wherein different components are assembled by adhesive interactions is a cocrystal, e.g. carbamazepine–saccharin,[46] a hydrate/solvate when one of the components is water or a solvent, e.g. carbamazepine dihydrate and carbamazepine–acetone solvate.[47] A solid solution is a variable stoichiometry multi-component crystalline solid formed by substitutional incorporation of a component, element or compound, in the lattice of another component and sustained by cohesive interactions, e.g. as in copper–nickel[1] and sym-triiodophenol–triiodoresorcinol[33c] solid solutions. A eutectic is a conglomerate of solid solutions or a conglomerate of lattice structures of different materials, elements or compounds, e.g. lead–tin,[1] and $KNO_3$–$NaNO_2$–$NaNO_3$ salt bath.[48] Thus, solid solutions and/or eutectics possessing strong cohesive interactions and weak adhesive interactions retain their parent lattice structures (Scheme 2). The other multi-component crystalline solids, e.g. salts, cocrystals etc. have unique crystal structures as they are sustained by stronger adhesive interactions which direct their unique crystal structures.

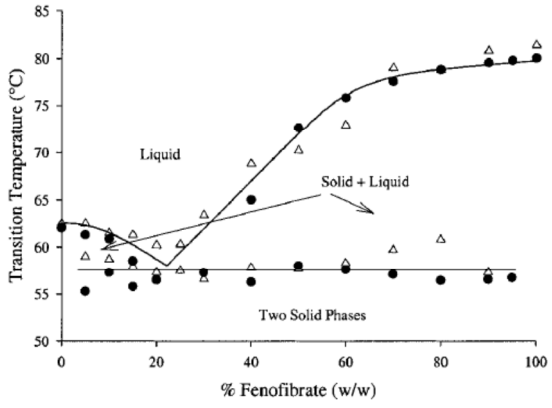
**Eutectics in the Pharmaceutical Literature**

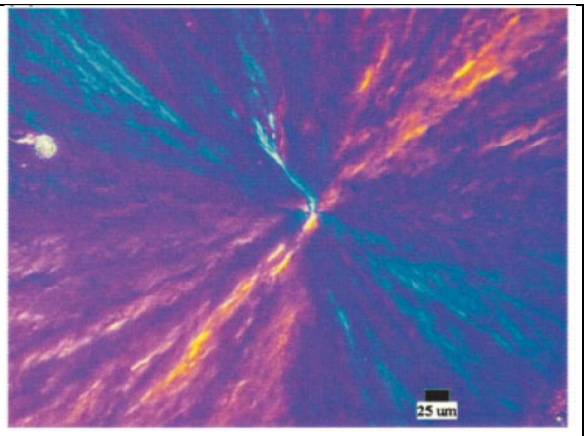
Historically, eutectics were studied and classified as solid dispersions and even related to solid solutions in the pharmaceutical literature.[4a,b,c,7] A solid dispersion is a dispersion of one or more components in a carrier or solid matrix and is prepared by the same co-melting and solvent-mediated co-precipitation methods employed for preparing eutectics.[4a] Furthermore, a eutectic and a solid dispersion share the common feature of heterogeneous structural organization (phase separation) in the crystal lattice. Solid dispersions have more structural aperiodicity and higher thermodynamic functions and hence exhibit faster dissolution rates, a property utilized for poorly soluble drugs.[4a] These common features meant that eutectics and solid dispersions were often studied together and the terms were synonymously used.[4a,b,c,7] For example, fenofibrate–polyethylene glycol, marketed under the brand name Fenoglide,[49] is a eutectic solid dispersion of the drug and a polymer.[7e] It is the dispersion of fenofibrate (drug) in polyethylene glycol (carrier polymer) matrix which exhibits the attributes of crystallinity and low melting, characteristic of a eutectic. Its eutectic microstructure is lamellar (Figure 5).[7e] In the past, eutectics and solid dispersions were explored as alternatives to the less stable amorphous drug formulations.[7a] The first generation pharmaceutical solid dispersions (1960s),[7a,b]



Chemical Communications Accepted Manuscript

which contained both the drug and the carrier in a crystalline state, were prepared with the idea to improve drug bioavailability by exploiting the higher water-solubilizing effect of the carrier. However, the stability conferred by the crystallinity of the solid dispersion became its solubility limiting factor, with the result that drug release was slow compared to amorphous formulations. Thus, the latter generation solid dispersions (1970s-present)[7a,b] were developed as amorphous solid dispersions by using amorphous polymers as carriers. A sufficiently high $T_g$ (glass transition temperature) of 75 °C or higher of the amorphous polymer (e.g. Polyvinylpyrrolidone (PVP)[50] or Hypromellose (HPMC)[51]) stabilize the highly soluble drug formulation.[50,51] Today, amorphous solid dispersions have become a popular platform to overcome poor drug solubility and bioavailability in the pharmaceutical industry with several marketed drug formulations.[49a,52] We emphasize that an authentic eutectic is different from a solid dispersion in terms of structural organization, molecular arrangement, and local ordering. A solid dispersion can be amorphous or crystalline with a higher degree of aperiodicity,[4a] but a eutectic is necessarily crystalline and composed of solid solutions. Therefore, eutectics will, in general, have higher stability functions than solid dispersions.




(a) (b)

**Figure 5** (a) Phase diagram of Fenofibrate–Polyethylene glycol solid dispersion. (b) Eutectic of 15% w/w composition at 57 °C shows a lamellar microstructure. Extracted from Ref. 7e.

The literature on drug eutectics dates back to the early 1960s starting with publications from Sekiguchi[4b] and Goldberg[4c] who prepared sulfathiazole–urea and chloramphenicol–urea, respectively, by the fusion method for dissolution and bioavailability improvement. The phase diagram of sulfathiazole–urea system[4b,c] (Figure 6) shows that the eutectic has a solid-solid solubility region. The maximum solubility of urea in sulfathiazole is 8% w/w ($\alpha$ solid solution with 92% sulfathiazole, point A of



Chemical Communications Accepted Manuscript

Figure 6), whereas for sulfathiazole in urea is 10% w/w ($\beta$ solid solution with 90% urea, point B of Figure 6). The eutectic composition consists of about 51 parts saturated $\alpha$ SS and 49 parts $\beta$ SS. When this eutectic composition is placed in water, the highly soluble urea from the $\beta$ SS phase dissolves quickly leaving about 10% sulfathiazole in a state of molecular sub-division which dissolves immediately. The presence of 10% urea in the $\alpha$ SS of 90% sulfathiazole weakens the crystal lattice and facilitates faster dissolution of sulfathiazole compared to the pure drug (but slower than the $\beta$ phase). Thus the combination of solid solutions at the eutectic composition cause a substantial increase in the rate of gastrointestinal absorption of sulfathiazole.[4b] Administration of sulfathiazole−urea eutectic to human subjects exhibited higher amounts of drug absorption (in the blood) and excretion (from the urine) of the eutectic in the first 4-5 h of administration but after that time the results were comparable to the pure drug.[4b] In case of chloramphenicol–urea eutectic composition,[4c] the lower experimental solubility than the calculated values was attributed to stronger chloramphenicol···urea interactions in the $\beta$ SS of the eutectic. A liquefied form (eutectic) of the well known analgesic Aspirin (acetylsalicylic acid) prepared by gentle mechanical mixing of 1 part aspirin with 2-3 parts glycerin or propylene glycol (w/v) is useful as an ointment for topical applications and also to increase the shelf-life of aspirin by controlling its hydrolysis.[53] The anti-inflammatory drug Ibuprofen, which showed instability due to melting point depression caused by eutectic formation in the drug formulation,[8d] exhibited faster transdermal penetration as a eutectic with several terpenes.[54] Fast forward to the current decade, drug-drug eutectics[5,8a,10] have gained importance in the context of multi-drug therapy, with focus on local anesthetic drugs for enhanced anesthetic and analgesic applications (e.g. Lidocaine–Prilocaine, and their combinations with Tetracaine, Bipuvacaine, etc.).[5,55] Anti-tuberculosis combination drugs are found to form eutectics upon thermal treatment (Pyrazinamide–Isoniazid[10] and Rifampicin–Isoniazid[56]). Apart from the fusion- and solvent-based methods, eutectics can also be prepared by compaction (acetaminophen–propylphenazone)[8a] and grinding (curcumin–hydroquinone).[11] Aspirin eutectics are reported by melting[53] and grinding[57] techniques.

Whereas the abovementioned drug eutectics fulfill the desired goal of enhanced physico-chemical properties, the design element was more semi-empirical and trial-and-error rather than chemical and deliberate. Eutectics are not so popular as solid dispersions and the more recent cocrystals, even though they appear to have the potential of imparting solubility and stability advantage to drugs. There will be always a few down-side issues with any technology, and eutectics are no exception. The slight aversion to eutectics in the pharmaceutical industry could possibly be due to the lack of a proper understanding of their microstructures and difficulties in their complete characterization.



Chemical Communications Accepted Manuscript

We attempt to improve the current understanding of eutectics in terms of structural design and function, with the intent to pave the way for a proper appreciation of eutectics in the pharmaceutical and materials field.

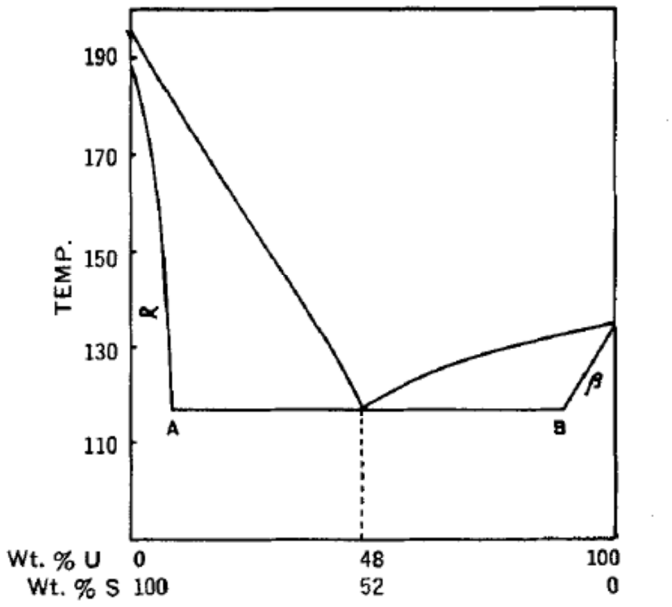



Fig. 3.—Phase diagram for mixtures of sulfathiazole (S) and urea (U). (From *Reference 7.*)

**Figure 6** Phase diagram of Sulfathiazole–Urea system. Extracted from Ref. 4c.

**Design and Characterization of Eutectics**

The benzoic acid–benzamide eutectic[6b,36] discussed earlier elucidates two important points: (1) selection of the partner molecules by design, and (2) characterization of the microstructure. In the absence of strong adhesive interactions to give a cocrystal, the system organizes the components in phase separated domains to give a eutectic. In the latter case, the lack of quantitative analytical techniques for characterization, apart from simple melting point depression, need to be addressed with current day technologies.

