

Cocrystals: A Review of Recent Trends in Pharmaceutical and Material Science Applications

MANJUNATH G. JAVOOR¹, PRADIP KUMAR MONDAL² and DEEPAK CHOPRA^{2*}

¹Department of Chemistry, NITK, Surathkal, Mangalore 575025.

²Department of Chemistry, Indian Institute of Science
Education and Research Bhopal, Bhauri, Bhopal 462066, India.

Corresponding author Email: dchopra@iiserb.ac.in

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ABSTRACT

Over the last two decades, the design of multicomponent molecular crystals or cocrystals has grown out to be an interesting and promising area of research in pharmaceuticals and material science. Cocrystallization is at the interface of crystal engineering and supramolecular chemistry and allows us to vary the physicochemical properties of solids according to the need, through manipulation of various intermolecular interactions. In this short review, we focus on some recent reports on pharmaceutical cocrystals and emerging subclasses of cocrystals, namely: Charge transfer cocrystals, Energetic cocrystals, and Ternary cocrystals and discuss about their methods of characterization and applications of importance in the industry.

Key words: Pharmaceutical cocrystals, Charge transfer cocrystals, Energetic cocrystals, Ternary cocrystals, Physicochemical properties.

INTRODUCTION

The advent of crystal engineering has transformed the pace of research in molecular solids. Attaining the desired properties in molecular solids by controlled manipulation of intermolecular interactions holds the key to success in this area of research. For that matter, strength and directionality of weak intermolecular interactions are important features to be taken into account. Crystal engineering, through supramolecular synthons, allows us to design cocrystals with desired physicochemical properties^{3,5}. Cocrystallization^{6,8} and polymorphism^{9,11} are two important applications of crystal engineering. A cocrystal entails two or more neutral molecules to be held together by weak intermolecular interactions in a definite ratio. Since intermolecular interactions guide properties of molecular solids, cocrystal formation is of great interest to crystal engineers. Primary non-covalent interactions such as strong hydrogen bonds decide

the framework of multicomponent crystal and secondary, weaker interactions such as halogen bonds, van der Waals forces act as auxiliary scaffolds to stabilize the framework¹². Initially, cocrystals have been exploited in pharmaceutical research to alter the physicochemical properties of a drug such as bio availability, solubility, stability, melting point and shelf life^{13,15}. With this growing success in pharmaceuticals^{16,17}, cocrystallization as a tool to alter the properties of solids is spreading into research in material science. It is now being used in the design of organic functional materials and energetic materials. Charge transfer cocrystals^{18,20} have found a place in the design of optoelectronic devices such as Field effect transistors (FETs), diodes. Many of the energetic materials are highly sensitive and possess low power and undesirable detonation properties. Cocrystal formation of an energetic substance with suitable cocrystal former can greatly alter its sensitivity and density (and hence the power)^{21,26}. More recently, researchers

have opened up a new class of cocrystals called ternary cocrystals, which involves binding of three neutral molecular entities through weak interactions which are interesting as well as challenging. Over the years, cocrystallization has been used as a tool to vary the properties of a solid and hence this area has generated a lot of interest and attention. With the help of crystal structure prediction (CSP), it is now possible to know the crystal structure and motifs involved in the framework of cocrystals²⁷. A crystal engineer can have an idea if the experiments involving high-cost drug molecules and other compounds will yield fruitful results. Here we present a brief review of pharmaceutical and material science applications of cocrystals.

Pharmaceutical cocrystals

A pharmaceutical cocrystals a homogeneous crystalline entity which contains an active pharmaceutical ingredient (API) and a cocrystal former (GRAS molecule) in a stoichiometric ratio, in the same crystal lattice stabilized by non-covalent interactions such as hydrogen bonds, π - π interactions, ionic interactions, and van der Waals forces^{28,30}. The majority of the drug molecules in the market are sold out in their salt forms, and some molecules, though potential drug candidates, cannot form salts due to the absence of ionizable sites in the molecule. Cocrystallization comes in handy in such cases, which allows us to use them as neutral molecules along with coformers without loss of biological activity.

