Effect of inductive effect on the formation of cocrystals and eutectics†

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There is a growing need to understand the factors that control the formation of different yet related multi-component adducts such as cocrystals, solid solutions and eutectics from both fundamental and application perspectives. Benzoic acid and its structural analogues, having gradation in inductive force strengths, are found to serve as excellent coformers to comprehend the formation of above adducts with the antiprotozoal drug ornidazole. The combination of the drug with para-amino and -hydroxybenzoic acids resulted in cocrystals in accordance with the induction strength complementarity between the participant hydrogen bond donor–acceptor groups. The lack of adequate inductive forces for combinations with benzoic acid and other coformers was exploited to make eutectics of the drug. The isomorphous/isostructural relationship between para-amino and -hydroxybenzoic acid–drug cocrystals was utilized to make solid solutions, i.e. solid solutions of cocrystals. All in all, we successfully steered and expanded the supramolecular solid-form space of ornidazole.

Introduction

Cocrystallization,1 the art of making cocrystals for novel and desired applications, also encompasses the study of the formation of other multi-component organic solids such as solid solutions, eutectics, etc.2 However, as a phenomenon, it is less understood in terms of the factors that govern it and less studied reliably/specifically in obtaining a desired cocrystallization product. In continuation of the recent efforts to improve the overall understanding of the cause and effect and thus the success rate of cocrystallization,2a,b,3 we undertook the task of desirably making cocrystals, solid solutions, and eutectics in a series. The precedent for the formation of cocrystals is the occurrence of adequate hetero-molecular interactions in the combination, while for eutectics it is the absence thereof.2a,b The isomorphous and isostructural relationship between the components is well known to result in solid solutions of their combination;4 however, reports on solid solutions that are formed from cocrystals are sparse.5 In this study, we analyzed the inductive effect of hydrogen-bonding functional groups on the formation of cocrystals and eutectics. Although the inductive effect is more often referred to in the context of covalent reactivity of functional groups,6 the generation of dipoles and consequent attractive/repulsive forces (electrophilicity/nucleophilicity) in the molecular niche is also relevant to their supramolecular reactivity, i.e. non-covalent interactions in terms of supramolecular recognition and binding. Thus, the higher the electronegativity difference and bond polarization in a functional group, the greater will be its tendency to form electrostatic interactions with complementary functionalities. Altogether, the strength of hydrogen and halogen bonds, which are primarily electrostatic,7 depends both on the induction strength of donor and acceptor functional groups and on their complementarity. Therefore, on the basis of the relative differences in the electronic effects of hydrogen/halogen bonding groups, it should be possible to tune adduct formation given the variability in induction and electrostatics, and therefore interactions, for different combinations.

Ornidazole (abbreviated as ORL, Fig. 1) is a third-generation nitroimidazole solid drug with antiprotozoal and antibacterial effects8 and is listed in the Indian Pharmacopoeia.9 It is also marketed as a combination formulation with the fluoroquinolone antibiotic Ofloxacin to treat bacterial infections.10 Further, it is indicated for the treatment of Crohn’s disease11 and poultry infections.12 Several salts,13 a cocrystal14 and a hemihydrate15 of ornidazole were reported. ORL is highly soluble16 and relatively stable,14,17 and hence, solid-form screening with the objective of improving its physico-chemical properties is needless. However, to comprehend the cocrystallization phenomenon and thus to obtain the desired adducts,2b ORL,
with its potent hydrogen-bonding functionalities (nitro and imidazole groups), serves as an excellent model drug system. Benzoic acid and its structural analogues (Fig. 1), having gradation in inductive force strengths of their functional groups, are selected as coformers to form different adducts with ORL. Two cocrystals, two solid solutions of cocrystals, and three eutectics of the drug are obtained and the issues with respect to their formation are discussed. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) are used to establish the integrity of the new adducts.

**Results and discussion**

Cocrystallization experiments were performed by the solid-state grinding method²ᵃ,ᵇ,¹⁸ (detailed in the Experimental section). Ground products were analyzed by powder XRD and DSC to establish the cocrystal/eutectic product based on the fact that the former shows distinct PXRD patterns and melting behavior and the latter shows only a lowering in melting point compared to the parent materials²ᵃ,ᵇ. para-Amino and -hydroxybenzoic acids gave 1:1 cocrystals with ornidazole (PABA–ORL and PHBA–ORL), which were found to be isomorphous and isostructural. The isomorphous/isostructural relationship between the two cocrystals was exploited to make their solid solutions, precisely solid solutions of cocrystals (PABA:PHBA–ORL with PABA and PHBA in 0.33:0.67 and 0.46:0.54 ratios in the two structures, respectively). Crystal structures of the above adducts will be discussed later. Benzoic acid and para-methyl and -iodobenzoic acids formed eutectics with the drug as analyzed in terms of phase diagrams (discussed later). PXRD patterns of cocrystal and eutectic systems are shown in Fig. 2 and 3, respectively.