Eutectics and solid solutions can be formed by unary (atom or molecule) as well as multinary (salt or cocrystal) species (Table 3). The deliberate design of eutectics is more subtle and challenging because one has to identify molecules with mismatched geometry and avoid strong heteromolecular synthons in the combination, in effect an anti-crystal engineering approach.[58] Such strategies are not new but less studied, e.g. in ionic liquids (ILs) and deep eutectic solvents (DESs),[58] amorphous materials[59] and supramolecular gels.[60] We successfully exploited the propensity for cohesive interactions in competition with weak adhesive interactions to give eutectics of the anti-tuberculosis drug ethambutol dihydrochloride (discussed later).



Chemical Communications Accepted Manuscript

**Table 3** Examples of Solid solutions and Eutectics.

| Solid | Unary | | Multinary | |
|---|---|---|---|---|
| | **Atom** | **Molecule** | **Salt** | **Cocrystal** |
| Solid solution | Copper–Nickel[1] | Benzoic acid–4-fluorobenzoic acid[34] | NaCl–NaBr[13] | (Isonicotinamide–Succinic acid)–(Isonicotinamide–Fumaric acid)[17a] |
| Eutectic | Lead–Tin[1] | Benzoic acid–Benzamide[6b,36b] | ($KNO_3$)–($NaNO_2$–$NaNO_3$)[48] | (Pyrazinamide–Succinic acid)–(Isoniazid–Succinic acid)[10] |

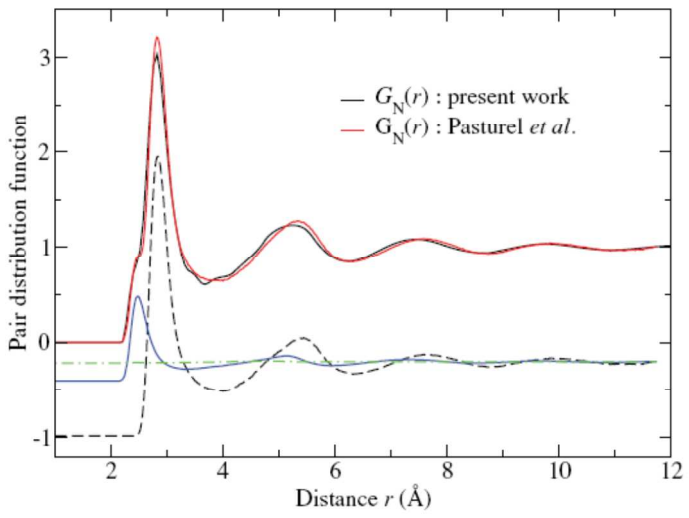
The characterization of eutectics is a real challenge because depression in melting point by thermal methods (DSC, Kofler's hot stage microscope, heat-cool-reheat) is the only indicator of eutectic formation. At next level, the phase diagram will show the extent of solid-solid solubility and the eutectic composition.[1,4a,13,14] However, phase diagram plots are a full scale study on the composition of matter requiring significant amounts of samples and time, instead of a rapid analytical measurement. Powder X-ray diffraction and spectroscopy techniques, routinely used for the characterization of other multi-component solids such as salts and cocrystals,[61] are not sensitive enough to diagnose solid solution/eutectic formation. This is because the inclusion of a second (minor) component happens substitutionally or interstitially in the first (major) component, and so the molecular arrangement in the crystal lattice (domain structure) is largely unaltered compared to the individual components (Scheme 2). Consequently there is little change in the X-ray diffraction lines or spectral peaks for solid solutions/eutectics compared to the individual components. We feel that eutectics are formed more often than believed and perhaps overlooked as unintended products of cocrystallization because there is no simple and quick signature technique (other than thermal methods) to distinguish a eutectic from a physical mixture. The result is often erroneously interpreted as no cocrystal formation without making a serious effort to characterize the eutectic phase. An unfortunate casualty is that an excellent opportunity to prepare novel solid forms of improved physico-chemical advantage is lost.

In reality, apart from a few inorganic systems,[1,14] eutectic microstructures are generally poorly understood. X-ray crystal structure determination elucidates the identity and bonding interactions and structural organization of materials in the crystal lattice. The crystal structure of even a single eutectic is not known, despite their long history. Solid solutions are possible to characterize by single crystal X-ray diffraction as the site

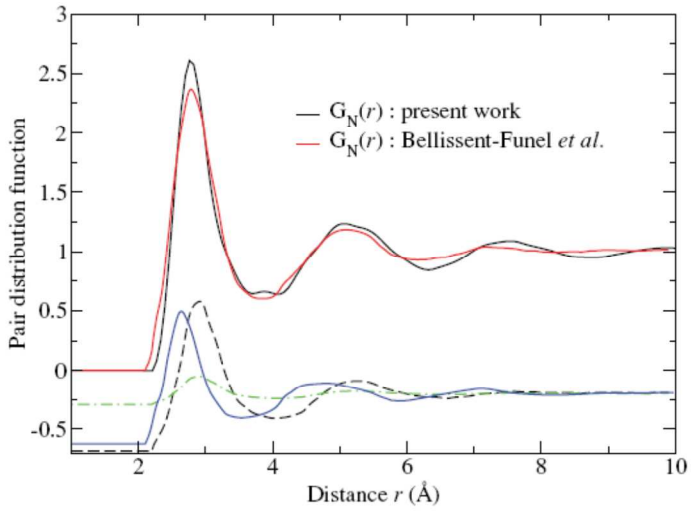
Chemical Communications Accepted Manuscript

occupancy factor (s.o.f.) of atoms can be used to determine the integrity and stoichiometry of the components.[13,15] The absence of crystal structure data for eutectics arises from the inherent heterogeneity (different crystal structures) of its component solid solutions in the crystal lattice, which makes it a formidable challenge to assign the relative occupancies of the component solid solutions and to ascertain their domain organization. At the molecular level, the lattice positions of neighboring molecules, which are symmetry dependent within a solid solution domain, become symmetry independent with respect to the different solid solution domains. The current structure solution methods, which operate with single space group models,[62] are therefore inadequate to solve the crystal structures of eutectic solids. Atomic pair distribution function (PDF) analysis,[63] which is based on real space fitting for a pair of atoms separated by a distance '*r*', is useful to probe the local structure (short range) of amorphous and crystalline (also nanocrystalline) solids.[64] It is a method of significant potential to study the eutectic microstructure.[4a,65] The PDF method is sensitive to local structure ordering, because its Fourier Transform includes the diffuse scattering intensity, in addition to the conventional Bragg reflections.[63] PDF estimates the instantaneous atomic arrangements and reveals the local structure (low *r* region) from the average crystallographic structure (high *r* region). Frequent atom contacts register as distinct peaks to give the PDF, *G(r)*, vs. the atomic radial distance (*r*) plot.[63] The PDF method revealed the local structure of inorganic eutectics, such as gold–silicon and silver–germanium (Figure 7),[65] but this method has so far not been routinely applied to organic counterparts. The utility of PDF in the characterization of Felodipine–Eudragit E solid dispersion is an early pharmaceutical example,[66] wherein conventional PXRD was inconclusive (Figure 8). However, the PDF approach has the intrinsic limitation of low intensity from a laboratory diffractometer, a feature which further attenuates the intensity of low symmetry organic materials which have many diffraction lines. Hence high energy flux and synthrotron sources are necessary for PDF quality data analysis.[63,67] The related method of structure determination from powder diffraction (SDPD)[68] is another technique that can shed light on the eutectic microstructure depending on the solid−solid solubility limits. Whereas homogeneity will be lost beyond a weak solid solution, say 10%, for a combination from either side of the phase diagram, the break point will give some information about the transformation of solid solution to heterogeneous eutectic solid solutions at the micro level. These methods can also unravel the less understood incoherent interactions[25] that bind the solid solution domains of a eutectic. The challenge therefore is to dissect the eutectic material into solid solutions and understand their domain organization at a greater resolution and microscopic detail.

Chemical Communications Accepted Manuscript

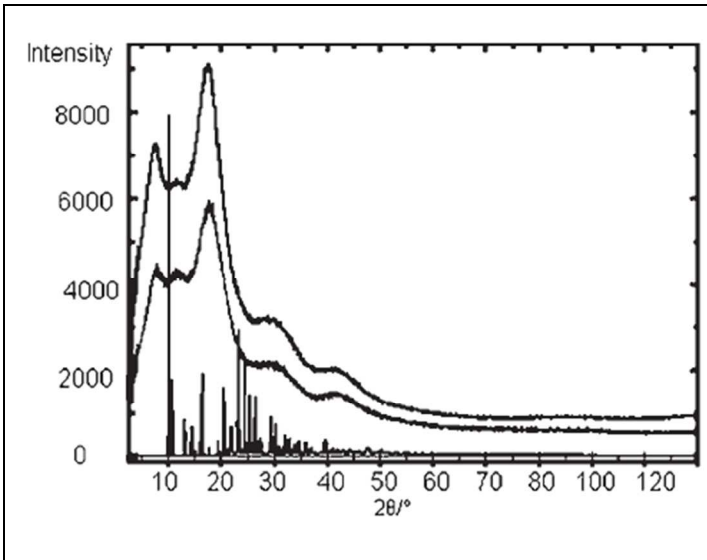



(a) Gold (dotted black); $Gold_{0.81}$–$Silicon_{0.19}$ eutectic (solid blue); Silicon (dotted green); solid red and black curves are of liquid eutectic.

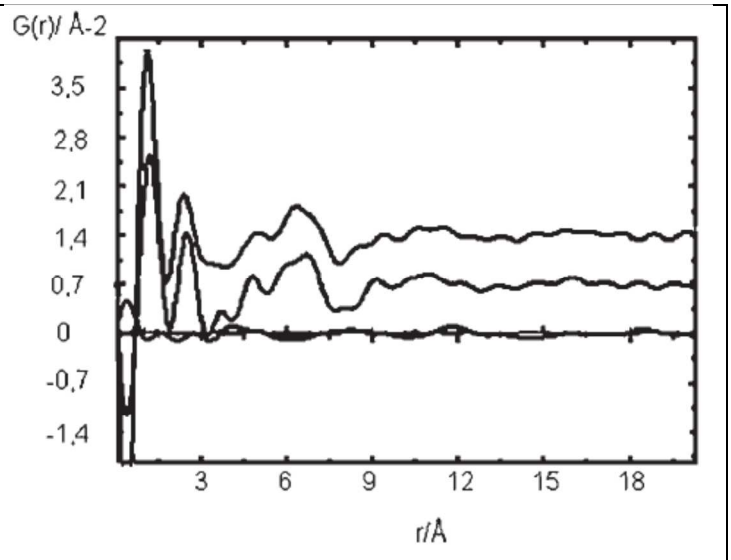



(b) Silver (dotted black); $Silver_{0.76}$–$Germanium_{0.24}$ eutectic (solid blue); Germanium (dotted green); solid red and black curves are of liquid eutectic.

**Figure 7** Comparison of PDFs of eutectics with those of their parent components shows clear-cut differences in their local structure. Extracted from Ref. 65.