The majority of the drugs are ineffective in their bioactivity due to low solubility and permeability, which limits their clinical applications. Over the years, cocrystallization is widely used in the field of pharmaceuticals for improving the physicochemical properties of the drug molecules such as solubility, bioavailability, permeability, stability, melting point and shelf life^{31,32}. Because of the simple and profitable methods involved in designing a cocrystal, and performance, it is now a most viable method for improving the physicochemical properties of drugs. It is to be noted that, there is no particular method to design cocrystals of all the drugs. The strategy which works for one may not work for the other; each drug has to be dealt separately keeping the property to be varied in mind. The solubility of a drug depends on melting point, dielectric constant, temperature, and

pH. Recently, new cocrystals of Hydrochlorothiazide (HCT) with piperazine (PPZ), tetramethylpyrazine (TMPZ), picolinamide (PCM), malonamide (MAM), isonicotinic acid (INIC), and with a tuberculosis drug isoniazid (INZ) were reported³³, among them HCT-PPZ showed seven-fold increase in solubility (Figure 1). Permeability is another important property of an API which depends on absorption of the drug on the cell membrane. Both solubility and permeability were enhanced in the case of HCT-PPZ which is essential for bioavailability of the drug. It can be clearly seen that cocrystals always need not have a higher solubility than the drug (HCT-MAM and HCT-TMPZ have solubilities lower than HCT).

The diffusion behavior of the new solid forms of HCT was studied using a Franz diffusion cell, the plot of flux of the drug at the time indicate that HCT-PPZ and HCT-PCM cocrystals exhibit better diffusion behavior among all the cocrystals (Figure 2). It is suggested that coformers that cause higher solubility in cocrystals lead to higher diffusion.

Our group has reported ten different cocrystals, one polymorph of a cocrystal and a salt of an organofluorine drug riluzole with various carboxylic acids and pyridine derivatives¹². The new crystalline phases are stabilized by primary and secondary intermolecular interactions, with a melting point range between 90-140°C closely related to MP of original API (118°C). Cocrystals exhibited enhanced solubility and dissolution rate in comparison to riluzole¹². The structure of compounds used in the study and the plot of the cumulative amount of cocrystal dissolved against time is given in Figure 3a and 3b respectively.

Charge Transfer cocrystals

Single component organic materials used in designing organic semiconductors have attained limited success. Organic cocrystals involving ordered stacking of donors and acceptors offer unique physicochemical properties which are desirable for applications in optoelectronic devices (like Field Effect Transistors and optical diodes)^{34,35}. This has led to growing interest in yet another nascent subclass of cocrystals, namely, charge transfer cocrystals which have greater implications for designing optoelectronic devices. The most

important factor as far as charge transfer cocrystals are concerned is ionicity or degree of charge transfer between a donor (D) and an acceptor (A). Ionicity or degree of CT is directly related to conducting ability^{36,37} and lattice instability³⁸ of cocrystals. As of now, there exists no particular method for confirming the degree of charge transfer, and its elusive nature requires further research in this area. *Hu et al*, have reported a novel, 2-D light emitting charge transfer (1:1) cocrystal of a 1,2-di(4-pyridyl)ethylene (Bpe) and 1,2,4,5-tetracyanobenzene (TCNB) molecules (Figure 4)³⁹.

They have noted that “To the best of our knowledge, the CT nature of crystals of Donor-Acceptor complexes is difficult to verify accurately.” Both spectroscopic and theoretical methods were used to confirm the charge transfer nature in BPe-TCNB cocrystals. Xu *et al*¹⁸ have demonstrated the role of solvents in controlling the molar ratio and different charge transfer interaction modes by studying 1-phenyl-3-(pyren-1yl) prop-2-en-1-one (PPPO) as electron donor (D) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) as electron acceptor (A) to form CT complexes (Figure 5)¹⁸.

In recent years, the design of charge transfer cocrystals involving the use of conjugated aromatic hydrocarbons as electron donors and halogenated acceptors finds applications in electronics and photonics^{40,42}. Due to its excellent efficiency and stability of assembling cocrystals with electron donors, TCNQ is one of the most widely used acceptors in the field of CT complexes. Recently, E. D. Como and coworkers⁴³ have synthesized CT cocrystals of perylene with TCNQ and its fluorine

derivatives (Figure 6). Fluorine derivatives have strong acceptor abilities than TCNQ, leading to greater ionicity of CT interactions formed.

