Rapid preparation of pharmaceutical co-crystals with thermal ink-jet printing

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Abstract

Thermal ink-jet printing (TIJP) is shown to be a rapid (minutes) method with which to prepare pharmaceutical co-crystals; co-crystals were identified in all cases where the co-formers could be dissolved in water and/or water/ethanol solutions.

The bioavailability of a drug substance administered in the solid state is frequently dependent on physical form, the more thermodynamically favourable forms typically achieving lower blood plasma concentrations.[1] Identifying and isolating all possible forms early in the drug development process is thus critical to ensuring the final product is safe and efficacious yet retains an acceptable stability profile. Attention is usually focused on polymorphs orhydrates/solvates, but more recently the paradigm of pharmaceutical co-crystals (defined as a unit cell comprising at least two compounds, both of which interact through hydrogen bonding and/or any other non-covalent bonds and which are solids at room temperature and pressure[2]) has become popular. Co-crystals offer the possibility of co-formulating at least two drug substances in one crystal form, the physicochemical properties of which are more advantageous than those of either drug substance in one of their pure crystalline forms. An additional advantage is that co-crystal formation may reduce the impact of polymorphism for highly polymorphic compounds.[3]

Co-crystal screening typically proceeds by allowing the co-formers to crystallise from solution. A range of molar ratios is tested and crystallisation occurs typically over an extended time period (on the order of days). For example, Seaton *et al.*[4] grew 2 : 1 co-crystals of benzoic acid (BA) and isonicotinamide (IsoNCT) from aqueous solution over 1 month. Such time scales are not particularly convenient for early development phase screening, when a rapid assessment of likely co-crystal formation is needed. Thus, new methods for co-crystal screening, especially if they are quick and utilise small amounts of material, will always be of value.

Thermal ink-jet printing (TIJP) has potential for rapid preparation of crystal forms. The print head produces a fine aerosol (typically comprising 5–15 pL droplets) that is deposited onto a flat substrate. Desktop thermal ink-jet printers are cheap to purchase and easily modified to print pharmaceutical solutions, (the ink in the print cartridge is simply rinsed out

and replaced with the solution to be jetted).‡ The printer can print aqueous or ethanol/water solutions without adding components to modify surface tension (such additives might otherwise be incorporated into any crystal structures produced) and it is possible to print onto any substrate that will pass through the printer rollers (for instance, paper, acetate, PTFE sheet or thick aluminium foil).[5] The rapid rate of evaporation from the aerosolised droplets leads to fast crystallisation, often favouring formation of metastable forms. A further benefit is that the volume of solution needed is small (typically 0.1–0.5 mL) and so the method is particularly suited to preformulation characterisation. TIJP has been used in this way to prepare single compound crystals[6,7] but its use for isolating co-crystals is unexplored.

A range of known co-crystal formers was selected in order to assess the general utility of the method‡ (benzoic acid (BA), carbamazepine (CBZ), isonicotinamide (IsoNCT), nicotinamide (NCT), saccharin (SAC), and theophylline(THP)). The stoichiometry of the IsoNCT–BA co-crystal varies depending on solvent and molar ratio; in water an excess of IsoNCT favours the 1 : 1 complex and an excess of BA favours the 2 : 1 complex. In ethanol the 1 : 1 complex is formed, irrespective of the molar ratio dissolved.[4] In the case of the NCT–IsoNCT system, the 1 : 1 NCT–IsoNCT co-crystal is favoured whatever organic solvent is used.[8] Similarly, SAC–CBZ[9] and THP–NCT[10] have been seen to form 1 : 1 co-crystals. Additionally, a selection of benzoic acid derivatives‡ (4-aminobenzoic acid (ABZ), 4-hydroxybenzoic acid (HBZ) and methyl-4-aminobenzoate (MABZA)) were selected in order to assess the applicability of TIJP to preformulation screening of structurally related compounds.

Encouragingly, although the volume of solution jetted during a single TIJP print pass is very small, sufficient material is deposited to form distinct crystals (Fig. 1, top left, showing 2 : 1 BA–IsoNCT co-crystals), although to build up enough material for analysis several print passes were required (Fig. 1 top right and bottom left). The crystals formed after 20 print passes look slightly less defined than those after 5 passes, which is presumably an effect of repeated dissolution and recrystallisation as each print pass is completed. 10 print passes was found to give optimum results.