(a)

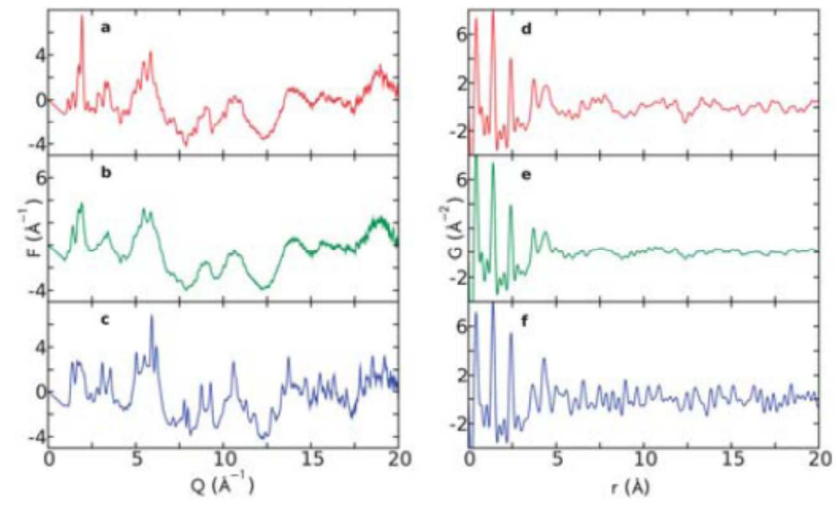



(b)

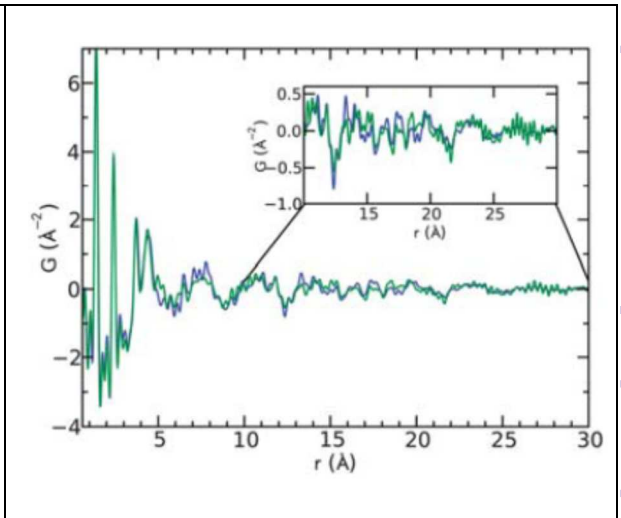
**Figure 8** (a) PXRD and (b) PDF of Eudragit E (top), Felodipine (lower) and 10% Felodipine–Eudragit E solid dispersion (middle). The former technique is insensitive while the latter plot is more diagnostic for solid dispersion. Extracted from Ref. 66.

Chemical Communications Accepted Manuscript

Towards this last objective, which we project will be a significant advance in eutectics research using the new PDF technology compared to what is prior art,[63a,64a-d] a recent paper[67] provides the resolution limits at which microstructures can now be analyzed. Billing et al.[67] characterized melt-quenched carbamazepine (CBZ) as a nanocrystalline form of CBZ polymorph III (at 4.5 nm resolution) by collecting X-ray data on a synchrotron beamline with high scattering magnitude. To differentiate the PDF obtained on a conventional laboratory diffractometer, they refer to this approach as TSPDF (total scattering PDF).[67] In this method, the scattering vector ($Q_{max}$) was achieved in the order of 20 Å to deduce both the structure function, $F(Q)$, and TSPDF, $G(r)$, each of which convincingly showed that the melt-quenched material has closer resemblance to CBZ III than that to polymorph I (Figure 9a). Furthermore, the TSPDF allowed a clear correlation between the melt-quenched material and CBZ III, and characterized it as nanocrystalline CBZ III with an average particle size of 4.5 nm (Figure 9b). Transforming $F(Q)$ to $G(r)$ allows comparison and interpretation in real space. The key to high quality TSPDF is not just synchrotron radiation but it is equally important to collect reflections to high $Q$ with good statistics. This pioneering experiment[67] highlights the significance of TSPDF to understand and differentiate the internal structure of nanocrystalline/ semi-crystalline materials and could provide a new direction to applying the same technique for the characterization of eutectics at a nano level, akin to the popular powder XRD for polycrystalline materials.




(a)




(b)

**Figure 9** (a) Total scattering diffraction $F(Q)$ patterns and TSPDFs $G(r)$ of CBZ samples. Panels (a) and (d) correspond to CBZ III, (b) and (e) to the melt-quenched sample and (c) and (f) to CBZ I; (a), (b), (c) show the $F(Q)$ whilst (d), (e), (f) show $G(r)$. (b) Comparison of $G(r)$ of the melt-quenched sample (green) with CBZ III (blue) shows excellent



Chemical Communications Accepted Manuscript

correlation (PolySNAP correlation coefficient is 0.8601) and match of the nanocrystallite material with CBZ III. Extracted from Ref. 67.

**Hygroscopic Stable Ethambutol Dihydrochloride Eutectics**

Ethambutol (abbreviated as EMB) is a frontline anti-tuberculosis drug administered with Rifampicin, Isoniazid and Pyrazinamide in Fixed Dose Combination (FDC) formulations.[69] It is a chiral basic drug formulated as its dihydrochloride salt (S,S-EDH, Figure 10), which is synonymously used to represent the drug.[69,70] Anti-TB FDC products are unstable due to drug-drug interactions between the component drugs.[71] The hygroscopicity of ethambutol dihydrochloride accelerates degradation of rifampicin and isoniazid in the FDC formulation, resulting in the instability and loss of potency of the FDC products upon storage.[69a,71] This problem is currently overcome by separately coating each drug with a polymer to minimize mutual interactions and water uptake by the FDC and then blended to make up the final product formulation.[72] In a salt screen of ethambutol base, with the intent of obtaining a less hygroscopic salt of EMB as an alternative to the existing hydrochloride salt, we obtained several hygroscopic salts and ionic liquids.[73] Related studies on EMB salts did not focus on their physico-chemical property improvement.[74] A SWOT analysis (strengths, weakness, opportunity, threats) of different solid-state forms (Table 4) suggested cocrystals and/or eutectics as promising leads. Solid dispersions, cyclodextrin inclusion complexes, nanoparticles, etc.[4a,7a,75] were excluded from the present study. Cocrystals and eutectics were shortlisted as the most suitable strategies to address the hygroscopicity problem of the marketed ethambutol dihydrochloride salt. Amorphous forms were downgraded because of stability concerns and gel-filled capsules due to degradation of TB-FDC drugs in a liquid-like formulation.

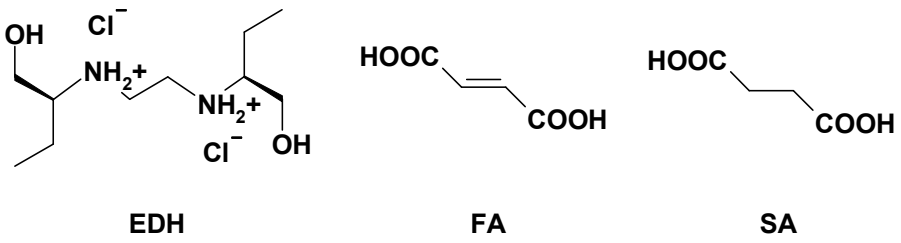



**Figure 10** Molecular structures of the compounds of this study.

**Table 4** Scheme of solid formulation options to tackle the hygroscopicity problem of Ethambutol dihydrochloride.

| API form | Ethambutol (base) | Ethambutol dihydrochloride (salt) |
|---|---|---|



Chemical Communications Accepted Manuscript

| | | |
|---|---|---|
| Amorphous | Possible option, but because of its high thermodynamic functions[76] the amorphous phase can transform or be hygroscopic. | Not considered for the same reasons as mentioned in the left panel. |
| Polymorph | Possible option.[a] | Already four polymorphs are reported.[77] |
| Salt | Salt screening resulted in hygroscopic salts and ionic liquids.[73] | --- |
| Cocrystal | Possible option. | Possible to make cocrystals of salt, e.g. as for Fluoxetine HCl.[78] |
| Solid solution | Possible option.[b] | Possible option.[b] |
| Eutectic | EMB is a low melting base (88 °C),[73a] and a eutectic will lower the m.p. further. Gel-filled capsule is an option, but not related to the present goal. | EDH has high m.p. (200 °C) and therefore its eutectics are possible option. The high thermodynamic functions[6] will be advantageous for solubility and dissolution. |

[a] Polymorph screening is an exhaustive project and stability of the new form can be an issue. Hence this approach was not pursued in the present strategy.
[b] Solid solution requires isomorphous solid partners[1,24,33] from the safe list of chemicals,[79] which can be non-trivial, and hence this approach was not pursued.

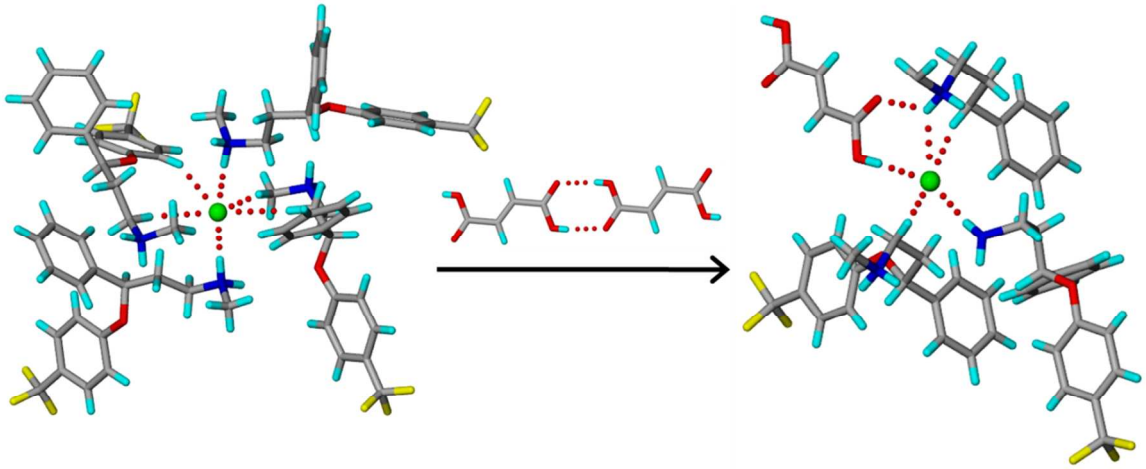
Cocrystallization of ethambutol base with several coformers such as urea, nicotinamide, glycine, cytosine, etc. did not give a new cocrystal. Given the low melting point of EMB, and the fact that a low melting eutectic will have stability issues,[80] the focus shifted to the HCl salt. Cocrystallization of ethambutol dihydrochloride (EDH) salt was then undertaken (Experimental details are given in the Supplementary Information). Dicarboxylic acid coformers fumaric acid (FA) and succinic acid (SA) (Figure 10), which are safe to use,[79] were selected based on their non-hygroscopic[81] and non-hydration nature.[15] The properties of partner molecules are known to modulate the behavior of cocrystals and eutectics,[10,11,19a,26a,b] e.g. the high soluble succinic acid and low soluble fumaric acid imparted their solubility property to the respective cocrystals and eutectics with pyrazinamide and isoniazid.[10] Solid state grinding[10,11,57,82] of EDH with FA/SA in 1:1 composition gave EDH–FA and EDH–SA within the eutectics phase space (see Figure S8 and S9 for DSC at three different drug : coformer compositions). Even though the exact eutectic composition was not determined by the phase diagram for the present



Chemical Communications Accepted Manuscript

discussion, the 1:1 stoichiometry adducts of EDH with FA and SA appear to offer promise as low hygroscopicity formulations of ethambutol dihydrochloride. The structural aspects of EDH eutectics are discussed first and their hygroscopic stability is demostrated next.