Very recently, Prof A. J. Matzger and co-workers have demonstrated the role of hydrogen bonding and halogen bonding on the packing and ionicity of CT- cocrystals [44]. They have synthesized CT cocrystals using 1, 5-diaminonaphthalene (DAN) as the donor and halogen substituted benzoquinones (XA, X= F, Cl, Br, I) as acceptors (Figure 7a). A comparison of the HOMO and LUMO energies of DAN (donor) and XA (acceptor) molecules is given in Figure 7b.

In this work, the dependence of the degree of ionization of cocrystal on electronegativity of the halogen substituent was demonstrated experimentally by using Raman spectroscopy. For this study, anion radicals of CA and BA were synthesized and were subjected to Raman spectroscopy along with CA, BA, DAN⁺CA cocrystal and DAN⁺BA cocrystal. The corresponding carbonyl peak in each spectrum (CA = 1689.7 cm⁻¹, CA^{•-} = 1588.2 cm⁻¹ and DAN⁺CA = 1663.3 cm⁻¹; BA = 1681.3 cm⁻¹, BA^{•-} = 1582.3 cm⁻¹ and DAN⁺BA = 1657.7 cm⁻¹ (Figure 8a and 8b) was used to estimate $\tilde{n}$ (ionicity) for both cocrystals. The more electronegative chlorine (3.0) substituted DAN⁺CA has an ionicity value of 0.27 e, and the less electronegative bromine (2.8) substituted DAN⁺BA has an ionicity value of 0.23 e, showing the direct relation between ionicity and electronegativity of halogen substituent.

Energetic materials, a class of materials which includes explosives, propellants and pyrotechnics suffer from undesirable properties such

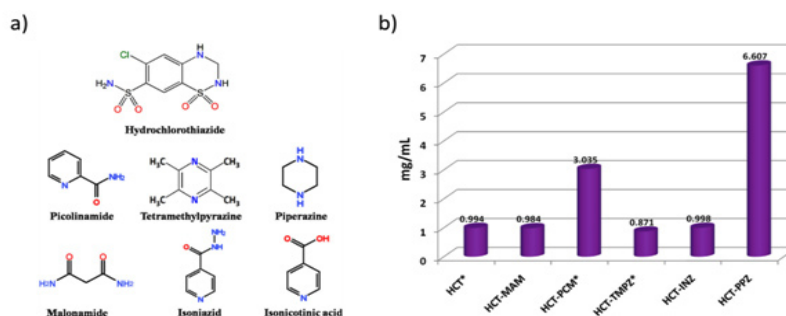


Fig. 1: a) Structure of HCT and cocrystals. b) Comparison of solubility of HCT and cocrystals. Asterisk mark denotes solubility after 4h(Reproduced with permission from reference 33. Copyright 2017 American Chemical Society).

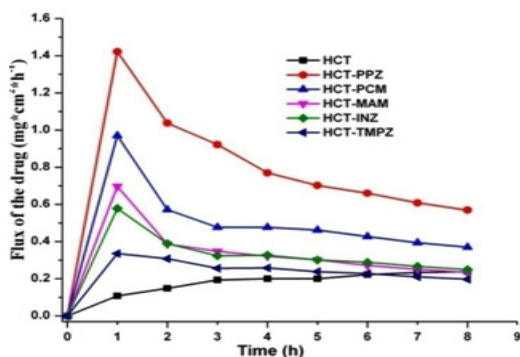


Fig. 2: Plot of Flux/permeability of cocrystals of HCT vs. time (Reproduced with permission from reference 33. Copyright 2017 American Chemical Society)

as poor stability, high sensitivity and low density (hence, low explosive power) which have limited their applications. Traditionally, the development and optimisation of properties of energetic materials was dependent on synthetic methods. In recent years, crystal engineering through cocrystallization has paved new ways to alter the physicochemical properties of energetic materials very efficiently. Cocrystallization offers a robust method for attaining desired sensitivity, stability, and high power energetic materials without requiring synthesis of new compounds.