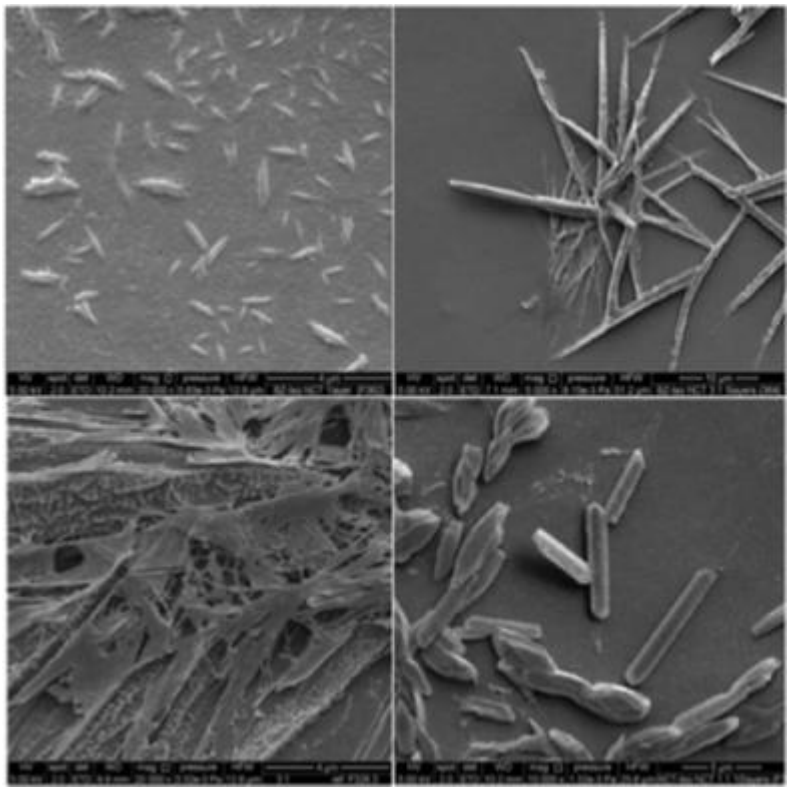

Fig. 1 SEM images of 2 : 1 BA–IsoNCT co-crystals made by TIJP after 1 (top left), 5 (top right) and 20 (bottom left) print passes. Also shown are 1 : 1 NCT–IsoNCT co-crystals produced after 10 print passes (bottom right).

Fig. 2 shows the XRPD patterns for BA, IsoNCT, 2 : 1 BA : IsoNCT crystallised from solution and 2 : 1 BA : IsoNCT prepared by TIJP. BA has a characteristic intensity maximum at 8.6° while IsoNCT has a characteristic maximum at 23.2°. Both maxima are absent from the co-crystal diffractograms, although we note that the maxima intensities are reduced for the printed samples, an effect we ascribe to their small particle size. The co-crystal samples, whether grown from solution or produced with TIJP have a characteristic set of intensity maxima (Table S1, ESI†) consistent with literature values.[11]