In terms of understanding the outcome of cocrystallization, the formation of EDH salt eutectics with FA and SA (in this study) may be contrasted with the salt-cocrystal adducts of Fluoxetine HCl with the same diacids.[78] A comparison of the crystal structures of Fluoxetine hydrochloride and Ethambutol hydrochloride explains the factors that govern these two distinct structural outcomes. In the crystal structure of fluoxetine hydrochloride,[83] each $Cl^-$ ion is bonded to one protonated secondary $NH_2^+$ group and four CHs while the other CHs make C–H···F interactions with the trifluoromethyl acceptor (Figure 11). The introduction of COOH group (of the coformer) means that strong OH donors can replace weak CHs bonded to $Cl^-$ ion of fluoxetine hydrochloride, and in effect provide the enthalpy gain (strong adhesive interactions) for cocrystal formation. The COOH homodimers ($O–H_{acid}\cdots O_{acid}$ bonds) of FA/SA are replaced by $O–H_{acid}\cdots Cl^-$ and $N^+–H\cdots O_{acid}$ ionic hydrogen bonds in fluoxetine hydrochloride–diacid salt-cocrystal (Figure 11). In the structure of EDH, each $Cl^-$ ion is bonded to alcoholic OH donor and a protonated secondary $NH_2^+$ group (Figure 12).[73a] In this situation, the COOH group of FA/SA will be replaced with the an almost equivalent $O–H_{acid}\cdots Cl^-$ hydrogen bond. At best, a few random interactions will provide the additional enthalpy to give a weak solid solution. Thus, the energy balance of H bonds and the overall size/ shape mismatch of EDH and diacid supermolecules for the combinations resulted in eutectic products due to the dominance of cohesive interactions (Figure 12). The analysis of fluoxetine HCl and EDH structures provides a rationalization for empirical design elements which lead to cocrystal or eutectic.



Chemical Communications Accepted Manuscript

**Figure 11** Fluoxetine hydrochloride−Fumaric acid salt-cocrystal (CSD Refcode: RAJFIS). The dominance of strong O–$H_{acid}$···$Cl^-$ and $N^+$–H···$O_{acid}$ adhesive interactions over the weaker cohesive C–H···$Cl^-$ bonds in Fluoxetine hydrochloride (CSD Refcode: FUDCOW) and the acid dimer of Fumaric acid (CSD Refcode: FUMAAC) explain the observed result. The succinic acid cocrystal structure is isomorphous and isostructural to that of fumaric acid.[78]

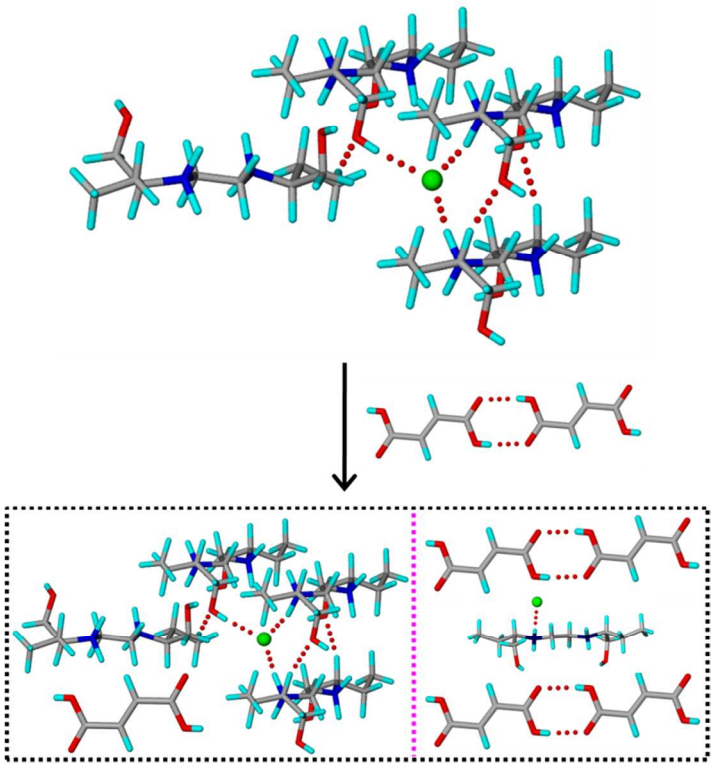


**Figure 12** A putative scheme to show the non-formation of a cocrystal between Ethambutol dihydrochloride (CCDC No. 929562, ref. 73a) and Fumaric acid (and also Succinic acid). The equivalent cohesive (O–$H_{alcohol}$···$Cl^-$) and adhesive (O–$H_{acid}$···$Cl^-$) interactions provide no significant enthalpic drive for new adhesive interactions. Thus, each component retains its strong cohesive interactions in the eutectic product with weak adhesive interactions between the two species (a phase separated product).

**Characterization and Hygroscopicity of EDH Eutectic Compositions**

The melting point of EDH eutectic-like compositions are lowered proportionally by the coformer (EDH 200 °C, FA 295 °C, SA 190 °C), with the fumaric acid adduct exhibiting a higher melting point than that of succinic acid (EDH–FA 174 °C, EDH–SA 141 °C; Figure 13). The PXRD patterns (Figure 14) and $^{13}C$ ss-NMR spectra (Figure 15) of the 1:1 compositions match closely with those of the components. All these plots suggest that



Chemical Communications Accepted Manuscript

there is no cocrystal formation, and that the product microstructure matches with the lattice structures of the components as phase separated (solid solution) domains based on PXRD lines and NMR peaks comparison (similar to those displayed in Scheme 2).

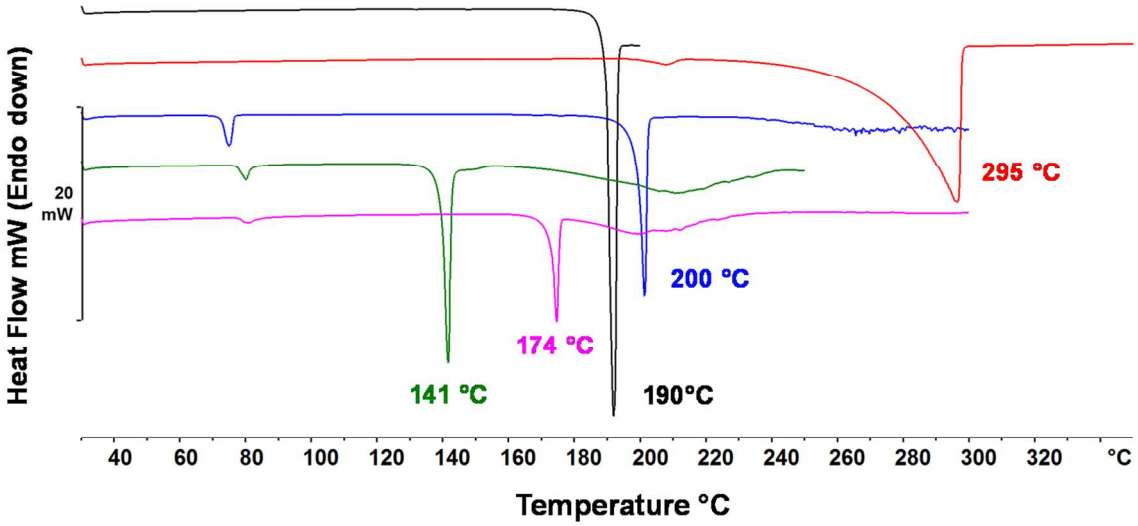
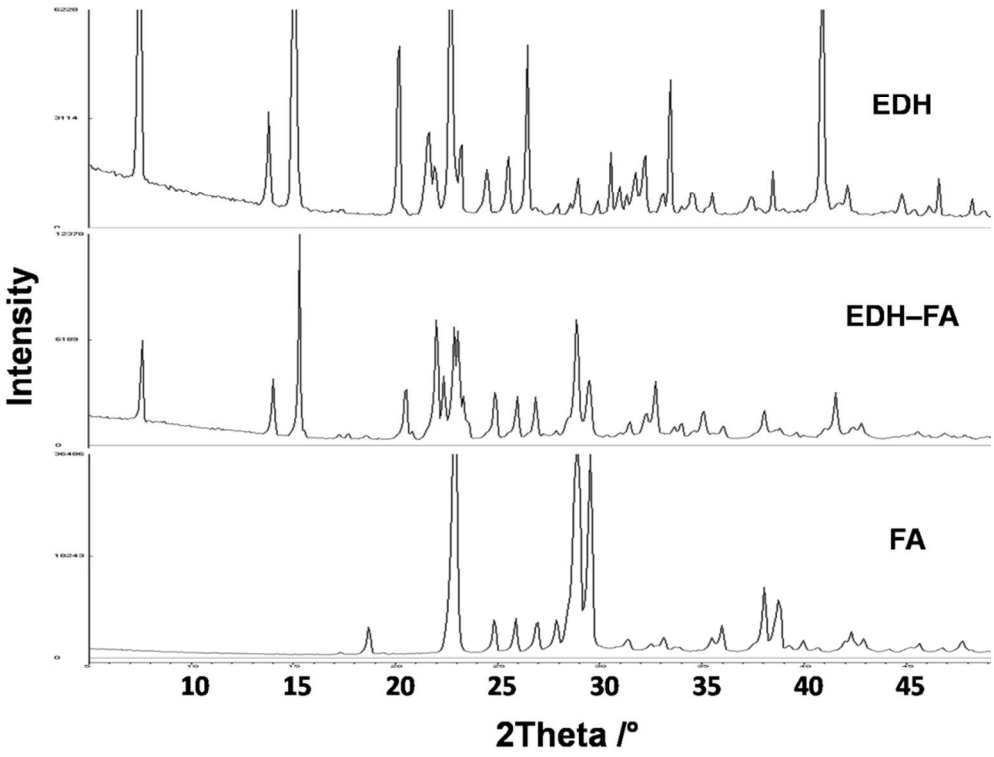


