Pharm Res (2010) 27:2725–2733
DOI 10.1007/s11095-010-0273-9

RESEARCH PAPER

Cocrystalization and Simultaneous Agglomeration Using Hot Melt Extrusion

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Received: 27 March 2010 / Accepted: 9 September 2010 / Published online: 25 September 2010
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ABSTRACT

Purpose To explore hot melt extrusion (HME) as a scalable, solvent-free, continuous technology to design cocrystals in agglomerated form.

Methods Cocrystal agglomerates of ibuprofen and nicotinamide in 1:1 ratio were produced using HME at different barrel temperature profiles, screw speeds, and screw configurations. Product was characterized for crystallinity by XRPD and DSC, while the morphology was determined by SEM. Dissolution rate and tabletting properties were compared with ibuprofen.

Results Process parameters significantly affected the extent of cocrystallization which improved with temperature, applied shear and residence time. Processing above eutectic point was required for cocrystallization to occur, and it improved with mixing intensity by changing screw configuration. Product was in the form of spherical agglomerates, which showed directly compressible nature with enhanced dissolution rate compared to ibuprofen. This marks an important advantage over the conventional techniques, as it negates the need for further size modification steps.

Conclusions A single-step, scalable, solvent-free, continuous cocrystallization and agglomeration technology was developed using HME, offering flexibility for tailoring the cocrystal purity. HME being an established technology readily addresses the regulatory demand of quality by design (QbD) and process analytical technology (PAT), offering high potential for pharmaceuticals.

KEY WORDS cocrystals · hot melt extrusion · ibuprofen · thermo-mechanical process

ABBREVIATIONS

DSC	differential scanning calorimetry
HME	hot melt extrusion
Ibu-Nic cocrystal	ibuprofen-nicotinamide 1:1 cocrystal
NIR	near infra red
PAT	process analytical technology
PM	physical mixture of ibuprofen and nicotinamide
Py	mean yield pressure
QbD	quality by design
SEM	scanning electron microscopy
XRPD	X-ray powder diffractometry

INTRODUCTION

Cocrystallization is now recognized as an important method to achieve crystalline forms of molecules where alternatives to polymorphs or salts are desired. Formation of cocrystals provides a route to achieving enhanced material properties and is of particular interest in the pharmaceutical field. Cocrystals have already been proven useful in improving the stability (1), solubility (2, 3), dissolution rate (4), bioavailability (5), and mechanical properties (6, 7) of APIs. Pharmaceutical cocrystals are gaining increased interest as they are not restricted to pharmaceuticals which have an ionisable centre, as in the case of salts, and because a significant number of biologically non-toxic cocrystallizing molecules are available.

The discovery of cocrystals resulted from the mapping of two-component phase diagrams and the associated crystallization from the melt phase. Subsequently, various methods of forming cocrystals have been demonstrated, including slow evaporation (8), solution crystallization (9), solid-state

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grinding (10, 11) (dry grinding and grinding with solvent drop addition), slurry conversions (12) and sonocrystallization (13, 14). Solution-based methods often require a large amount of solvents and experimental conditions to be tested and can suffer from the risk of crystallizing the single component phases. Scale-up of this process is also challenging. Co-grinding of potential cocrystal formers either as dry solids or in the presence of small amounts of solvent has gained popularity on two accounts: first, it requires less or no solvent and is therefore viewed as environmentally friendly, and second, because it is well suited to use as a screening aid to generate novel cocrystalline phases not possible by crystallization from solution.

Various mechanisms have been suggested to explain cocrystallization by solid-state grinding. Kuroda *et al.* suggested that shearing and molecular diffusion processes occur during grinding to generate a different adduct structure to that recovered from solution (15), while Rastogi *et al.* suggested vapor diffusion as a mass transfer mechanism which occurs during solid-state grinding (16). Rothenberg and coworkers presented evidence suggesting that the formation of a liquid phase in the binary phase diagram is essential to facilitate intermolecular contacts and mass transfer (17). Chadwick *et al.* studied cocrystal formation at ambient temperature and highlighted the significance of an intermediate metastable eutectic liquid phase which facilitates the intermolecular mass transfer resulting in cocrystallization (18). At the same time, the shear induced by grinding acts as a driver to create high interfacial area between the starting material solid phases. They concluded that systems having a eutectic temperature below ambient will be susceptible to cocrystal formation by dry grinding. In systems having a eutectic temperature above ambient, the addition of a suitable solvent has assisted the formation of cocrystals. Shan *et al.* further explained solvent drop grinding on the basis of additional degrees of freedom, enhancement of molecular collisions and formation of cocrystal seeds (19).