The formation of a cocrystal/eutectic for the systems is analyzed as follows. It was established for a binary system with strong hydrogen bonding groups that the primary supramolecular growth unit should be at least three molecules long for a cocrystal to form, and if the unit is restricted to a finite heterodimer, the combination makes a eutectic.²ᵇ The strong hydrogen-bonding groups in ornidazole are imidazole and nitro groups which are well-known to form imidazole–carboxylic acid¹⁹ and nitro-amine¹⁷/hydroxy²⁰/iodo²ᵇ,²³ heterosynths and can, therefore, give rise to cocrystals. On this background, benzoic acid and its structural analogues containing the aforementioned complementary functional groups were chosen (Fig. 1) by keeping the carboxylic acid group common for all coformers and varying the functionality at the para position (hydrogen, amine, hydroxyl, methyl and iodo groups) of benzoic acid. Thus, all coformers can form a carboxylic acid–imidazole heterodimeric unit when combined with ornidazole; however, depending on the induction strength complementarity between the coformer’s para-functionality and ornidazole’s nitro group, the combination can propagate as a cocrystal growth unit or remain as a eutectic dimeric unit. We devised a scheme to show the formation of a cocrystal or eutectic for a given combination (Scheme 1) based on the gradation in inductive force strengths of the coformer’s para-functionality (decreasing +I effect: \(\text{NH}_2 > \text{OH} > \text{I} > \text{CH}_3 > \text{CH}\)) with respect to ornidazole’s highly –I nitro group.

PABA and PHBA, by forming strong amine/hydroxyl–nitro interactions, respectively, in accordance with induction strength complementarity (high +I vs. high –I effect) between the groups, yield supramolecular units beyond acid–imidazole heterodimers with ORL (Scheme 1) and therefore resulted in cocrystals. BA, PMBA and PIBA gave eutectics with the drug due to mismatch between their weakly inductive donor groups (–CH, –CH₃ and –I) and the strong nitro acceptor (low +I vs. high –I effect) for viable heteromolecular interactions (as compared to PABA/PHBA) (Scheme 1). As a result, the combinations cannot propagate as a cocrystal growth unit,
but the plausibility of discrete imidazole–acid interactions in the lattice space renders them to be eutectic systems. The PIBA–ORL combination is a borderline case, wherein the facile iodo–nitro heterosynthon could have given rise to a cocrystal but manifested as a eutectic system, which shows that induction strength and electrostatic behavior have a major role in governing the formation of a cocrystal/eutectic.

X-ray crystal structures of cocrystals (PABA–ORL and PHBA–ORL) and their solid solutions (PABA:PHBA–ORL)

The 1:1 PABA–ORL and PHBA–ORL cocrystals are solved in the monoclinic space group P2₁/n with similar unit cell dimensions, suggesting that they are isomorphous and isostructural. Crystallographic parameters are given in Table 1. The crystal structures are corrugated sheets formed by antiparallel tapes of alternate PABA/PHBA and ORL molecules connected by acid–imidazole and amine/hydroxyl–nitro interactions (Fig. 4). Based on the isomorphous/isostructural features between the two cocrystals, solid solutions between them were attempted and two were successfully isolated. Understandably, both the solid solutions are isomorphous and isostructural to their parent cocrystals (Table 1 and Fig. 4). The integrity of the solid solution is established by a low R-factor achieved upon assigning both nitrogen (of the PABA amine component) and oxygen (of the PHBA hydroxyl component) at the same position in the refinement model. Consequent occupancy refinements resulted in 0.33 : 0.67 and 0.46 : 0.54 ratios of PABA : PHBA in the two solid solutions. The assignment of these occupancies is analyzed by difference Fourier maps (Fig. 5) generated with full occupancy of individual components compared with that of the amine + hydroxyl refinement model. The residual density at the individual nitrogen atom or oxygen atom (Fig. 5) validates the occupancy assignment of the amine + hydroxyl refinement model. On the other hand, not surprisingly, the thermal behavior of solid solutions is different from that of their parent cocrystals and is discussed next.