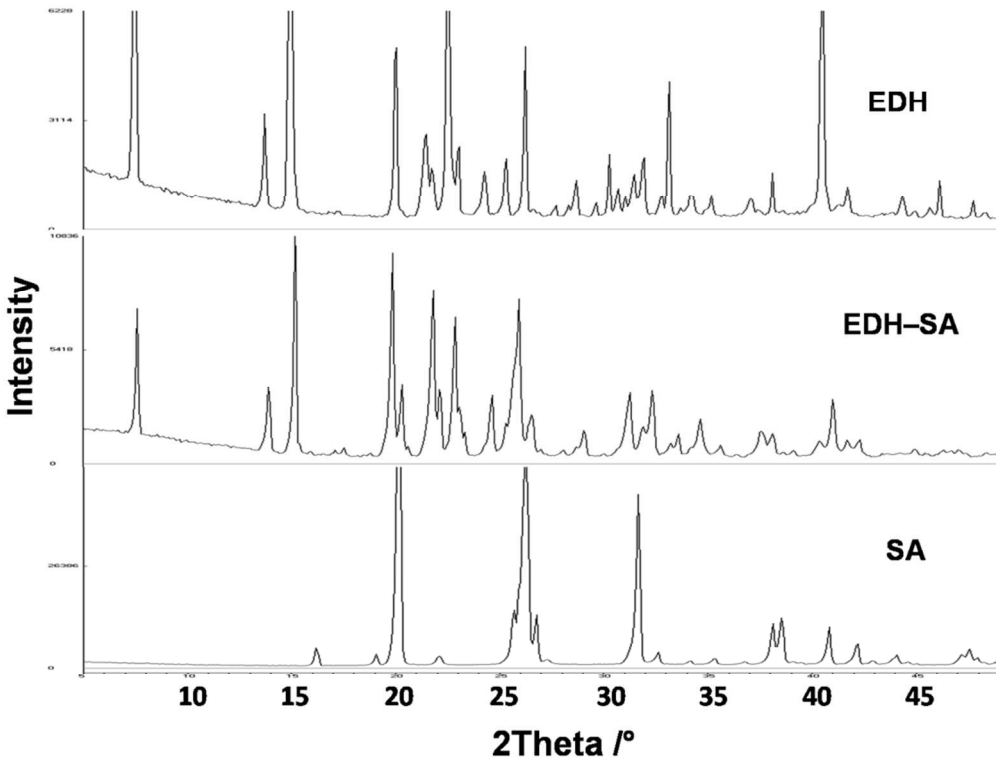

**Figure 13** DSC of EDH (blue), FA (red), SA (black), EDH–FA (magenta) and EDH–SA (green). The small endotherm at 75 °C is a polymorphic phase transition of EDH (form II → form I),[77] which is also observed in the eutectic compositions.




(a)

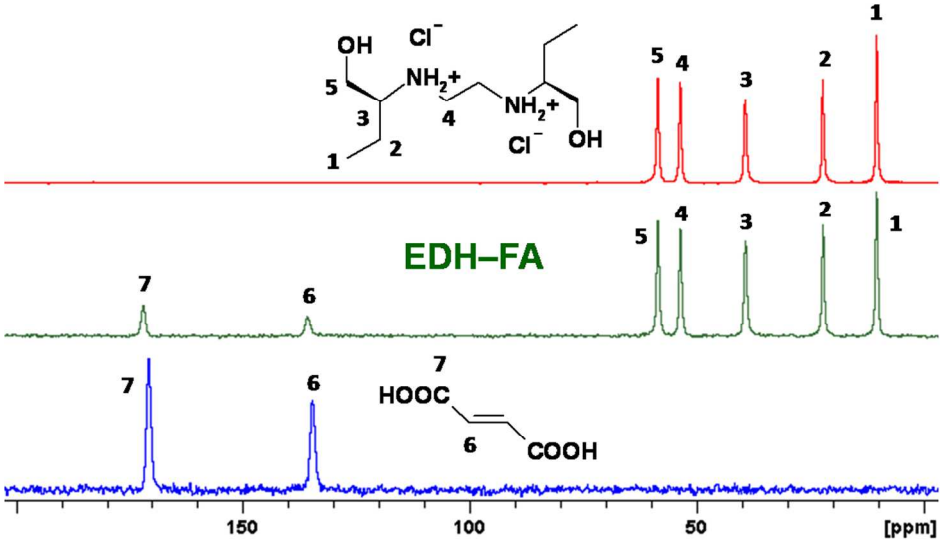


Chemical Communications Accepted Manuscript



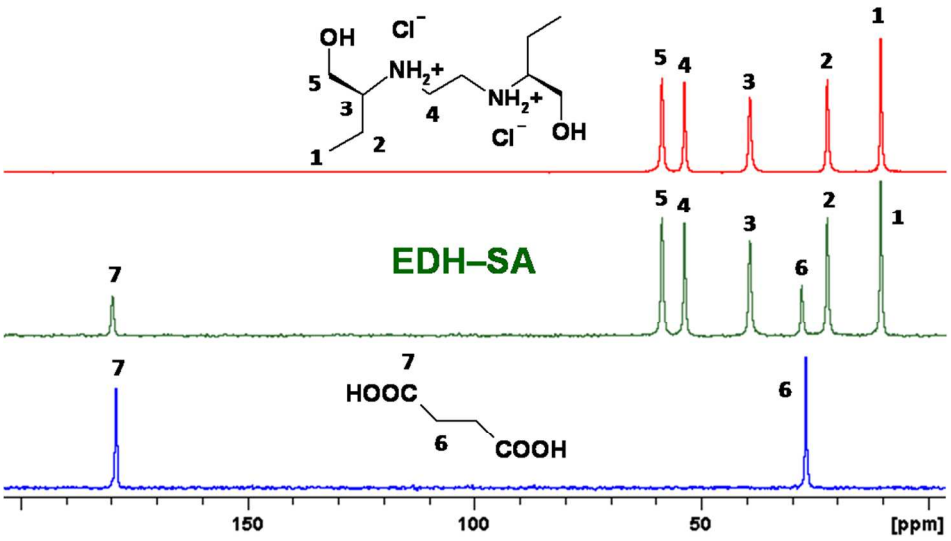

(b)

**Figure 14** PXRD pattern of (a) EDH–FA and (b) EDH–SA eutectics show good match of the diffraction peaks with those of the parent components.




(a)

Chemical Communications Accepted Manuscript




(b)

**Figure 15** $^{13}$C ss-NMR spectra of (a) EDH–FA and (b) EDH–SA eutectics show good match of chemical shifts with those of the individual components.

A study of EDH compositions of FA and SA (1:1 in each case) under accelerated stability conditions of 40 °C and 75% RH (WHO/ICH guidebook)[84] for two months (Experimental details are given in the Supplementary Information) confirmed the superiority of EDH eutectics. The chemical stability of the samples was confirmed by PXRD and NMR and their water uptake behavior (hygroscopicity) was monitored by KF titration and TGA (Table 5). EDH absorbed 5% water in the above conditions at 15 days and became semisolid after 30 days (20% water content) and finally turned liquid-like at 60 days (Figure 16). There is a qualitative trend between the melting point of the eutectic and its hygroscopic stability. The higher melting EDH–FA eutectic exhibited only 3% water uptake compared to 14% for the lower melting EDH–SA eutectic; the latter turned semisolid-like at 60 days (Figure 16, Table 5). Thus EDH–FA retained its solid-state integrity for 2 months in the stability chamber and is less hygroscopic compared to EDH–SA, while both the eutectic structures are superior to the EDH salt.

**Table 5** Hygroscopic behavior of EDH eutectics at 40 °C, 75% RH.

| Compound | % water uptake | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 day | | At 15 days | | At 30 days | | At 60 days | |
| | KF | TGA | KF | TGA | KF | TGA | KF | TGA |
| EDH | 0.3 | 0.2 | 5.4 | 5.2 | 19.3 | 20.2 | 45.8 | 45.6 |
| EDH–SA | 0.2 | 0.2 | 0.9 | 1.3 | 5.8 | 5.9 | 13.8 | 13.7 |
| EDH–FA | 0.2 | 0.2 | 0.2 | 0.2 | 0.4 | 0.5 | 3.0 | 2.9 |



Chemical Communications Accepted Manuscript

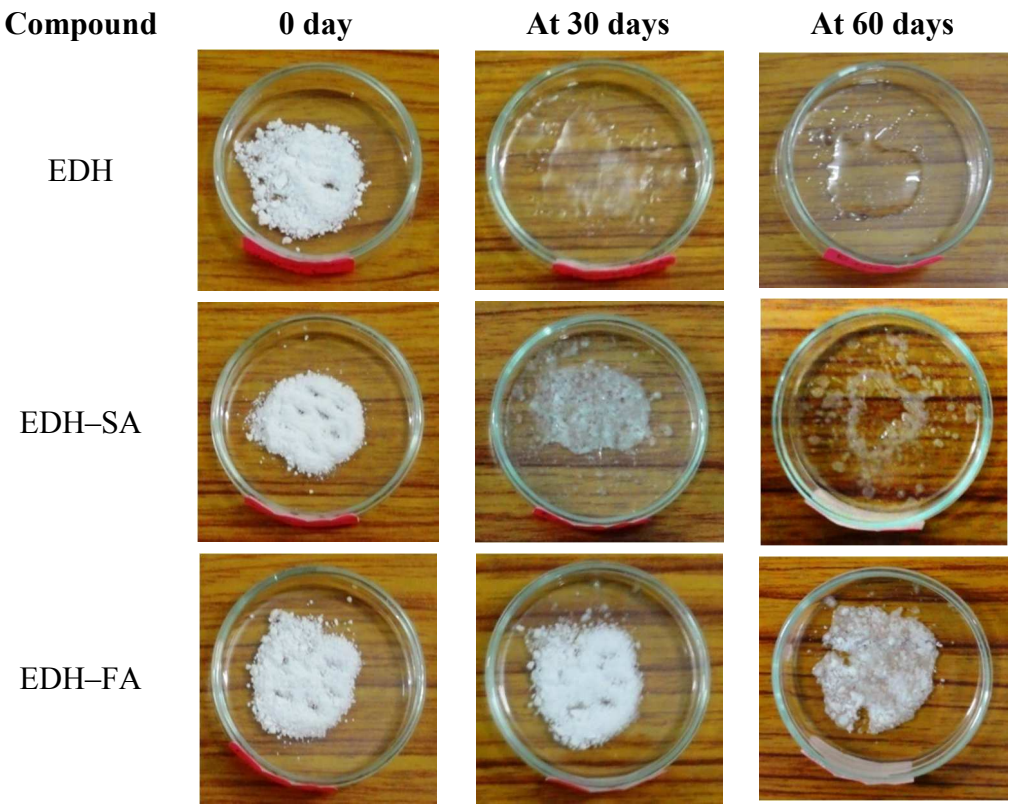



**Figure 16** The physical state of EDH compounds to show their hygroscopic behavior at 40 °C and 75% RH as a function of time. Both the eutectics exhibit greater hygroscopic stability than EDH.

## Conclusions and Future Directions

Eutectics are a long-known class of multi-component crystalline solids but a proper understanding of their lattice structure and molecular organization at the nanoscale is still rudimentary. We hope to expand the understanding of the structures and properties of these important solid-state materials. Based on a knowledge of the eutectic microstructure in inorganic solids, the structural similarities (and differences) of eutectics, solid solutions and cocrystals were related to organic systems. This led us to propose modified definitions for these materials and we classify a eutectic as 'a conglomerate of solid solutions'. It is well known for inorganic systems that atomic size and crystal structure match will lead to solid solution whereas the product is a eutectic when the structures are mismatched.[1,14] We highlighted examples of cocrystallization experiments which resulted in cocrystal or eutectic depending on the nature and strength of adhesive and cohesive interactions by analyzing the role of (i) geometry of functional groups, (ii) intermolecular interactions strengths, and (iii) molecular shape and overall packing.