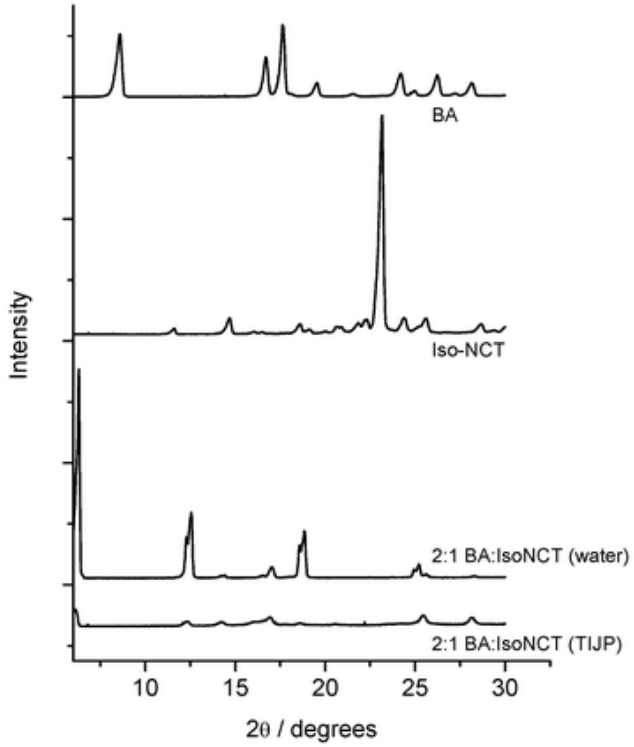

Fig. 2 XRPD data for 2 : 1 BA–IsoNCT co-crystals.

Fig. 3 shows the FTIR spectra for the same set of compounds. There are no comparable data available for comparison in the literature, but both co-crystal samples show characteristic absorption bands at 3158 and 3352 cm^{-1}, which are absent from the spectra of IsoNCT (3041 and 3326 cm^{-1}) and BA (multiple absorbance bands in this region).

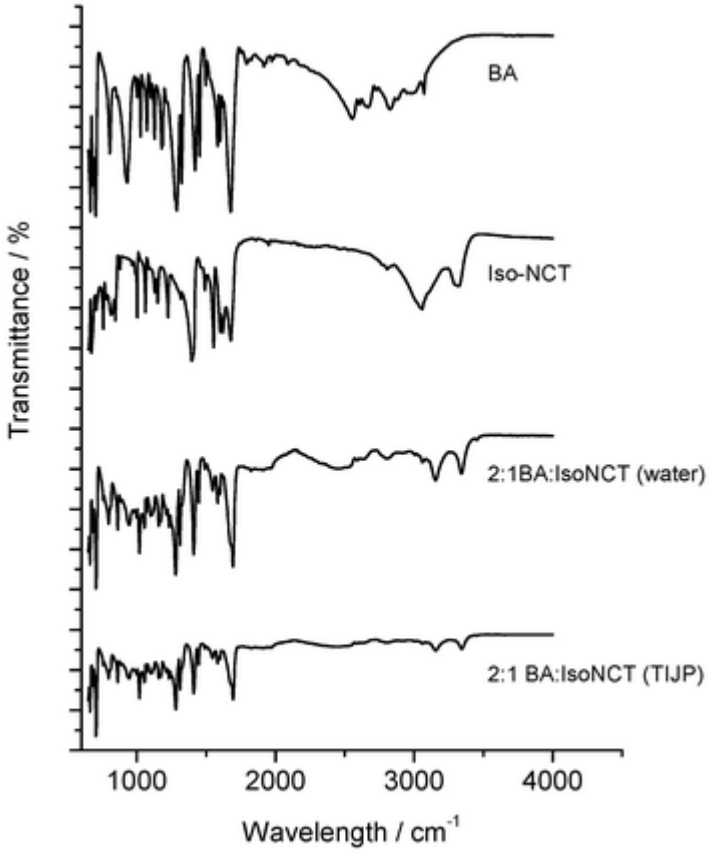

Fig. 3 FTIR spectra for 2 : 1 BA–IsoNCT co-crystals.

Fig. 4 shows the DSC thermal traces for BA, IsoNCT, 2 : 1 BA : IsoNCT crystallised from aqueous solution and BA : IsoNCT prepared by TIJP. It is apparent that the thermal behaviour of the co-crystal is distinct from that of BA or IsoNCT as pure substances. BA melts at 122.2 ± 0.5 °C (lit.[11] 122 °C); the endotherm is not a single event (there is a prolonged endothermic signal until *ca.* 155 °C), probably a result of evaporation. IsoNCT melts at 156.4 ± 0.1 °C (lit.[8]157.7 ± 0.3 °C). The 2 : 1 BA : IsoNCT co-crystal exhibits more complex behaviour. The initial endotherm corresponds to melting of the co-crystal (142.4 ± 0.2 °C, lit.[4] 143.6 ± 0.3 °C); recrystallisation to the 1 : 1 BA–IsoNCT co-crystal occurs with concomitant sublimation of the excess BA. The 1 : 1 co-crystal melts at 157.2 ± 0.6 °C. Similar thermal behaviour was noted by Seaton *et al*.[11] The melting endotherms of the printed and solution-crystallised co-crystals appear slightly different in shape, but the melting ranges are equivalent, so we ascribe this effect to differences in particle size distribution.