A particular class of energetic materials, azoles are of great interest from the point of crystal

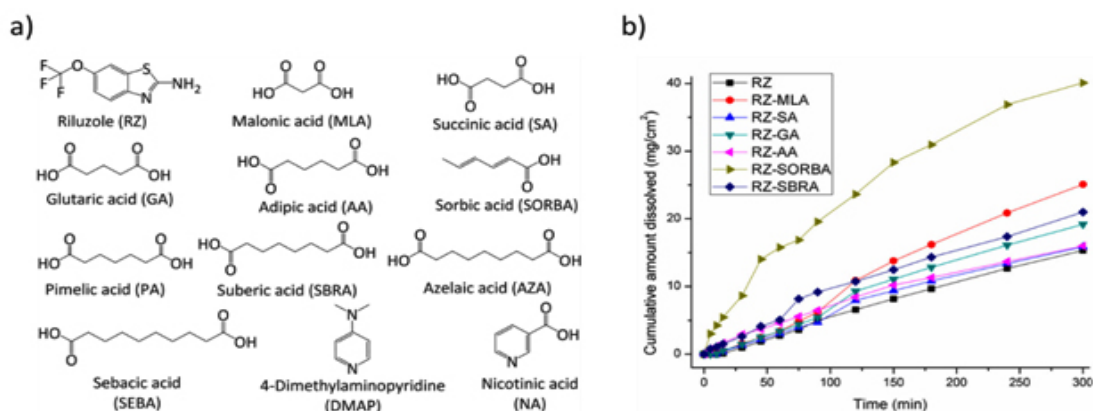


Fig. 3: a) Structure of the drug riluzole and cocrformers used in the study. b) The intrinsic dissolution rate measurements of riluzole cocrystals and salt in pH 7 buffer medium (Reproduced with permission from reference 12. Copyright 2017 American Chemical Society).

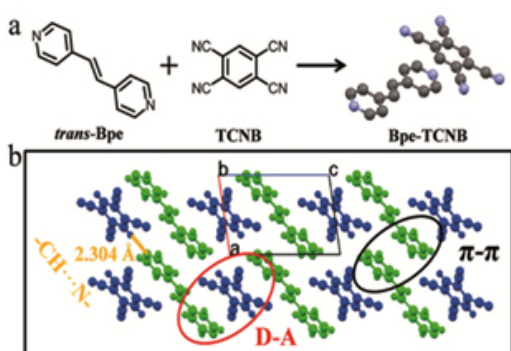


Fig. 4: a) Structure of trans-Bpe, TCNB, and the molecular structure Bpe-TCNB complex obtained. b) The self-assembly intermolecular interactions involved ($\pi \cdots \pi$, $D \cdots A$, and $C-H \cdots N$) (Reproduced with permission from reference 39. Copyright 2015 John Wiley and Sons).

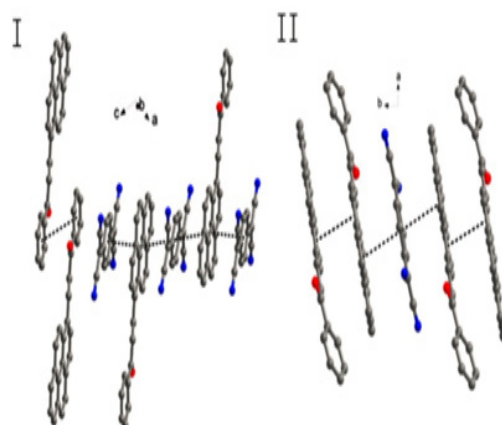


Fig. 5: The intermolecular $\pi \cdots \pi$ and $C-H \cdots \pi$ interactions involved in CT complexes I and II (Reproduced with permission from reference 18. Copyright 2015 American Chemical Society).