![Scheme 1](image-url)

**Scheme 1** (a) PABA and PHBA form cocrystals with ORL as the propagation of the carboxylic acid–imidazole heterodimer occur by strongly complementary amine/hydroxyl–nitro interactions. (b) BA, PIBA and PHBA lacking viable inductive donor groups to complement the strong nitro acceptor cannot make supramolecular growth units beyond finite acid–imidazole heterodimers with ORL and therefore produce eutectics.

![Fig. 3](image-url)

**Fig. 3** PXRD patterns of (a) BA–ORL, (b) PMBA–ORL and (c) PIBA–ORL combinations show no new or distinct peaks compared to those of their parent compounds, suggesting them to be either simple mixtures or eutectic mixtures. Thermal analysis established the combinations as eutectic systems.
Thermal analysis

DSC on PABA–ORL and PHBA–ORL cocrystals established them to exhibit intermediate melting points compared to their parent compounds (Fig. 6). Similarly, PABA:PHBA–ORL solid solutions exhibited intermediate melting points compared to their parent cocrystals (Fig. 6). The melting points of the cocrystals and of their solid solutions are found to be

### Table 1  Crystallographic parameters

<table>
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<tr>
<th>Compound</th>
<th>PABA–ORL</th>
<th>PHBA–ORL</th>
<th>PABA(0.46):PHBA(0.54)–ORL</th>
<th>PABA(0.33):PHBA(0.67)–ORL</th>
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<tr>
<td>Formula</td>
<td>C₁₄H₁₇N₄O₅Cl</td>
<td>C₁₄H₁₆N₃O₆Cl</td>
<td>C₁₄H₁₆.5ClN₃.₅O₅.₅</td>
<td>C₁₄H₁₆.₂₅ClN₃.₂₅O₅.₇₅</td>
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<td>a (Å)</td>
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<td>6.976(3)</td>
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<td>7.062(9)</td>
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<td>b (Å)</td>
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<td>15.246(8)</td>
<td>15.083(1)</td>
<td>15.067(1)</td>
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<td>c (Å)</td>
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<td>14.610(7)</td>
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<td>β (°)</td>
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<td>8</td>
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<td>8</td>
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<tr>
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<td>No. of unique reflections</td>
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<td>No. of reflections used</td>
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<td>R_all, R_obs</td>
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<td>0.097, 0.062</td>
<td>0.082, 0.062</td>
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<td>wR²_all, wR²_obs</td>
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* Z = Z” (no. of crystallographically non-equivalent molecules of any type in the asymmetric unit)²² × no. of independent general positions of the space group.

Fig. 4 (a) PABA–ORL and (b) PHBA–ORL isostructural cocrystals. Anti-parallel tapes of alternate PABA/PHBA and ORL molecules connected by acid–imidazole and amine/hydroxyl–nitro interactions extend into corrugated sheets through C–H⋯O and C–H⋯Cl bonds. (c) PABA(0.46):PHBA(0.54)–ORL and (d) PABA(0.33):PHBA(0.67)–ORL solid solutions are isostructural to their parent cocrystals. The amine/hydroxyl position is indicated by red circles.
proportional to those of their parent materials (Table 2). High melting PHBA (215 °C) resulted in higher melting cocrystals (PHBA–ORL 134 °C) and solid solutions (127 and 123 °C; both contain higher amounts of PHBA), and low melting PABA (187 °C) gave a lower melting cocrystal (PABA–ORL 118 °C).

Phase diagram analysis is known to simultaneously establish a given combination as a eutectic system and rule out the possibility of cocrystal formation (also in a different stoichiometric ratio). Hence, we constructed phase diagrams

### Table 2 Melting points of the compounds in °C

<table>
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<th>Coformer</th>
<th>Adduct</th>
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<tr>
<td>PABA: 187</td>
<td>PABA–ORL: 118</td>
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<tr>
<td>PHBA: 215</td>
<td>PHBA–ORL: 134</td>
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<tr>
<td>BA: 122</td>
<td>BA–ORL: 58</td>
</tr>
<tr>
<td>PMBA: 178</td>
<td>PMBA–ORL: 78</td>
</tr>
<tr>
<td>PIBA: 227</td>
<td>PIBA–ORL: 84</td>
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</table>