Chemical Communications Accepted Manuscript

Eutectics are generally not considered to be a part of crystal engineering.[9] We now show that the design principles for cocrystals can be extended to eutectics in an empirical way. When the adhesive interactions dominate, the result is a cocrystal; when the adhesive and cohesive interactions are balanced and there is size/ shape match, the product is a solid solution; and when the cohesive interactions take over for size/shape mismatched components, the product is a eutectic. Secondly, eutectics will improve the success rate of cocrystal approach as alternate pharmaceutical materials. Moreover, eutectics strengthen the patentability criterion of non-obviousness for cocrystals.[9c] The last decade witnessed a major thrust on cocrystals, culminating with the recent US-FDA classification of pharmaceutical cocrystals as drug product intermediates.[85] We project that the current decade will be about pharmaceutical eutectics[86] on par with pharmaceutical cocrystals,[26,30,85] salts[87] and hydrates.[88] There is rarely a one-size-fits-all solution to the problems arising from solid form efficacy of drugs, and hence a deeper understanding of eutectics will create new supramolecular space for exploration. The fine balance between the often opposing factors of solubility and stability in drug formulation research and development[4a,26b,61b,89] may be optimizable for eutectics. The success with solubility/ dissolution enhancement of anti-TB drugs pyrazinamide and isoniazid through eutectics,[10] together with hygroscopicity control in ethambutol dihydrochloride eutectics (reported in this study) provide an example of affordable solutions in human health for the developing world.[90] To summarize, eutectics can confer the dual advantages of solubility (because of high thermodynamic functions) and stability (due to their crystalline nature) as bioavailable drug forms.

To exploit the full potential of eutectics as novel organic materials, advances in XRD techniques must dovetail into the preparatory and property studies on eutectics. The several reports of unsuccessful cocrystallization experiments[12c,36b,91] could actually be latent eutectics,[10,11] after a thorough analytical study. Synchrotron intensity data quality collected to high angle region (short intermolecular distances) followed by pair distribution function analysis (PDF/TSPDF)[63-67] and structure determination from powder diffraction (SDPD)[68] techniques will be able to provide detailed information about the eutectic microstructure at the nanoscale. A low cost alternative to PDF analysis of reasonably good quality and resolution is to collect XRD reflections using higher energy Mo-source instead of Cu anode.[92] We believe that assimilation of advances in cocrystals, solid solutions and eutectics and characterization by XRD-PDF technique will lead to a profitable resurrection in eutectics research.

Chemical Communications Accepted Manuscript

**Acknowledgments**

SC thanks the ICMR for fellowship. We thank the DST (JC Bose SR/S2/JCB-06/2009), CSIR (Pharmaceutical cocrystals 01(2410)/10/EMR-II), and SERB-DST (Novel APIs SR/S1/OC-37/2011) for research funding. DST (IRPHA) and UGC (PURSE grant) are thanked for providing instrumentation and infrastructure facilities. AN thanks UoH for one year sabbatical leave and Durham University for Senior Research Fellowship in May-June 2013 during which time reading and writing of major portions of this manuscript were completed.

**Electronic Supplementary Information†**

Experimental and spectral details of EDH eutectics, PXRD of benzoic acid and curcumin cocrystals/ eutectics, and DSC of EDH-SA/FA binary compositions.

**Notes and References**

1. D. R. Askeland and P. P. Fulay, *Essentials of Materials Science and Engineering*, 2nd Ed., Cengage Learning, 2009.
2. M. Prasad, *Refrigeration and Air Conditioning*, 2nd Ed., New Age International Publishers, 2006.
3. (a) A. Karaipekli and A. Sari, *J. Indus. Eng. Chem*., 2010, **16**, 767; (b) L. Shilei, Z. Neng and F. Guohui, *Ener. Build.*, 2006, **38**, 708.
4. (a) M. D. Moore and P. L. D. Wildfong, *J. Pharm. Innov.*, 2009, **4**, 36; (b) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull*., 1961, **9**, 866 & 1964, **12**, 134; (c) A. H. Goldberg, M. Gibaldi and J. L. Kanig, *J. Pharm. Sci*., 1965, **54**, 1145; (d) R. L. Hudson, V. P. Osburn and R. Brashear, *J. Chem. Educ*., 1990, **67**, 156; (e) N. Clavaguera, J. Saurina, J. Lheritier, J. Masse, A. Chauvet and M. T. Clavaguera-Mora, *Thermochim. Acta*, 1997, **290**, 173; (f) http://www.who.int/immunization_delivery/systems_policy/TLAC-Report_2009-09.pdf (accessed on 31 Oct. 2013).
5. B. F. J. Broberg and H. C. A. Evers, *US Pat*., 4529601, 1985.
6. (a) S. S. Das, N. P. Singh, T. Agrawal, P. Gupta, S. N. Tiwari and N. B. Singh, *Mol. Cryst. Liq. Cryst.*, 2009, **501**, 107; (b) N. B. Singh, S. S. Das, N. P. Singh and T. Agrawal, *J. Cryst. Growth*, 2008, **310**, 2878.
7. (a) T. Vasconcelos, B. Sarmento and P. Costa, *Drug Disc. Today*, 2007, **12**, 1068; (b) A. B. T. Serajuddin, *J. Pharm. Sci*., 1999, **88**, 1058; (c) W. L. Chiou and S. Riegelman, *J. Pharm. Sci*., 1971, **60**, 1281; (d) S. R. Vippagunta, Z. Wang, S. Hornung and S. L. Krill, *J. Pharm. Sci*., 2007, **96**, 294; (e) D. Law, W. Wang, E. A. Schmitt, Y. Qiu, S. L. Krill and J. J. Fort, *J. Pharm. Sci*., 2003, **92**, 505.



Chemical Communications Accepted Manuscript

8. Because of their low melting nature eutectics can be both advantageous (confer solubility/dissolution rate improvement) and disadvantageous (compromised stability) in pharmaceutical formulation. (a) M. Bi, S. -J. Hwang and K. R. Morris, *Ther. Acta*, 2003, **404**, 213; (b) Y. Sakata, E. Tanabe, T. Sumikawa, S. Shiraishi, Y. Tokudome and M. Otsuka, *Int. J. Pharm*., 2007, **335**, 12; (c) S. Žalak, M. Z. I. Khan, V. Gabelica, M. Tudja and E. Meštrović, *Chem. Pharm. Bull*., 1999, **47**, 302; (d) T. H. Weng and M. G. Williams, *US Pat*., 5512300, 1996.
9. (a) G. R. Desiraju, J. J. Vittal and A. Ramanan, *Crystal Engineering: A Textbook*, World Scientific, 2011; (b) A. Nangia and G. R. Desiraju, *Top. Curr. Chem*., 1998, **198**, 57; (c) G. R. Desiraju, *J. Am. Chem. Soc*., 2013, **135**, 9952.
10. S. Cherukuvada and A. Nangia, *CrystEngComm*, 2012, **14**, 2579.
11. N. R. Goud, K. Suresh, P. Sanphui and A. Nangia, *Int. J. Pharm*., 2012, **439**, 63.
12. (a) E. Lu, N. Rodríguez-Hornedo and R. Suryanarayanan, *CrystEngComm*, 2008, **10**, 665; (b) J. Lu, Y. -P. Li, J. Wang, Z. Li, S. Rohani and C. -B. Ching, *J. Cryst. Growth*, 2011, **335**, 110; (c) M. A. Mohammad, A. Alhalaweh and S. P. Velaga, *Int. J. Pharm*., 2011, **407**, 63.
13. A. I. Kitaigorodsky, *Mixed Crystals*, Springer-Verlag, 1984.
14. W. F. Smith and J. Hashemi, *Foundations of Materials Science and Engineering*, 4th Ed., McGraw-Hill, 2006.
15. Cambridge Structural Database, ver. 5.34, ConQuest 1.15, http://www.ccdc.cam.ac.uk (accessed on 31 Oct. 2013). (a) I. J. Bruno, J. C. Cole, P. R. Edgington, M. Kessler, C. F. Macrae, P. McCabe, J. Pearson and R. Taylor, *Acta Crystallogr. Sect. B: Struct. Sci.*, 2002, **58**, 389; (b) F. H. Allen and W. D. S. Motherwell, *Acta Crystallogr. Sect. B: Struct. Sci.*, 2002, **58**, 407.
16. Solid solutions, eutectics and cocrystals are classified as mixed crystals (Ref. 13). Historically, cocrystals were variably called as complex, molecular complex, hydrogen-bonded complex, solid-state complex, compound, molecular compound, addition compound, molecular crystal, heteromolecular crystal, etc., and encompass hydrates, solvates and clathrates, which became popular as novel pharmaceutical solids. (a) G. P. Stahly, *Cryst. Growth Des*., 2009, **9**, 4212; (b) N. Schultheiss and A. Newman, *Cryst. Growth Des.*, 2009, **9**, 2950.
17. (a) M. A. Oliveira, M. L. Peterson and D. Klein, *Cryst. Growth Des*., 2008, **8**, 4487; (b) M. Dabros, P. L. Emery and V. R. Thalladi, *Angew. Chem. Int. Ed*., 2007, **46**, 4132.
18. (a) K. Chadwick, R. Davey and W. Cross, *CrystEngComm*, 2007, **9**, 732; (b) T. Friščić and W. Jones, *Cryst. Growth Des.*, 2009, **9**, 1621.