Slow evaporation and grinding are the two most common techniques used to promote cocrystal growth. However, these approaches possess inherent scale-up limitations and are better suited to small-scale screening operations (20, 21). Relatively few reports describe attempts to develop scalable cocrystallization techniques; these have included the use of supercritical fluid (22, 23) and ultrasound (13). A more suitable approach is required to make cocrystallization feasible on a manufacturing scale. We have invented a scalable HME technology to produce pharmaceutical cocrystals (24) using a combination of controlled heat and shear deformation. A similar technique has recently been reported to form cocrystals of caffeine and AMG 517 (25). HME is a widely used processing technology in the polymer and food industries and has been recently demonstrated to be a viable method to prepare several types of dosage forms and drug delivery systems (26, 27). Since its introduction into the pharmaceutical industry, use of HME has grown steadily due to advantages such as being a continuous, single-step, solvent-free and readily scalable process. The novelty of this work is development of a solvent-free continuous process, which we demonstrate here using a well-studied model pair, ibuprofen-nicotinamide, also known to form a eutectic.

MATERIALS AND METHODS

Materials

Ibuprofen was purchased from Jay Radhe Sales (Ahmadabad, India) and nicotinamide from Sigma Aldrich. All other chemicals and solvents were of analytical grade. Ibuprofen was micronized in a spiral jet mill (FPS, Italy) using grinding pressure of 3 bar and injector pressure of 8 bar. The micronized material (D_{50}=7 μm and polydispersity=2.41) was used for comparative evaluation.

Cocrystallization in Hot Melt Extruder

Ibuprofen (103.15 gm) and nicotinamide (61.6 gm) in 1:1 molar ratios were blended in a Turbula mixer for 10 min. Cocrystallization was carried out using a 16 mm co-rotating twin screw extruder (Pharmalab, Thermo Scientific, UK) having length-to-diameter ratio of 40:1, with three different extruder screw configurations. The extruder was operated without a die. Powdered feedstock material was fed into the extruder at a rate of 0.2 kg/h using a gravimetric twin-screw feeder (Brabender, Germany) at three different extruder barrel temperature profiles (T70, T80 and T90), as shown in Table I, at screw speeds of 20, 30 and 40 rpm. Extruder screw configurations were selected to achieve a range of shearing intensities (Table II and Fig. 1).

Differential Scanning Calorimetry (DSC)

Thermal profiles were generated in the range of 25–150°C using a TA instruments Q2000 DSC with RCS90 cooling unit. Temperature calibration was performed using an indium metal standard supplied with the instrument at the respective heating rate. Accurately weighed samples (1.5–2.5 mg) were placed in aluminium pans using similar empty pans as a reference. A heating rate of $10°C\,min^{-1}$ was employed, and an inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

X-ray Powder Diffraction (XRPD)

Crystallinity of extruded material was assessed by X-ray powder diffraction using a Bruker D8 diffractometer

Table I Temperature Profiles (°C) Across the Different Zones of the Extruder Barrel

Code	Zone 10	Zone 9	Zone 8	Zone 7	Zone 6	Zone 5	Zone 4	Zone 3	Zone 2
T70	60	70	70	70	65	60	45	35	25
T80	70	80	80	80	75	70	50	40	25
T90	80	80	90	90	80	75	50	40	25

(wavelength of X-rays 0.154 nm Cu source, voltage 40 kV, and filament emission 40 mA). Samples were scanned from 2 to 30° (2θ) using a 0.01° step width and a 1 s time count. The receiving slit was 1° and the scatter slit was 0.2°.