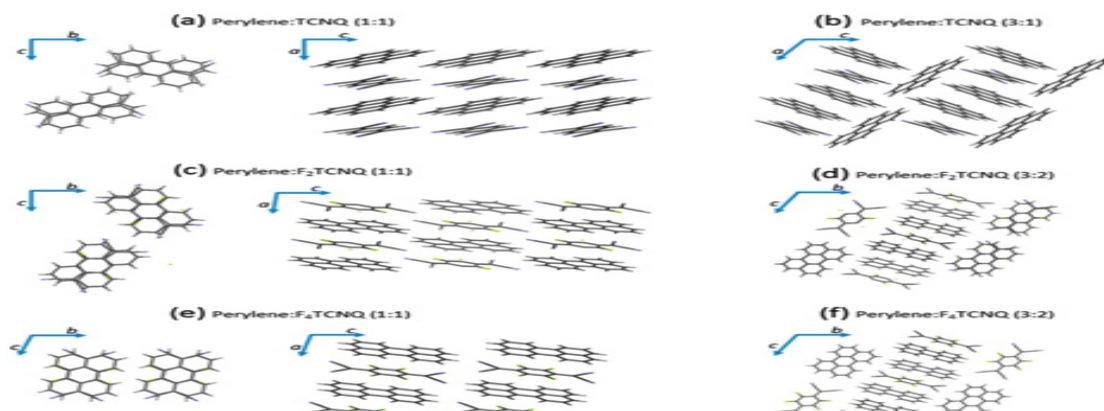


Fig. 6: Structural motifs of (a) perylene:TCNQ (1:1), (b) perylene:TCNQ(3:1), (c) perylene: TCNQ-F2 (1:1), (d) perylene:TCNQ-F2 (3:2), (e) perylene:TCNQ-F4 (1:1), and (f) perylene:TCNQ-F4 (3:2) (Reproduced with permission from reference 43. Copyright 2016 American Chemical Society).

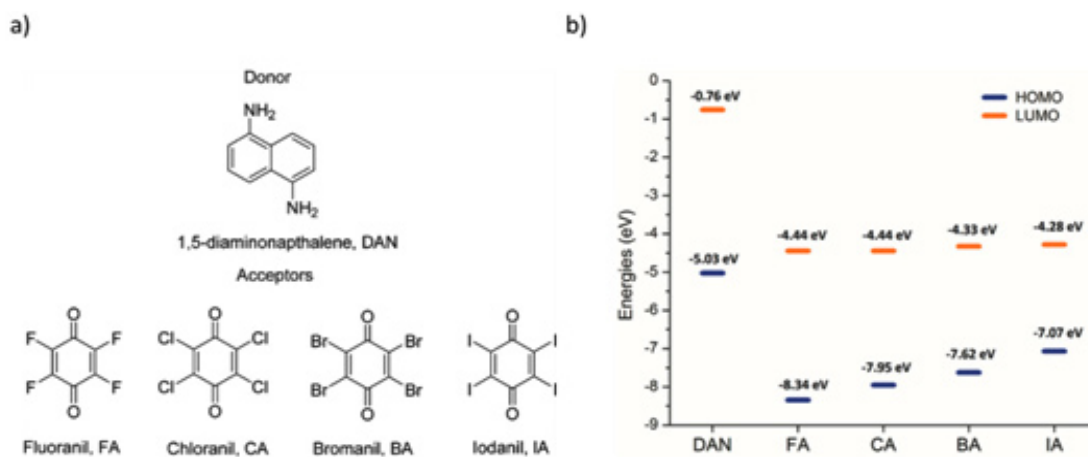


Fig. 7: a) Structures of donor and acceptors used in CT cocrystal synthesis. b) A Comparison

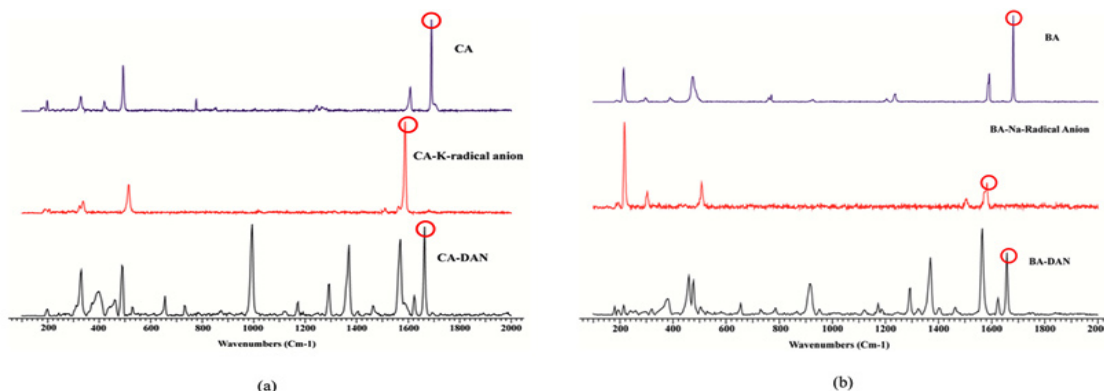


Fig. 8: (a) Raman spectra (Stacked) of the pure component CA, CA radical anion, and cocrystal (CA-DAN). The carbonyl peak used to estimate ionicity is marked by the red ring. (b) Raman spectra of the BA pure component, BA radical anion, and DAN-BA cocrystal. The carbonyl peak used to estimate ionicity is marked by the red ring (Reproduced with permission from reference 44. Copyright 2017 American Chemical Society).