Chemical Communications Accepted Manuscript

19. (a) D. J. Good and N. Rodríguez-Hornedo, *Cryst. Growth Des*., 2010, **10**, 1028; (b) N. Huang and N. Rodríguez-Hornedo, *CrystEngComm*, 2011, **13**, 5409.
20. Cocrystals, solid solutions and eutectics for chiral compounds are termed as racemic compound or racemate, pseudoracemate, and racemic mixture or conglomerate. (a) R. A. Storey and I. Ymén, Eds., *Solid State Characterization of Pharmaceuticals*, 1st Ed., Blackwell Publishing, 2011; (b) R. E. Davis, K. A. Lorimer, M. A. Wilkowski, J. H. Rivers, K. A. Wheeler and J. Bowers, *ACA Trans*., 2004, **39**, 41. Important features of these solids are discussed in Ref. 12c.
21. http://oxforddictionaries.com/definition/english/eutectic (accessed on 31 Oct. 2013).
22. http://www.britannica.com/EBchecked/topic/196700/eutectic (accessed on 31 Oct. 2013).
23. http://goldbook.iupac.org/E02225.html (accessed on 31 Oct. 2013).
24. http://reference.iucr.org/dictionary/Isomorphous_crystals (accessed on 31 Oct. 2013).
25. The domain boundaries of solid solutions in a eutectic have imperfect arrangement and distribution of components and weak non-covalent interactions and unfulfilled bonds (Ref. 4a).
26. (a) R. Thakuria, A. Delori, W. Jones, M. P. Lipert, L. Roy and N. Rodríguez-Hornedo, *Int. J. Pharm*., 2013, **453**, 101; (b) N. J. Babu and A. Nangia, *Cryst. Growth Des.*, 2011, **11**, 2662; (c) N. Shan and M. J. Zaworotko, *Drug Discov. Today*, 2008, **13**, 440; (d) A. V. Trask, *Mol. Pharmaceutics*, 2007, **4**, 301; (e) N. Blagden, M. de Matas, P. T. Gavan and P. York, *Adv. Drug Deliv. Rev.*, 2007, **59**, 617; (f) J. A. McMahon, J. A. Bis, P. Vishweshwar, T. R. Shattock, O. L. McLaughlin and M. J. Zaworotko, *Z. Kristallogr*., 2005, **220**, 340; (g) Ö. Almarsson, M. L. Peterson and M. J. Zaworotko, *Pharm. Pat. Anal*. 2012, **3**, 313; (h) S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury, G. R. Desiraju, A. G. Dikundwar, R. Dubey, N. Duggirala, P. P. Ghogale, S. Ghosh, P. K. Goswami, N. R. Goud, R. K. R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A. S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C. M. Reddy, N. Rodriguez-Hornedo, R. D. Rogers, T. N. G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C. C. Sun, J. A. Swift, R. Thaimattam, T. S. Thakur, R. K. Thaper, S. P. Thomas, S. Tothadi, V. R. Vangala, P. Vishweshwar, D. R. Weyna and M. J. Zaworotko, *Cryst. Growth Des*., 2012, **12**, 2147.
27. W. Jones, W. D. Motherwell and A. V. Trask, *MRS Bull*., 2006, **341**, 875.
28. G. R. Desiraju, *Angew. Chem. Int. Ed.*, 1995, **34**, 2311.

Chemical Communications Accepted Manuscript

29. R. D. B. Walsh, M. W. Bradner, S. Fleischman, L. A. Morales, B. Moulton, N. Rodríguez-Hornedo and M. J. Zaworotko, *Chem. Commun.*, 2003, 186.
30. P. Vishweshwar, J. A. McMahon, J. A. Bis and M. J. Zaworotko, *J. Pharm. Sci.*, 2006, **95**, 499.
31. (a) T. Steiner, *Acta Crystallogr. Sect. B: Struct. Sci.*, 2001, **57**, 103; (b) F. H. Allen, W. D. S. Motherwell, P. R. Raithby, G. R. Shields and R. Taylor, *New J. Chem.*, 1999, **23**, 25.
32. Solid solutions and eutectic mixtures are sometimes confused as (physical) mixtures. A mixture contains more than one type of phase whose characteristics are retained when the mixture is formed. In contrast, the components of a solid solution (homogenous phase) and eutectic (heterogeneous separation) do not retain their individual characteristics, e.g. the materials can be easily distinguished by their melting behavior. A simple mixture exhibits more than one melting event corresponding to its individual components, a solid solution exhibits solidus-liquidus melting behavior, and a eutectic exhibits a single low melting point compared to its components.
33. (a) http://reference.iucr.org/dictionary/Isostructural_crystals (accessed on 31 Oct. 2013); (b) A. Kálmán, L. Párkáanyi and G. Argay, *Acta Crystallogr. Sect. B: Struct. Sci.*, 1993, **49**, 1039; (c) N. K. Nath, B. K. Saha and A. Nangia, *New J. Chem.*, 2008, **32**, 1693; (d) S. K. Chandran, R. Thakuria and A. Nangia, *CrystEngComm*, 2008, **10**, 1891; (e) N. K. Nath and A. Nangia, *Cryst. Growth Des.*, 2012, **12**, 5411.
34. N. Yamamoto, T. Taga and K. Machida, *Acta Crystallogr. Sect. B: Struct. Sci.*, 1989, **45**, 162.
35. L. S. Reddy, P. M. Bhatt, R. Banerjee, A. Nangia and G. J. Kruger, *Chem. Asian J.*, 2007, **2**, 505.
36. (a) H. G. Brittain, *Cryst. Growth Des.*, 2009, **9**, 2942; (b) C. C. Seaton and A. Parkin, *Cryst. Growth Des.*, 2011, **11**, 1502.
37. P. Sanphui, N. R. Goud, U. B. R. Khandavilli and A. Nangia, *Cryst. Growth Des.*, 2011, **11**, 4135.
38. P. Sanphui, N. R. Goud, U. B. R. Khandavilli, S. Bhanoth and A. Nangia, *Chem. Commun.*, 2011, **47**, 5013.
39. (a) M. C. Etter, *J. Phys. Chem.*, 1991, **95**, 4601; (b) M. C. Etter, *Acc. Chem. Res.*, 1990, **23**, 120.
40. J. Robertson and E. P. O'Reilly, *Phys. Rev. B*, 1987, **35**, 2946.
41. Z. P. Lu, C. T. Liu, J. R. Thompson and W. D. Porter, *Phys. Rev. Lett.*, 2004, **92**, 245503.

Chemical Communications Accepted Manuscript

42. (a) B. B. Laird, *University Chemistry*, McGraw-Hill Companies Inc., New York, 2009; (b) J. Bernstein, *Polymorphism in Molecular Crystals*; Clarendon, Oxford, U. K., 2002.
43. G. Han, P. S. Chow and R. B. H. Tan, *Cryst. Growth Des*., 2012, **12**, 2213.
44. A. Sarkar and S. Mahapatra, *Cryst. Growth Des*., 2010, **10**, 2129.
45. (a) S. Cherukuvada, G. Bolla, K. Sikligar and A. Nangia, *Cryst. Growth Des*., 2013, **13**, 1551; (b) D. Braga, L. Maini, G. de Sanctis, K. Rubini, F. Grepioni, M. R. Chierotti and R. Gobetto, *Chem. Eur. J*., 2003, **9**, 5538; (c) S. N. Black, E. A. Collier, R. J. Davey and R. J. Roberts, *J. Pharm. Sci*., 2007, **96**, 1053; (d) B. Sarma, N. K. Nath, B. R. Bhogala and A. Nangia, *Cryst. Growth Des*., 2009, **9**, 1546.
46. W. W. Porter III, S. C. Elie and A. J. Matzger, *Cryst. Growth Des*., 2008, **8**, 14.
47. R. K. Harris, P. Y. Ghi, H. Puschmann, D. C. Apperley, U. J. Griesser, R. B. Hammond, C. Ma, K. J. Roberts, G. J. Pearce, J. R. Yates and C. J. Pickard, *Org. Pro. Res. Dev*., 2005, **9**, 902.
48. The salts potassium nitrate, sodium nitrite and sodium nitrate (m.p. 334 °C, 284 °C and 307 °C respectively; *CRC Handbook of Chemistry and Physics*, ed. D. R. Lide, 90$^{th}$ ed., CD-ROM ver, CRC Press/Taylor & Francis, 2010) in the ratio 53:40:7 form a eutectic composition of melting point 140 °C. See E. G. Bohlmann, *Heat Transfer Salt for High Temperature Steam Generation*, Oak Ridge National Laboratory, 1972.
49. (a) I. Duarte, M. Temtem, M. Gil and F. Gaspar, *Indus. Pharm*., 2011, **30**, 4; (b) http://www.fenoglide.com/assets/000/000/000/226.pdf (accessed on 31 Oct. 2013).
50. E. Karavas, G. Ktistis, A. Xenakis and E. Georgarakis, *Drug Dev. Indus. Pharm*., 2005, **31**, 473.
51. G. Verreck, K. Six, G. V. Mooter, L. Baert, J. Peeters and M. E. Brewster, *Int. J. Pharm*., 2003, **251**, 165.
52. (a) http://apps.who.int/prequal/whopar/whoparproducts/HA411Part6v1.pdf (accessed on 31 Oct. 2013); (b) P. M. V. Gilis, V. F. V. De Condé and R. P. G. Vandecruys, *US Pat*., 5633015, 1997.
53. M. Faeges, *GB Pat*., 1147348, 1969.
54. P. W. Stott, A. C. Williams and B. W. Barry, *J. Contr. Rel*., 1998, **50**, 297.
55. (a) M. M. Denton and J. A. Rogers, *WO Pat.*, 2008/073324 A1, 2008; (b) O. Pacheco, E. Russo, V. Russo and J. A. Martins, *WO Pat*., 2004/103260 A2, 2004.
56. E. P. Lavor, F. D. Freire, C. F. S. Aragão, F. N. Raffin and T. F. A. de Lima e Moura, *J. Ther. Anal. Calorim.*, 2012, **108**, 207.


Chemical Communications Accepted Manuscript

57. (a) A. Górniak, A. Wojakowska, B. Karolewicz and J. Pluta, *J. Ther. Anal. Calorim.*, 2011, **104**, 1195; (c) A. Górniak, B. Karolewicz, E. Żurawska-Plaksej and J. Pluta, *J. Ther. Anal. Calorim.*, 2013, **111**, 2125.
58. Strategies of selecting starting materials devoid of strong supramolecular synthons with molecular asymmetry and showing charge delocalization have been suggested for the design of ionic liquids and deep eutectic solvents. (a) P. M. Dean, J. Turanjanin, M. Y.- Fujita, D. R. MacFarlane and J. L. Scott, *Cryst. Growth Des.*, 2009, **9**, 1137; (b) E. W. Castner, Jr. and J. F. Wishart, *J. Chem. Phys*., 2010, **132**, 120901; (c) A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc*., 2004, **126**, 9142; (d) P. B. de María and Z. Maugeri, *Curr. Opi. Chem. Bio*., 2010, **15**, 1.
59. (a) J. N. Moorthy, P. Venkatakrishnan, P. Natarajan, D. -F. Huang and T. J. Chow, *J. Am. Chem. Soc*., 2008, **130**, 17320; (b) O. Lebel, T. Maris, M. -E. Perron, E. Demers and J. D. Wuest, *J. Am. Chem. Soc*., 2006, **128**, 10372.
60. (a) M. M. Piepenbrock, N. Clarke and J. W. Steed, *Langmuir*, 2009, **25**, 8451; (b) S. Varghese, A. K. Lele and R. A. Mashelkar, *J. Chem. Phys*., 2000, **112**, 3063.
61. (a) S. L. Childs, G. P. Stahly and A. Park, *Mol. Pharmaceutics*, 2007, **4**, 323; (b) J. Lu and S. Rohani, *Curr. Med. Chem*., 2009, **16**, 884; (c) Z. J. Li, Y. Abramov, J. Bordner, J. Leonard, A. Medek and A. V. Trask, *J. Am. Chem. Soc.*, 2006, **128**, 8199; (d) A. Mukherjee, S. Tothadi, S. Chakraborty, S. Ganguly and G. R. Desiraju, *CrystEngComm*, 2013, **15**, 4640.
62. (a) G. M. Sheldrick, *SHELXS-97* and *SHELXL-97*, University of Göttingen, Göttingen, Germany, 1997; (b) O. V. Dolomanov, A. J. Blake, N. R. Champness and M. Schröder, *J. Appl. Crystallogr*., 2003, **36**, 1283.
63. (a) T. Egami and S. J. L. Billinge, *Underneath the Bragg Peaks: Structural analysis of complex materials*, Pergamon, Elsevier, Oxford, 2003; (b) P. Juhás, L. Granlund, S. R. Gujarathi, P. M. Duxbury and S. J. L. Billinge, *J. Appl. Cryst*., 2010, **43**, 623.
64. (a) S. J. L. Billinge and M. G. Kanatzidis, *Chem. Commun.*, 2004, 749; (b) T. Proffen, K. L. Page, S. E. McLain, B. Clausen, T. W. Darling, J. A. TenCate, S. -Y. Lee and E. Ustundag, *Z. Kristallogr*., 2005, **220**, 1002; (c) V. Petkov, M. Gateshki, J. Choi, E. G. Gillan and Y. Ren, *J. Mater. Chem*., 2005, **15**, 4654; (d) M. D. Moore, A. M. Steinbach, I. S. Buckner and P. L. D. Wildfong, *Pharm. Res*., 2009, **26**, 2429; (e) J. P. Boetker, V. Koradia, T. Rades, J. Rantanen and M. Savolainen, *Pharmaceutics*, 2012, **4**, 93.
65. P. Chirawatkul, A. Zeidler, P. S. Salmon, S. Takeda, Y. Kawakita, T. Usuki and H. E. Fischer, *Phys. Rev. B*, 2011, **83**, 014203.