Scanning Electron Microscopy (SEM)

Samples were mounted on aluminium pin-stubs (Agar Scientific, Stansted, U.K.) for SEM using self-adhesive carbon mounts (Agar Scientific). The mounted samples were examined using an FEI Quanta 400 Scanning Electron Microscope (Cambridge, U.K.) in high vacuum operated at an acceleration voltage of 20 kV. XTM Microscope control software version 2.3 was used for imaging.

Compaction and Compressibility Study

Compressibility studies were carried out using a compaction press (Caleva Process Solutions Ltd., UK) fitted with a 10 mm diameter flat-faced punch. The die wall was cleaned with acetone and pre-lubricated with magnesium stearate before each compression. Three-hundred mg samples were hand filled into the die. Compression and decompression was operated at 100 mm/min, dwell load level 5,000 N, dwell time 0.1 s, and the volume changes against compression force were recorded. The thickness of tablets was measured using a thickness gauge (Mitutoyo, Japan), and the hardness was tested using a hardness tester (Schleuniger-4 M, Copley).

In Vitro Drug Release

Dissolution studies were performed using a USP 26 type II dissolution test apparatus (Copley Scientific, Nottingham, UK). Samples were placed in a dissolution vessel containing 900 ml deionized water maintained at 37±0.5°C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After centrifugation, filtration through 0.45 μm filter paper and dilution, concentration of ibuprofen was determined by HPLC, and data were analysed by PCP-Disso software V3, Poona College of Pharmacy, Pune, India

The HPLC system specifications were as follows: Waters Alliance separation module 2695 equipped with automatic injector and UV-visible detector (Waters 2487 Dual alpha absorbance detector). Chromatographic separation was achieved using hypersil GOLD, RP C18, 250×4.6 mm, 5 μm analytical column (Thermo Electron Corporation, USA). The mobile phase consisting of water (pH 2.5) and acetonitrile (50:50) was passed through 0.45 μm membrane filter and degassed by ultrasonication. The flow rate was

Table II Screw Configurations Ordered from Feed to Discharge

Conf A		Conf B		Conf C	
Length (D)[a]	Element type	Length (D)[a]	Element type	Length (D)[a]	Element type
38.5	Forward conveying	11	Forward conveying	19	Forward conveying
1.5	Discharge	1	30° forward mixing	1	30° forward mixing
		1	60° forward mixing	1	60° forward mixing
		1	90° mixing	1	90° mixing
		6	Forward conveying	2	Forward conveying
		1.5	60° forward mixing	0.5	0° mixing
		8	Forward conveying	1	Forward conveying
		1	60° forward mixing	0.5	0° mixing
		2	90° forward mixing	2	Forward conveying
		6	Forward conveying	0.5	0° mixing
		1.5	Discharge	1	Forward conveying
				0.5	0° mixing
				2	90° mixing
				6.5	Forward conveying
				1.5	Discharge

[a] In terms of number of diameters, 1D = 16 mm

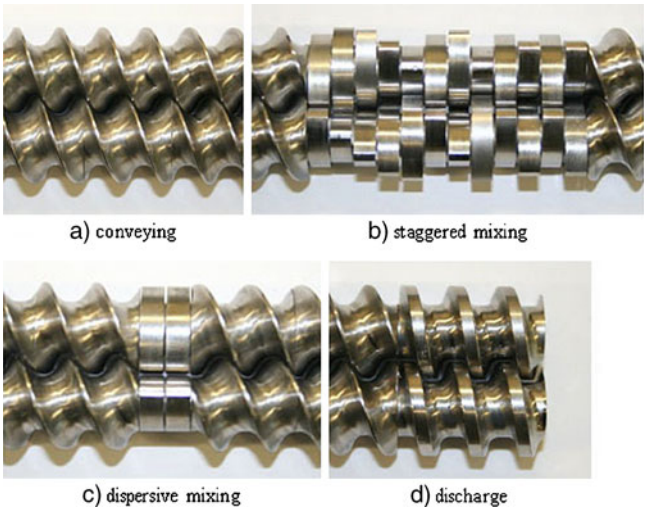

Fig. 1 Photographs of screw elements used in conf A, B and C.

maintained at 1.5 mL/min, and the measurements were made at 214 nm. The column temperature was maintained at 30°C throughout the measurement. Data acquisition and analysis was carried out using MassLynx software, version 4.0. The calibration curve of ibuprofen covered a concentration range of 0–20 μg/ml.