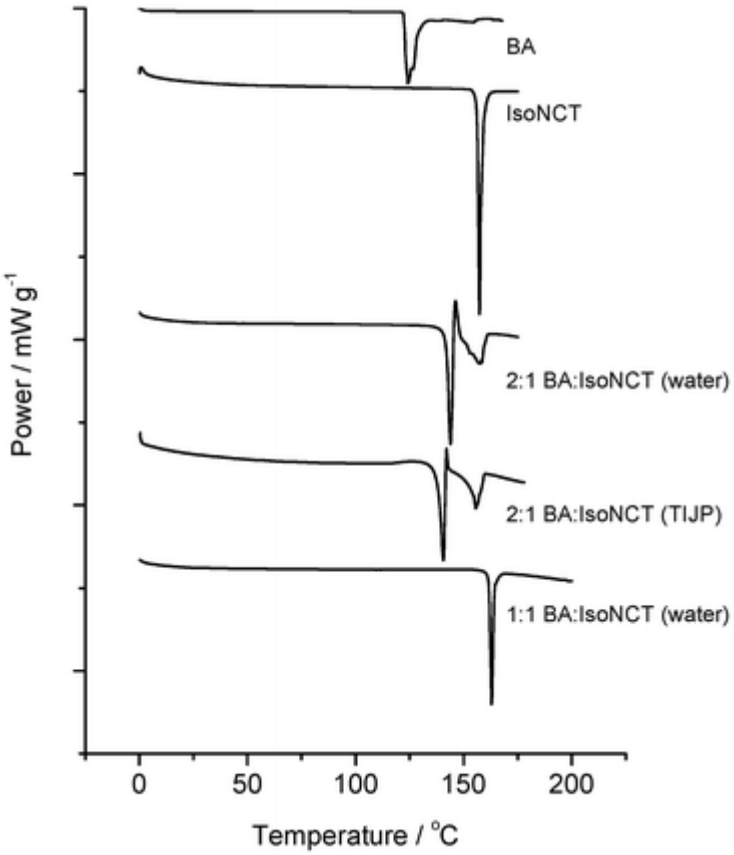

Fig. 4 DSC data for 2 : 1 BA–IsoNCT co-crystals.

To confirm the conversion of the 2 : 1 to the 1 : 1 form, Raman spectra were recorded *in situ* during the DSC run, Fig. 5. Both the 1 : 1 and 2 : 1 co-crystals have characteristic maxima at 1000 and 1017 cm^{-1}; however, for the 1 : 1 form the 1017 cm^{-1} peak is largest and for the 2 : 1 form the 1000 cm^{-1} peak is largest. It can be seen that at 130 °C the sample is in the 2 : 1 form, but that by 150 °C conversion to the 1 : 1 form has occurred.