Chemical Communications Accepted Manuscript

66. K. Nollenberger, A. Gryczke, CH. Meier, J. Dressman, M. U. Schmidt and S. Brühne, *J. Pharm. Sci*., 2009, **98**, 1476.
67. S. J. L. Billinge, T. Dykhne, P. Juhás, E. Božin, R. Taylor, A. J. Florence and K. Shankland, *CrystEngComm*, 2010, **12**, 1366.
68. (a) S. H. Lapidus, P. W. Stephens, K. K. Arora, T. R. Shattock and M. J. Zaworotko, *Cryst. Growth Des*., 2010, **10**, 4630; (b) U. Das, B. Chattopadhyay, M. Mukherjee and A. K. Mukherjee, *Cryst. Growth Des*., 2012, **12**, 466; (c) P. Sanphui, G. Bolla, U. Das, A. K, Mukherjee and A. Nangia, *CrystEngComm*, 2013, **15**, 34; (d) D. Braga, F. Grepioni, L. Maini, G. I. Lampronti, D. Capucci and C. Cuocci, *CrystEngComm*, 2012, **14**, 3521.
69. (a) H. Bhutani, S. Singh, K. C. Jindal and A. K. Charkraborti, *J. Pharm. Biomed. Anal.*, 2005, **39**, 892; (b) B. Blomberg, S. Spinachi, B. Fourie and R. Laing, *Bull. World Health Org.*, 2001, **79**, 61.
70. R. G. Wilkinson, R. G. Shepherd, J. P. Thomas and C. Baughn, *J. Am. Chem. Soc.*, 1961, **83**, 2212.
71. S. Singh and B. Mohan, *Int. J. Tuberc. Lung Dis.*, 2003, **7**, 298.
72. http://apps.who.int/prequal/whopar/whoparproducts/TB168Part6v1.pdf (accessed on 31 Oct. 2013).
73. (a) S. Cherukuvada and A. Nangia, *Cryst. Growth Des*., 2013, **13**, 1752; (b) S. Cherukuvada and A. Nangia, *CrystEngComm*, 2012, **14**, 7840.
74. (a) G. -Y. Bai, H. -S. Ning, Y. -C. Zhang, T. Zeng and J. -S. Li, *Acta Crystallogr.*, 2006, **E62**, o3364; (b) R. Godfrey, R. Hargreaves and P. B. Hitchcock, *Acta Crystallogr.*, 1992, **C48**, 79; (c) G. -Y. Bai, H. -S. Ning, J. Simpson, X. -Y. Kin and N. Li, *Acta Crystallogr.*, 2006, **E62**, o4567; (d) Mitsui Toatsu Inc. and Mitsui Pharmaceuticals Inc. *GB Pat*., 1365473, 1973; (e) S. -W. Park, Korean Advanced Institute of Science and Technology, *US Pat*., 4450274, 1984.
75. (a) A. Fahr and X. Liu, *Expert Opin. Drug Deliv*., 2007, **4**, 403; (b) V. J. Stella and K. W. Nti-Addae, *Adv. Drug Deliv. Rev*., 2007, **59**, 677; (c) H. Matsumoto, T. Hamawaki, H. Ota, T. Kimura, T. Goto, K. Sano, Y. Hayashi and Y. Kiso, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1227.
76. (a) L. R. Hilden and K. R. Morris, *J. Pharm. Sci*., 2004, **93**, 3; (b) L. Yu, *Adv. Drug Deliv. Rev*., 2001, **48**, 27; (c) R. Zallen, *Amorphous Solids*, John Wiley & Sons Inc., New York, 1983.
77. J. M. Rubin-Preminger, J. Bernstein, R. K. Harris, I. R. Evans and P. Y. Ghi, *Cryst. Growth Des.*, 2004, **4**, 431.
78. S. L. Childs, L. J. Chyall, J. T. Dunlap, V. N. Smolenskaya, B. C. Stahly and G. P. Stahly, *J. Am. Chem. Soc*., 2004, **126**, 13335.



Chemical Communications Accepted Manuscript

79. Safe and non-toxic chemicals that can be used in food and drugs can be selected from the GRAS (Generally Recognized As Safe) and EAFUS (Everything Added to Food in the United States) substances list available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm, and http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm115326.htm (accessed on 31 Oct. 2013).
80. (a) G. G. Z. Zhang, D. Law, E. A. Schmitt and Y. Qiu, *Adv. Drug Delivery Rev.*, 2004, **56**, 371; (b) K. R. Morris, U. J. Griesser, C. J. Eckhardt and J. G. Stowell, *Adv. Drug Delivery Rev.*, 2004, **48**, 91.
81. C. Peng, M. N. Chan and C. K. Chan, *Environ. Sci. Technol*., 2001, **35**, 4495.
82. (a) A. V. Trask and W. Jones, *Top. Curr. Chem*., 2005, **254**, 41; (b) N. Shan, F. Toda and W. Jones, *Chem. Commun.*, 2002, 2372.
83. D. W. Robertson, N. D. Jones, J. K. Swartzendruber, K. S. Yang and D. T. Wong, *J. Med. Chem*., 1988, **31**, 185.
84. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1F/Stability_Guideline_WHO.pdf (accessed on 31 Oct. 2013).
85. http://www.fda.gov/downloads/Drugs/Guidances/UCM281764.pdf (accessed on 31 Oct. 2013).
86. The word pharmaceutical eutectic was used in the following papers without discussion of its attributes as a distinct solid drug form vis-à-vis pharmaceutical cocrystal/salt/hydrate. (a) E. Gebremichael, Masters Dissertation, The University of Toledo, 2010. This thesis deals with pharmaceutical solid dispersions which exhibit eutectic nature; (b) H. Shekhar and V. Kant, *Int. J. PharmTech Res*., 2012, **4**, 1486. The binary phase diagram and eutectic of bioactive molecules nicotinamide and benzamide are discussed.
87. (a) P. H. Stahl and C. G. Wermuth, Eds., *Handbook of Pharmaceutical Salts, Properties, Selection and Use*, Wiley-VCH, 2002; (b) S. M. Berge, L. D. Bighley and D. C. Monkhouse, *J. Pharm. Sci*., 1977, **66**, 2.
88. (a) R. Shimanovich, M. Cooke and M. L. Peterson, *J. Pharm. Sci*., 2012, **101**, 4013; (b) R. K. Khankari and D. J. W. Grant, *Thermochim. Acta*, 1995, **248**, 61.
89. A. M. Thayer, *Chem. Eng. News*, 2010, **88**, 13.
90. (a) Global Tuberculosis Report 2012, World Health Organization; (b) Special Issue on Tuberculosis, *Cur. Sci*., 2013, **105**, pp. 0594-0675.
91. Unsuccessful cocrystallization experiments have escaped the attention of researchers and tend to be underreported. The non-formation of cocrystals is reported in a few papers but their authors do not report further analysis of the products. (a) S. Karki, T. Friščić, L. Fabián and W. Jones, *CrystEngComm*, 2010,

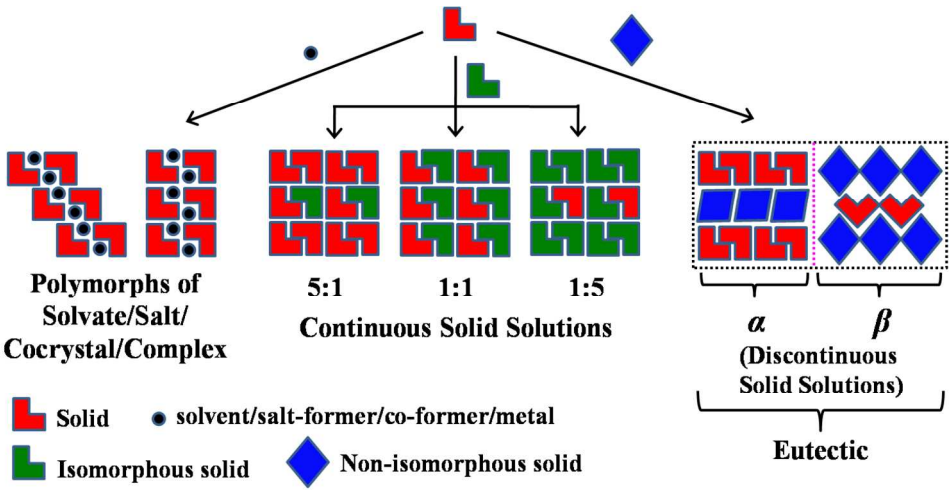


Chemical Communications Accepted Manuscript

**12**, 4038; (b) J. I. Arenas-Garcia, D. Herrera-Ruiz, K. Mondragón-Vásquez, H. Morales-Rojas and H. Höpfl, *Cryst. Growth Des*., 2010, **10**, 3732; (c) M. R. Caira, S. A. Bourne, H. Samsodien, E. Engel, W. Liebenberg, N. Stieger and M. Aucamp, *CrystEngComm*, 2011, **13**, 2541; (d) J. I. Arenas-Garcia, D. Herrera-Ruiz, K. Mondragón-Vásquez, H. Morales-Rojas and H. Höpfl, *Cryst. Growth Des*., 2012, **12**, 811; (e) A. Alhalaweh, S. George, S. Basavoju, S. L. Childs, S. A. A. Rizvi and S. P. Velaga, *CrystEngComm*, 2012, **14**, 5078; (f) A. Lemmerer, J. Bernstein and M. A. Spackman, *Chem. Commun*., 2012, **48**, 1883. Also Refs. 12c & 36b. These and other cases could perhaps be reinvestigated for eutectic formation by PDF analysis.

92. PANalytical workshop on XRD and XRF Techniques for Pharmaceuticals, 26 September 2013, Hyderabad.

**TOC Graphic**




The combination of isomorphous solids gives rise to continuous solid solutions and solids in which the adhesive interactions outweigh the cohesive ones lead to cocrystals. With weak adhesive, strong cohesive and a geometric misfit, the product is eutectic.

Chemical Communications Accepted Manuscript