RESULTS AND DISCUSSION

Ibuprofen and nicotinamide were subjected to thermal screening by DSC (Fig. 2). Ibuprofen exhibited a single endothermic peak at 79°C, while nicotinamide yielded a broad melting endotherm with onset at 128°C. Interestingly, the physical mixture of ibuprofen and nicotinamide in a 1:1 ratio (PM) showed an endothermic peak at 74°C followed by another melting endotherm at 90°C. The first endotherm could be attributed to the eutectic temperature of the mixture, and the latter indicates melting point of the cocrystal. This is in confirmation with a report by Berry *et al.*, who used the Kofler method to screen cocrystals and reported the melting point of ibuprofen-nicotinamide 1:1 cocrystal (Ibu-Nic cocrystal) to be 89.5°C (28). The observation is also in accordance with the report by Lu *et al.*, who have demonstrated that cocrystals can be formed in DSC if the physical mixture is heated past the eutectic melting temperature (29). This thermal method can serve as a simple and efficient method for cocrystal screening. However, scale-up or even production of enough samples for complete characterization is not possible.

The physical mixture of ibuprofen and nicotinamide was subjected to thermo-mechanical action within a continuous HME process. Since the eutectic melts at 74°C, physical mixtures were extruded above and below this temperature using a co-rotating twin screw extruder with different screw configurations (Conf A, Conf B and Conf C) to assess the effect of mixing and shear on cocrystal yield or purity. Conf A consisted of purely forward conveying elements with a metering element at the screw tips, and provided a minimum level of mixing intensity. Detailed screw configurations are displayed in Table II. Conf B provided intermediate levels of distributive mixing and is typical of the type of screw configurations used in conventional polymer compounding (mixing) operations. Distributive mixing (mixing by rearranging the flow path) as shown in Fig. 1a, was achieved here using a series of bi-lobal mixing paddles (of length equal to a quarter of the extruder screw diameter) arranged at specified angles from the preceding element: 30, 60 or 90°. These paddles are arranged in the forward conveying direction, i.e. 30° mixing paddles provide the most forward conveying, 60° provide less, and 90° provide zero forward conveying action and purely mixing (Fig. 1b). Conf C provided the highest levels of distributive and dispersive mixing. Dispersive mixing (high shearing action to break down agglomerates), as shown in Fig. 1c, was achieved by positioning pairs of mixing paddles together at the same orientation, i.e. without a staggering angle. This effectively created a single wide mixing paddle which forced more material to pass over the high shearing tips of the paddles.

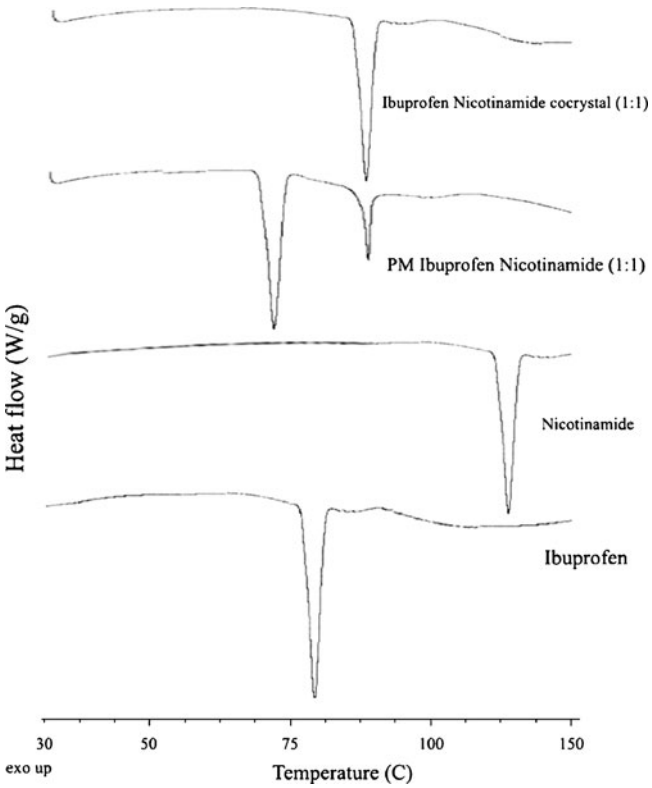

Fig. 2 DSC thermograms of ibuprofen, nicotinamide, PM Ibu-Nic (1:1) and Ibu-Nic (1:1) cocrystal.