engineering as they possess hydrogen bond donors (primary and secondary amines in aromatic systems). Matzger and coworkers have reported a series of three cocrystals of 5,5,2 -Dinitro-1H-1,2,4-triazole (DNBT), which is a high-density azole explosive, which has limited military applications²³. The structures of DNBT and three coformers: 5-amino-3-nitro-1H-1,2,4-triazole (ANTA), 1H,4H-3,6-dinitropyrazolo[4,3-c]pyrazole (DNPP), and 3,4-dinitropyrazole (3,4-DNP), and the hydrogen bond motifs utilized in cocrystal formation are given below in Figure 9.

Further, packing coefficient (C_p) which is a measure of the density of an energetic material, is estimated (Figure 10a), and the detonation velocities of all the three cocrystals were determined using Cheetha 6.0 software at 298K (Figure 10b)²³. All

the cocrystals prepared have the power of pure components with decreased impact sensitivity which can be attributed to the hydrogen bonding interactions in the cocrystals.

Another area of concern regarding energetic materials is their sensitivity towards external stimuli which hampers storage and handling. Currently, there are two methods available for loading the energetic materials into munitions: a) melting and casting, b) hydraulic pressing²⁶. The former method is more advantageous than the latter in terms of reduction of void space and greater processing efficiency.

Matzger *et al* have designed an energetic cocrystal of 3, 4-diaminofurazan (DAF) and 4-amino-3,5-dinitropyrazole(ADNP) is melt castable,

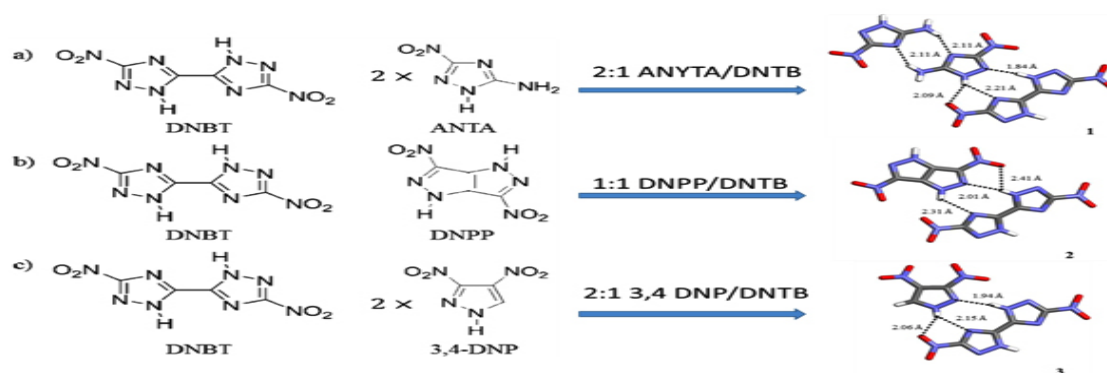


Fig. 9: Structures of DNBT and coformers and crystal structure of hydrogen bond motifs involved (numbers 1, 2, and 3 represent cocrystals of DNBT with ANTA, DNPP, and 3,4-DNP respectively) (Reproduced with permission from reference 23. Copyright 2015 American Chemical Society).