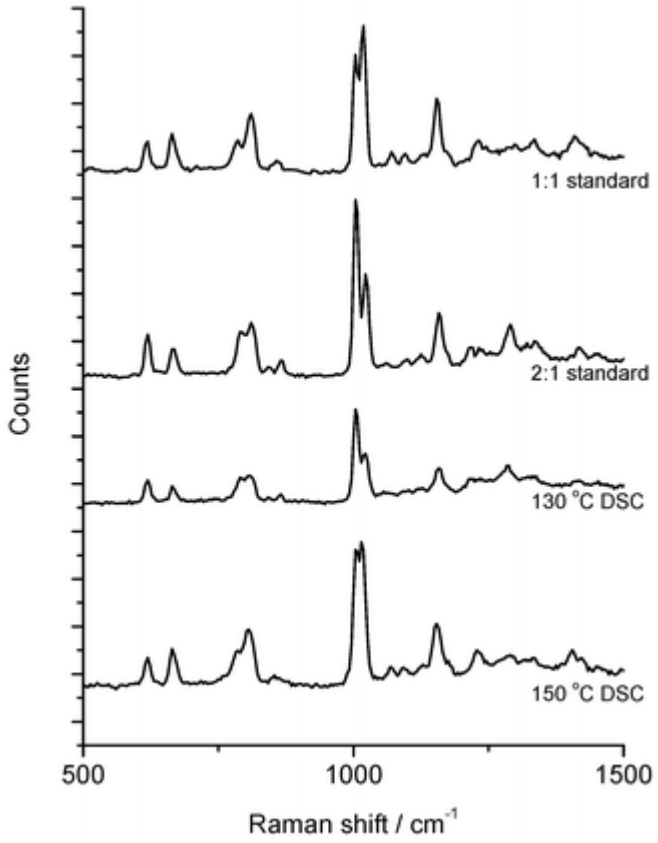

Fig. 5 Raman spectra for 2 : 1 and 1 : 1 BA–IsoNCT co-crystals as a function of temperature.

One limitation of TIJP, in terms of its application as a high-throughput preformulation screen, is that to investigate the effect of stoichiometry requires preparation and jetting of multiple solutions. In principle, the effect of stoichiometry could be investigated using a tricolour print cartridge, with solutions of individual co-formers in each cartridge. Judicious selection of the RGB values of the colour to be printed would then in principle allow printing of multiple solution ratios. However, our experience of HP systems is that the different cartridge sections produce droplets of different sizes and these are not controllable by the user. Hence, it would require extensive experimentation to determine the RGB values required to print specific volume ratios. It is also a requirement that the droplets coalesce prior to evaporation. This means investigation of potential stoichiometry is difficult at best with desktop printers but may be more practicable with a bespoke system. However, this limitation also applies to all current co-crystal screening methods.

In their study, Báthori *et al.*[8] did not try to crystallise NCT–IsoNCT from water so reference co-crystals were prepared from both water and ethanol‡. The XRPD patterns for all NCT–IsoNCT co-crystals are given in Fig. 6. NCT has a characteristic intensity maximum at 14.7° while IsoNCT has a characteristic maximum at 23.2°. Both maxima are absent from the co-crystal patterns. The co-crystal samples have a characteristic set of intensity maxima (Table S2, ESI†), although in this case no literature values are available for comparison.

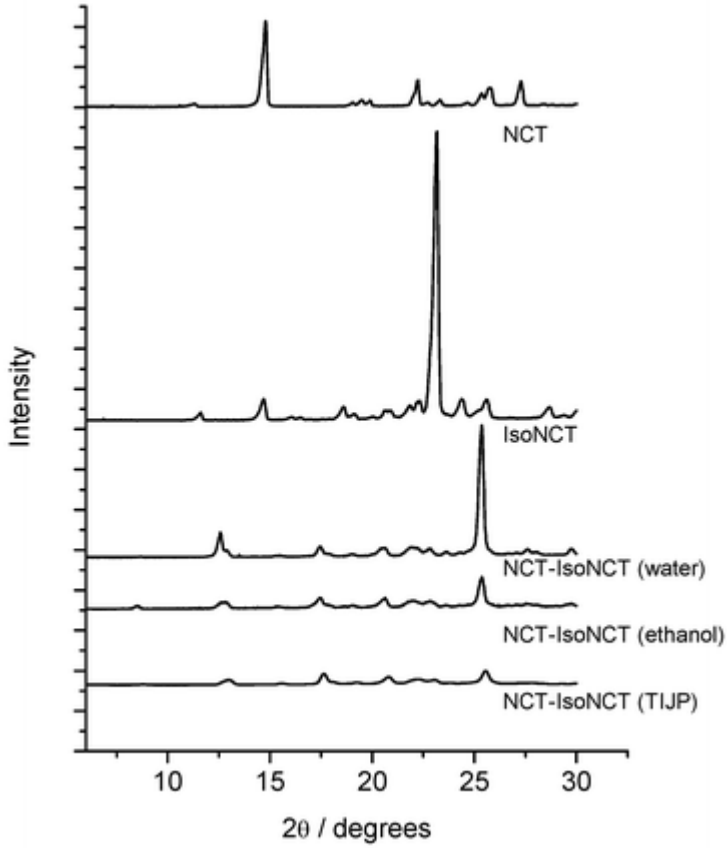

Fig. 6 XRPD data for 1 : 1 NCT–IsoNCT co-crystals.