The effect of process variables on cocrystal formation was monitored by comparing the XRPD patterns of ibuprofen, PM and the extruded product. The XRPD patterns of ibuprofen and PM displayed a prominent peak at 2θ=6° characteristic of ibuprofen. This peak was used to monitor the residual ibuprofen content in the extruded product, and the cocrystal formation was confirmed by monitoring the peak at 2θ=3.1°, characteristic of the Ibu-Nic cocrystal (28). XRPD patterns (Fig. 3) of the batches produced at T70 showed the appearance of a small new peak at 2θ=3.1°, but a prominent peak at 2θ=6 indicated large proportion of unreacted ibuprofen in the final product. At a set temperature of 70°C, cocrystal formation was found to be independent of screw geometry, as no increase was observed in the intensity of peak at 2θ=3.1° even after using the high intensity screw configurations.

XRPD patterns (Figs. 4, 5 and 6) of the batches produced at 80°C (T80) and 90°C (T90) showed the appearance of a prominent cocrystal peak with an associated suppression of the ibuprofen peak, indicating a dramatic improvement in cocrystal content. The effect of residence time and screw geometry was subsequently studied in further detail at these temperatures. XRPD patterns of batches produced using Conf A at T80 and T90

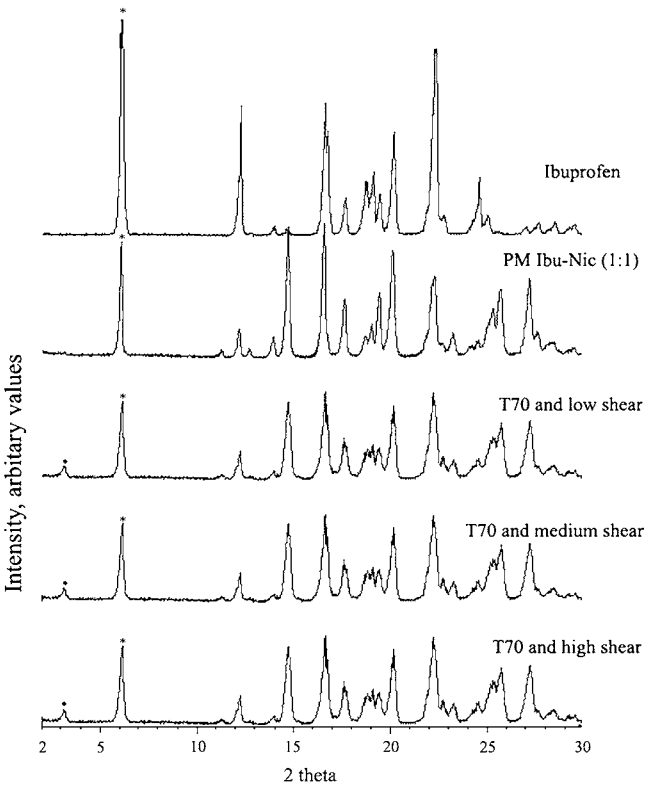

Fig. 3 XRPD patterns of ibuprofen, PM Ibu-Nic (1:1) and cocrystals prepared by HME with different shears at T70. (*) indicates peak characteristic of ibuprofen, and (•) indicates peak characteristic of Ibu-Nic (1:1) cocrystal.