**Fig. 5** Difference Fourier maps and contour plots of (a) PABA(0.46):PHBA(0.54)–ORL and (b) PABA(0.33):PHBA(0.67)–ORL solid solutions show lower residual density using the amine + hydroxyl model upon refinement.
for BA/PMBA/PIBA–ORL combinations. At first, we examined the eutectic behavior of the three combinations in 1 : 1 ratio by DSC (Fig. 7). Then, different molar compositions (1 : 2, 2 : 1, 1 : 3, 3 : 1, 1 : 4 and 4 : 1) for each of the combinations were analyzed using a melting point apparatus and the solidus/liquidus events were plotted. Only a single invariant low melting point is observed in common for all the different compositions of each combination and all of the three combinations exhibited a ‘V’-type phase diagram characteristic of a eutectic system (Fig. 8). Based on the solidus–liquidus behavior monitored using the melting point apparatus, the eutectic composition of each system is estimated to be 1 : 2 for BA–ORL and 1 : 4 for PMBA–ORL and PIBA–ORL (Fig. 8). Similar to the correlation observed between the melting points of cocrystals/solid solutions and their parent materials, the melting points of the eutectics are proportional to the melting points of their parent materials (Table 2).

Conclusions

We show that the inductive effect affects the outcome of the cocrystallization experiment based on which one can tune the formation of cocrystals and eutectics. We performed cocrystallization of ornidazole with the intent of steering its supramolecular solid-form space and obtaining the desired cocrystallization products. New cocrystals and eutectics of the drug were obtained that complied with our design strategy. A less explored case of cocrystal-forming solid solutions was also reported. Melting point correlations between adducts and their parent compounds are consistent with the trends observed in the graded organic systems. In this study, we found that the relative differences in inductive force strengths of coformers can tend to vary the interaction strengths between complementary hydrogen-bonding groups, in effect leading to formation of different adducts.
Experimental section

Materials

Commercially available ornidazole (Sigma-Aldrich, Bengaluru, India) and all other compounds (Alfa Aesar, Bengaluru, India) were used without further purification. Solvents were of analytical or chromatographic grade and purchased from local suppliers.

Methods

Solid-state grinding. Compounds in molar ratios combined on the 100 mg scale were subjected to manual grinding for 15 min using a mortar and pestle. The ground materials were analyzed by powder X-ray diffraction (PXRD) and thermal techniques to ascertain the formation of the cocrystal or eutectic.

Evaporative crystallization

1:1 PABA–ORL cocrystal. Ground mixture of PABA (14 mg, 0.1 mmol) and ornidazole (22 mg, 0.1 mmol) was dissolved in 5 mL of methanol and left for slow evaporation at room temperature. Light yellow block crystals were obtained after a few days upon solvent evaporation.

1:1 PHBA–ORL cocrystal. Ground mixture of PHBA (14 mg, 0.1 mmol) and ornidazole (22 mg, 0.1 mmol) was dissolved in 5 mL of methanol and left for slow evaporation at room temperature. Light yellow block crystals were obtained after a few days upon solvent evaporation.

PABA: PHBA–ORL solid solutions. PABA and PHBA taken together (4 and 10 mg (0.025 and 0.075 mmol), respectively, and vice versa in two batches) were mixed with ornidazole (22 mg, 0.1 mmol) and dissolved in 5 mL of methanol. Light red block crystals were obtained after a few days upon solvent evaporation at room temperature.

X-ray crystallography

X-ray reflections for PABA–ORL, PHBA–ORL and PABA:PHBA–ORL were collected at 120 K using an Oxford Xcalibur Mova E diffractometer equipped with an EOS CCD detector and a micro-focus sealed tube using Mo Kα radiation (λ = 0.7107 Å). Data collection and reduction were performed using CrysAlisPro (version 1.171.36.32)24 and OLEX2 (version 1.2)25 was used to solve and refine the crystal structures. All non-hydrogen atoms were refined anisotropically. In the case of solid solutions, all hydrogen atoms were fixed by considering the riding hydrogen atom model. All hydrogen atoms on heteroatoms were located from difference Fourier maps in the case of cocrystals. All C–H atoms were fixed geometrically. The final CIF files were validated with PLATON.26

Powder X-ray diffraction

PXRD were recorded with a PANalytical X’Pert diffractometer using Cu-Kα X-radiation (λ = 1.54056 Å) at 40 kV and 30 mA. X’Pert HighScore Plus (version 1.0d)27 was used to collect

(cocrystals or eutectics). Thus, an improved understanding of the phenomenon of cocrystallization in terms of molecular recognition and binding, which is significant from both fundamental and application facets, has been attained.
and plot the diffraction patterns. Diffraction patterns were collected over the $2\theta$ range of $5^\circ$–$40^\circ$ using a step size of 0.06° $2\theta$ and a time per step of 1 s.

**Thermal analysis**

DSC was performed using a Mettler Toledo DSC 822e module with samples placed on crimped but vented aluminum pans. Thermal analysis

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**References**


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