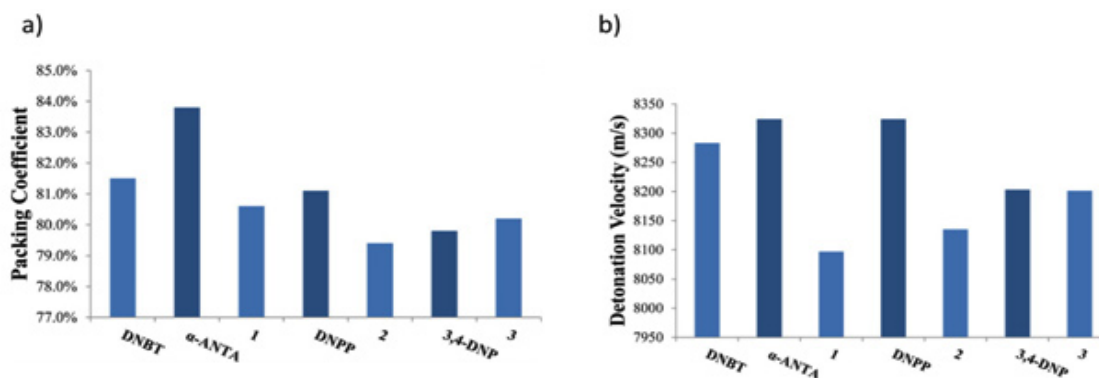


Fig. 10: a) Packing coefficients/ densities (C_k) of all the pure components and DNBT cocrystal 1-3 are calculated from the room-temperature (298 K) crystal lattices of each material. b) Detonation velocities of each pure component and DNBT cocrystal 1-3. (Reproduced with permission from reference 23. Copyright 2015 American Chemical Society)

a property which is not possessed by pure components²⁵. The structure of compounds used and hydrogen bonding interactions is given (Figure 11a and 11b respectively). It is known that a good melt castable material must possess, a low melting point, large range between the melting point and the start of decomposition, and high loading density²⁶. As observed from DSC curves of 1, ADNP and DAF (Figure 11c), the cocrystal 1 has a melting point around 172°C, which is lower than both ADNP and DAF. Further, there is a large difference in melting point and starting of decomposition, which is absent in ADNP. Thus, it qualifies to be a melt castable energetic material. In addition, theoretical estimation of detonation parameters (velocity and

pressure) using Cheetah 7.0 software indicates the high performance of ADNP/DAF cocrystal, which is intermediate in comparison to the pure components (Figure 11d).

There is limited literature available on cocrystallization of energetic materials as this is a new area yet to be ventured into. Cocrystallization as a tool to vary the properties of energetic materials has gained attention in recent years. We hope to see more reports in this area in the coming years.

Ternary cocrystals

So far, we discussed about cocrystals involving two components and their importance.

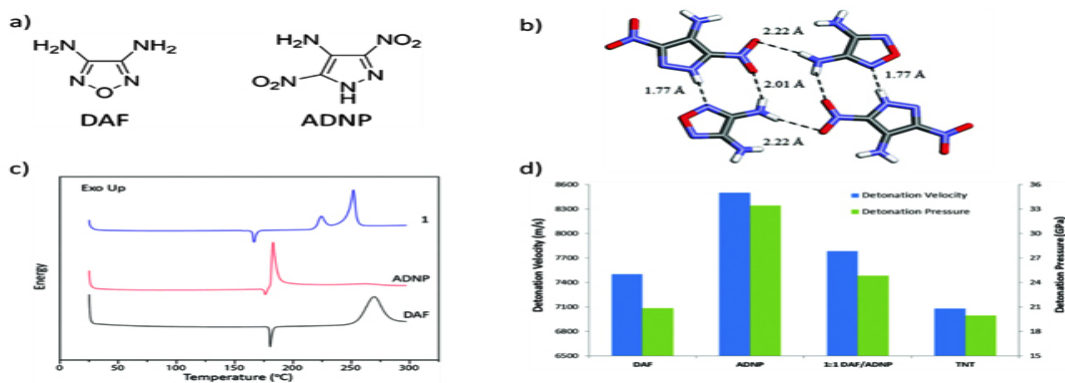


Fig. 11: a) Structures of compounds used in the study. b) Hydrogen bonding between DAF and ADNP. c) DSC traces of 1:1 cocrystal DAF/ADNP (1), pure components ADNP and DAF. d) Detonation parameters (velocity and pressure) of DAF, ADNP, 1 and TNT (Reproduced with permission from reference 25. Copyright 2017 Royal Society of Chemistry).