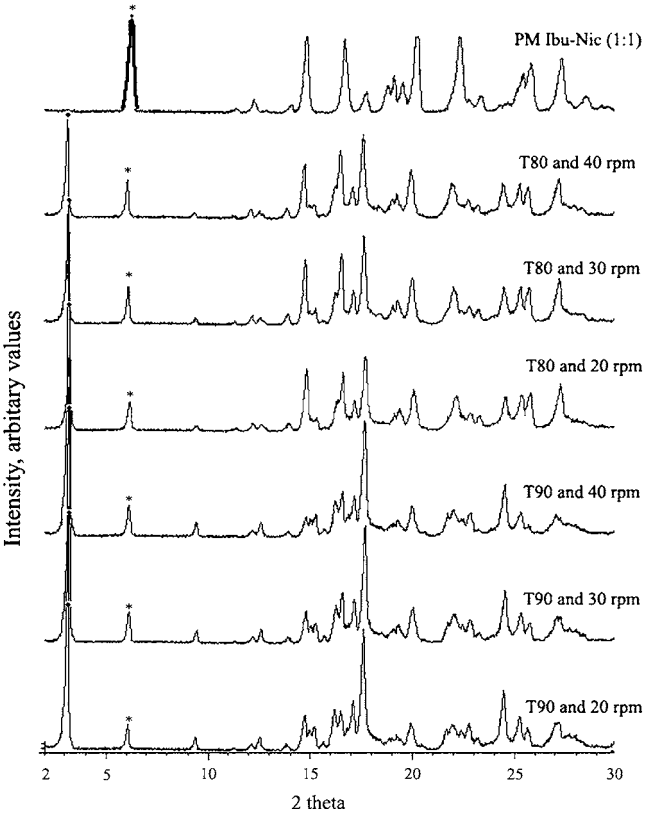

Fig. 4 XRPD patterns of PM Ibu-Nic (1:1) and cocrystals prepared by mechano-thermal process with conf A (low shear). (*) indicates peak characteristic of ibuprofen, and (•) indicates peak characteristic of Ibu-Nic (1:1) cocrystal.

with different screw speeds are shown in Fig. 4. At both temperatures the intensity of the cocrystal peak increased with decreasing screw speed. Cocrystal peak intensities were higher for batches produced at T90 than for those produced at T80. In all cases, the increase in the cocrystal peak intensity corresponded to a decrease in intensity of the ibuprofen peak. Increasing the shear intensity applied by the screws using Conf B at T80 and T90 led to notably higher cocrystal purity (Fig. 5) than for batches produced using Conf A (low shear). Increasing the residence time and operating temperature at this level of shear showed improvement in the cocrystal peak intensity. Batches produced using Conf C (high shear) displayed the highest cocrystal purity with small or no peaks corresponding to ibuprofen (Fig. 6). Further improvements in intensity of cocrystal peak were achieved by extruding at low screw speeds and higher temperatures. The ibuprofen peak disappeared completely when processed at 20 rpm and T90, indicating almost complete conversion of the ibuprofen into cocrystal.

In order to understand the effect of process variables, the ratio of the peak intensities at 2θ=6° and 2θ=3.1° was used as an indicator of cocrystal purity. This ratio is plotted for all

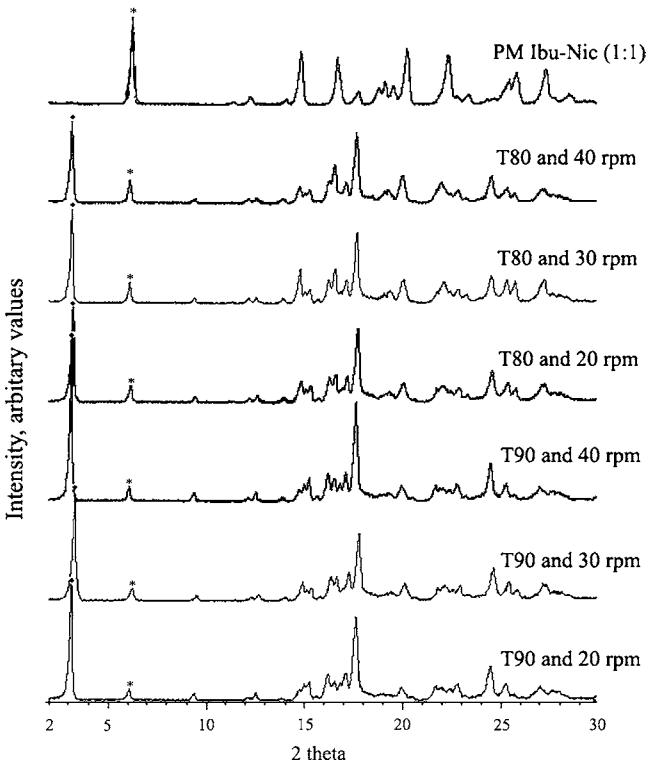

Fig. 5 XRPD patterns of PM Ibu-Nic (1:1) and cocrystals prepared by mechano-thermal process with conf B (Medium shear). (*) indicates peak characteristic of ibuprofen, and (•) indicates peak characteristic of Ibu-Nic (1:1) cocrystal.