The FTIR spectra are given in Fig. 7. Co-crystal samples show characteristic absorption maxima at 3020, 3167 and 3370 cm^{-1}, which are not present in the spectra of IsoNCT (3041 and 3326 cm^{-1}) and NCT (3151 and 3354 cm^{-1}). The DSC thermal traces (Fig. 8) are much simpler in this case, the 1 : 1 co-crystal melting at 120.5–121.0 °C (lit.[8] 121.0 °C).

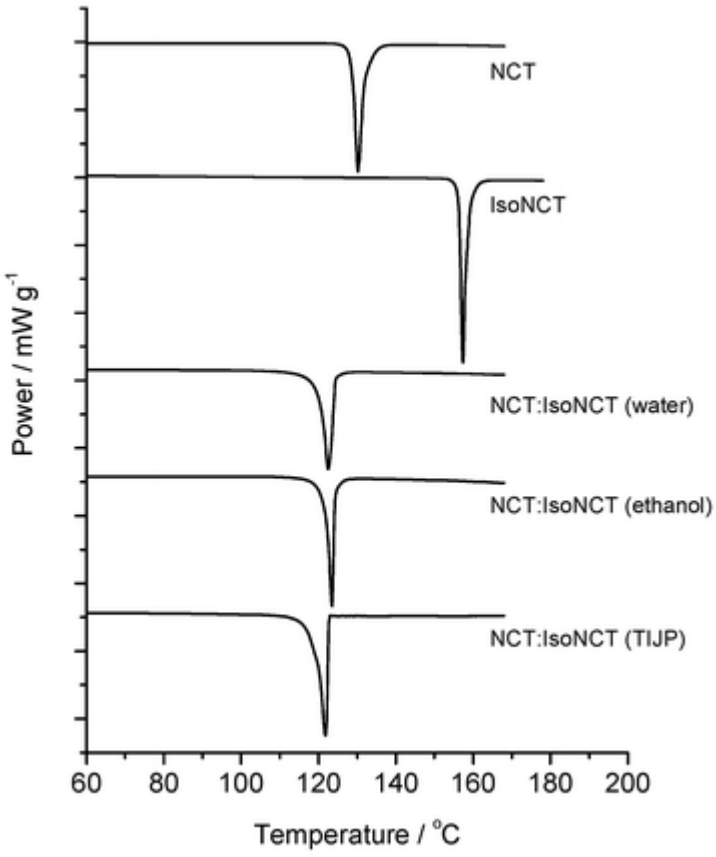

Fig. 7 FTIR spectra for 1 : 1 NCT–IsoNCT co-crystals.