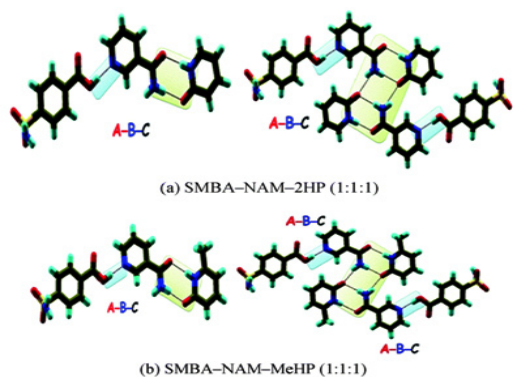


Fig. 12: (a) Hydrogen bonded motifs in SMBA-NAM-2HP (1:1:1) and (b) SMBA-NAM-MeHP (1:1:1) involving the amide-amide heterodimer and acid-pyridine synthons (Reproduced with permission from reference 46. Copyright 2015 Royal Society of Chemistry)

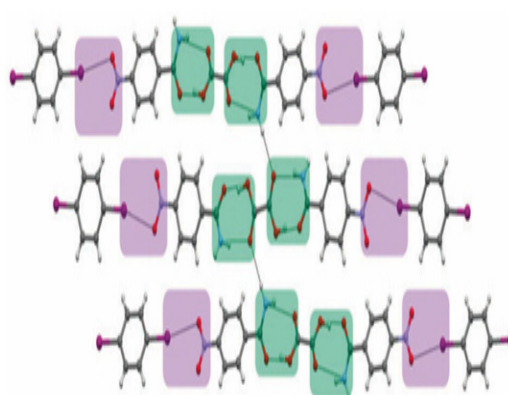


Fig. 13: The crystal packing in ternary cocrystals of 4-nitrobenzene: oxalic acid: 1,4-diiodo-benzene (2:1:1). Color code: acid-amide (green); I...O₂N (pink). (Reproduced with permission from reference 45. Copyright 2013 Royal Society of Chemistry)

A large volume of literature is available on binary cocrystals. Two component molecular crystals are comparatively easy to synthesize and are established in terms of design and assembly^{45,46}. Ternary cocrystals is a recent advancement in crystal engineering and are yet to be established, hence there is lot of room for optimization of strategies for designing ternary cocrystals. A ternary cocrystal is an assembly of three neutral solid compounds in a single crystal structure through hydrogen bonding and other weak interactions⁴⁶. On moving from binary to a ternary system, there are a number of ways in which three components can assemble themselves in a single crystal lattice. This makes the process of design extremely difficult and challenging. Added to this, availability of specific and universal interactions may lead to the formation of polymorphs^{47,50} of individual molecules, binary cocrystals, solvatomorphs, *etc.* This renders design of ternary cocrystals more challenging. Desiraju and coworkers have carefully noted: "Making a stoichiometric ternary cocrystal from three substances that are all solids under ambient conditions is far more difficult and demands a good knowledge of the interaction preferences"⁴⁵. A proper balance between intermolecular interactions and crystallization is necessary to obtain a ternary cocrystal. Ternary cocrystals provide a viable alternative to vary the physicochemical properties where binary cocrystals fail to do so.

In 2015, A. Nangia and coworkers reported five novel ternary cocrystals of p-sulfonamide benzoic acid (SMB) with pyridine amides and lactam cofomers by exploiting supramolecular synthons of the carboxylic acid and sulfonamide

functional groups⁴⁶. Two of which are shown in Figure 12.

In their work on designing ternary cocrystals using hydrogen and halogen bonds, G.R. Desiraju and coworkers have carefully noted: "a balance of interactions and solubilities is needed to get a ternary cocrystal"⁴⁵. 2:1:1 Ternary cocrystals of 4-nitrobenzamide: diacid: 1, 4-dihalogenated benzene was designed by graded selection of hydrogen and halogen bonds (Figure 13).

CONCLUSIONS

In conclusion, cocrystallization has become a very useful tool for a crystal engineer to modulate the properties of solid state materials. Recent developments in this area such as CT cocrystals, energetic cocrystals, and ternary cocrystals are yet to be established. As of now, the results of applications of cocrystallization in pharmaceuticals are fruitful only at microscopic level. Strategies to produce cocrystals in larger scales are yet to be ventured into, in order to yield fruitful results of whatever has been achieved at microscopic level. Needless to say, in the coming year's research in this area would be more focused on scaling up processes.

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