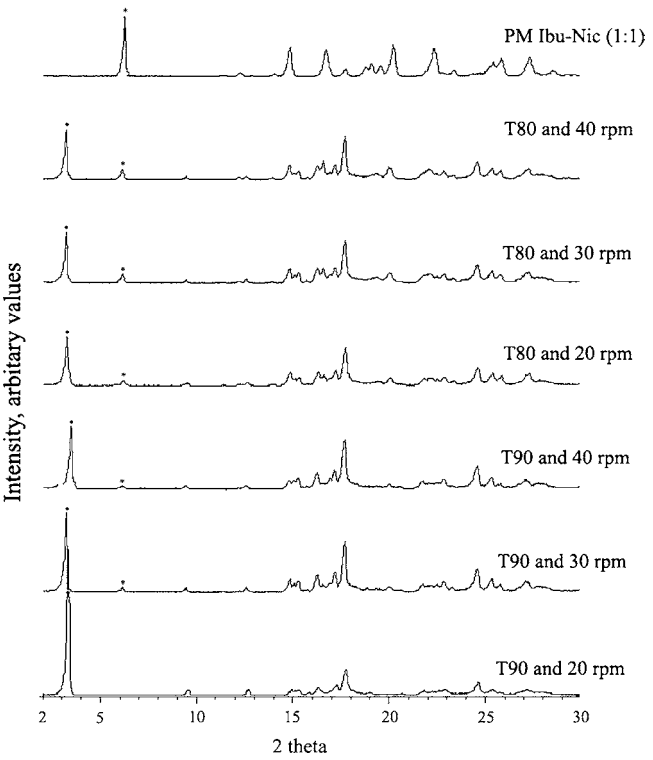

Fig. 6 XRPD patterns of PM Ibu-Nic (1:1) and cocrystals prepared by mechano-thermal process with conf C (high shear). (*) indicates peak characteristic of ibuprofen, and (•) indicates peak characteristic of Ibu-Nic (1:1) cocrystal.

experimental conditions in Fig. 7. Batches produced at 70°C (below the eutectic temperature) showed only traces of cocrystal with the majority of unreacted components. This indicates that the processing temperature was insufficient to affect mass transfer, which is essential in cocrystal formation. Chadwick *et al.* have demonstrated that the systems having eutectic temperatures below room temperature will be susceptible to cocrystal formation by dry grinding (18). However, they further suggested that for systems in which this temperature is above room temperature, cocrystallization will possibly require the addition of small amounts of solvent. We have demonstrated that elevating process temperature above the eutectic temperature, rather than adding solvents, can generate an intermediate melt phase for mass transfer. Above the eutectic temperature, the process of cocystallization proceeds by melting of mixture, which facilitates mass transfer due to additional degrees of freedom, enhancement of molecular collisions leading to nucleation, formation of cocrystal seeds and subsequent cocrystal growth. Cocrystal purity was found to improve with increasing processing temperature from T80 to T90 for almost all batches, even though both temperature profiles are above eutectic temperature. This can be explained by viscosity of the melt decreasing at higher processing temperatures leading to an improved interaction and mass transfer.