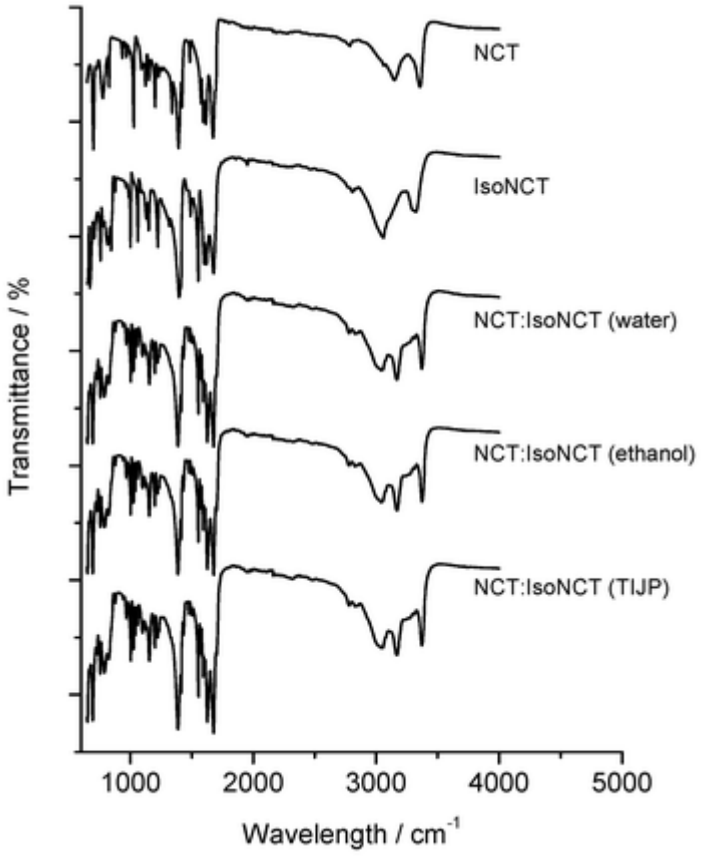

Fig. 8 DSC data for 1 : 1 NCT–IsoNCT co-crystals.

Having determined that TIJP is capable of producing co-crystals comparable to solvent precipitation methods, we printed a range of benzoic acid derivatives with Iso–NCT as well as the SAC–CBZ and THP–NCT systems and usedDSC and FTIR data to confirm co-crystal formation. DSC data are shown in Fig. 9. Melting point data are given in Table S3, ESI.† Characteristic FTIR maxima are given in Table S4, ESI.† It is apparent that all admixtures resulted in co-crystals being produced. The DSC data for systems including HBZ show degradation after the melt; similar degradation is seen for HBZ alone (data not shown). Similarly, ABZ has a tendency to sublime, which explains the broad endotherms after the melt in the ABZ systems. Interestingly, the CBZ–SAC system shows a glass transition at *ca.* 48 °C, followed by an exothermic crystallisation. The reported glass transition temperature of CBZ is 59 °C,[12] so it may be the case that SAC is acting as a plasticiser. However, it is clear in this case that the rapid evaporation rate of the jetted droplets has produced some amorphous material. Since the area of crystallisation (22.7 J g^{-1}) is lower than the enthalpy of the melt (108.3 J g^{-1}), it is likely that the material was rendered partially amorphous (*ca.* 21%) during printing.

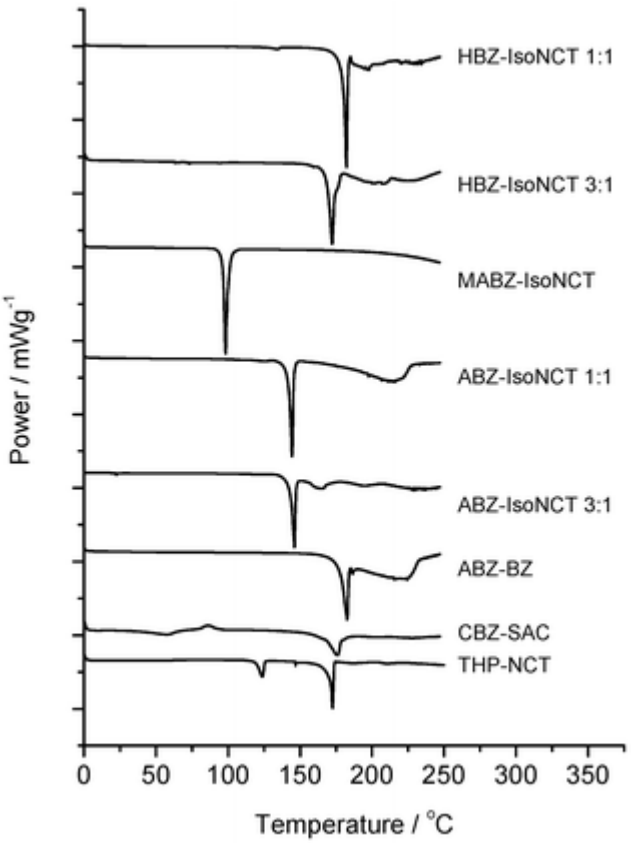

Fig. 9 DSC data for various co-crystals prepared with TIJP.

In addition to the benzoic acid derivatives listed in Tables S3 and S4, we also tried 4-methyl benzoic acid and butyl-4-hydroxy benzoic acid, but these were insoluble at 70 °C. This highlights another potential drawback of the technique, which is that the co-formers need good aqueous or ethanolic solubility. The plastic ink cartridge is not particularly resistant to other organic solvents, although this is a limitation that could be overcome by switching to a printer constructed from metal.

Conclusions

TIJP has been shown to be a rapid, cheap and easy method to prepare pharmaceutical co-crystals. It is possible to jet aqueous solutions without the need for surface tension or viscosity modifying agents. The small droplet size (5–15 pL) leads to rapid evaporation of the solvent and crystallisation of any solutes, which in turn favours isolation of metastable forms. One print pass is sufficient to cause crystal growth, but multiple print passes (at least 10) are preferable to produce sufficient material for analytical analysis. The technique would appear to offer potential for early-phase pharmaceutical co-crystal screening.

Acknowledgements

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Notes and references

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Footnotes

Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ce26519b

‡ 4-Aminobenzoic acid (ABZ), 4-hydroxybenzoic acid (HBZ), methyl-4-aminobenzoate (MABZA), 4-methylbenzoic acid (MBZ), butyl-4-hydroxybenzoate (BHB), saccharin (SAC), theophylline (THP), Carbamazepine (CBZ), Isonicotinamide (IsoNCT) and Nicotinamide (NCT) were purchased from Sigma–Aldrich (Dorset, UK) and used as received. Preparation of co-crystals from solution: aqueous solutions of BA and IsoNCT (3[thin space (1/6-em)]:[thin space (1/6-em)]1 molar ratio) were prepared by heating to 70 °C before leaving to cool to ambient temperature.4 Co-crystals grew over 30 days and were harvested by vacuum filtration. Aqueous and ethanolic8 solutions of NCT and IsoNCT (1[thin space (1/6-em)]:[thin space (1/6-em)]1 molar ratio) were prepared and stored at 40 °C. Co-crystals grew overnight and were harvested by filtration. Preparation of co-crystals by TIJP: all solutions were prepared by dissolving the appropriate masses of co-crystal formers in water or water/ethanol at 70 °C. Solutions were loaded into the printer cartridge at 70 °C and printed using a standard Hewlett-Packard HP460 Deskjet printer. The ink in the print cartridge (HP343, C8765EE, droplet volume 5 pL) was removed by cutting off the cartridge lid with a scalpel and removing the foam pads, followed by rinsing with copious volumes of distilled water followed by absolute ethanol. The cartridge was then refilled with the appropriate aqueous solution before being refitted into the carriage in the printer. The design of the printer carriage is such that the lid of the cartridge is held in place without the need for any further fixings or adhesive. Printing was achieved by creating (and printing) a black (RGB code 0, 0, 0) template in Word (Microsoft Inc, USA). Solutions were jetted onto acetate film (Ryman Ltd, UK). Between each print run, the acetate film was held in an oven (40 °C, 2 min) to ensure removal of any residual solvent. Printed co-crystal samples were removed from the acetate film with a spatula and stored in a desiccator over silica gel for at least 24 h prior to analysis to ensure removal of any residual solvent. SEM images were collected with a Quanta 200 FEG (FEI, Nether-lands). Samples were prepared by sputter-coating with gold for 3 min (Quorum model Q150). XRPD data were collected with a PW3830 diffractometer (Philips, Netherlands) operated with Cu Kalpha radiation (λ = 1.540598 Å) at 45 kV and 30 mA. Scanning was performed from 5° to 30° 2θ at 0.02° 2θ step size and 2.85 s per step. XPert data viewer software (version 1.0c, PANalytical B.V, Netherlands) was used to analyse the data. FTIR spectra were collected with a Spectrum 100 (PerkinElmer Ltd, UK) between 4000 to 650 cm−1 at ambient conditions. Spectra were analysed with Spectrum Express (application version 1.02.00.0014). DSC data were recorded with a Q2000 DSC (TA Instruments LLC, USA) at a scan rate of 10 °C min−1. Samples were loaded in crimped aluminium Tzero pans and an empty pan was used as a reference. The instrument was calibrated prior to use with a certified reference sample of indium. In-situ Raman spectra were recorded with a RIAS portable spectrometer (Renishaw PLC, UK) operated with 785 nm laser excitation and connected to the DSC via a fibre optic cable. Samples were loaded in open Tzero aluminium pans.