Increase in mixing and shear intensity improved cocrystal yield (Conf A < Conf B < Conf C). Higher intensity screw geometries achieve a greater degree of mixing, leading to an increased exposure of fresh surfaces for interaction. Increased shear induced by the screws expedites the process of mass transfer, enabling rapid cocrystallization while the material passes through the extruder. Conf A (with purely conveying elements and no mixing zones) imparted the lowest level of shear resulting in the low purity cocrystals. Conf B, with distributive mixing zones (intermediate levels of shear),

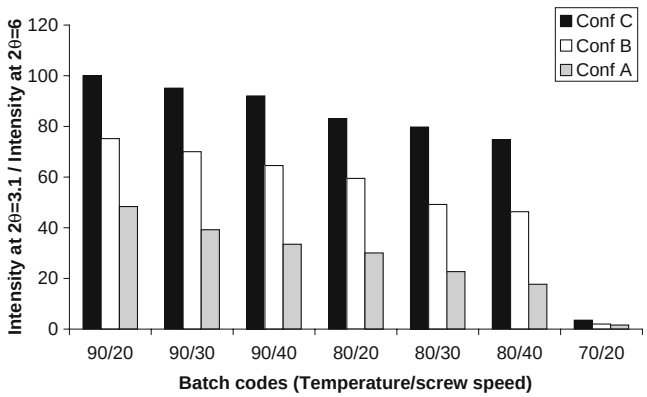

Fig. 7 Effect of barrel temperature and screw speed on extent of cocrystallization.

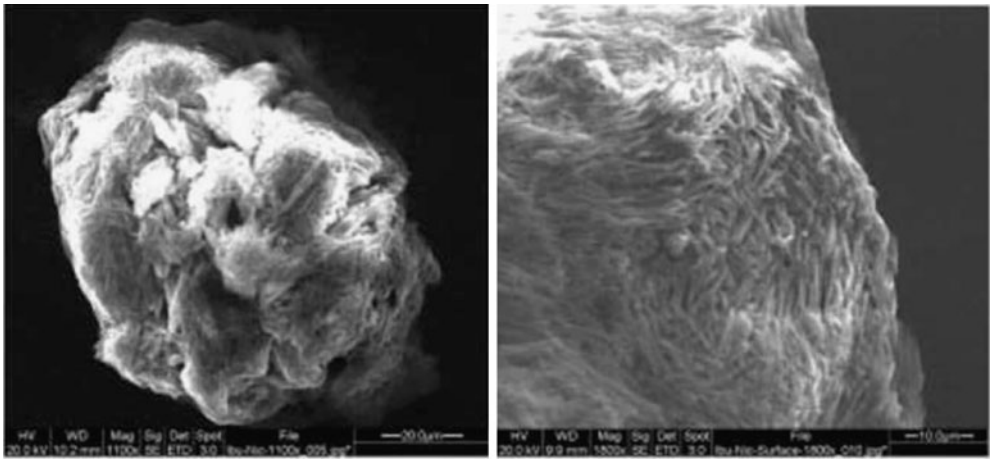

Fig. 8 Scanning electron microphographs of Ibu-Nic (1:1) cocrystal agglomerate at 1100x and its surface at 1800x.

improved the cocrystal purity, while Conf C, with distributive and dispersive mixing zones, imparted the highest shearing action, resulting in the high purity of cocrystals. Interestingly, the effect of screw configuration was observed at both the temperatures above eutectic, T80 and T90. However, the effect of temperature was less prominent when the batches were processed using Conf C, indicating the critical role of shear in cocrystal formation. The screw speed determines the residence time of the material in the extruder (30); therefore, the purity increased with decreasing screw speed. This effect was more prominent when the batches were produced using low and medium shear configurations. However, batches produced using Conf C showed less influence of screw speed at T80 and negligible difference at T90. In summary, screw geometry was found to have the most significant effect on the rate and extent of cocrystallization when processed above the eutectic temperature. Cocrystals produced at lowest extruder screw speed and highest shear configuration processed at T90 showed highest purity cocrystals with only one endothermic peak corresponding to a cocrystal melting at 89°C (Fig. 2), confirming the XRPD results. Product from this batch was evaluated for morphology, dissolution, compaction and compressibility.

Since the process involves application of shear to the molten material, the extruded product was obtained in the form of agglomerated granules, and, as such, highlights an important advantage over products obtained by conventional cocrystallization using solution or grinding techniques. Scanning electron microphotographs of ibuprofen nicotinamide cocrystals showed spherical agglomerates of cocrystals in the size range of 50 to 100 μm. Observation of cocrystal agglomerate surface under high magnification revealed that the agglomerates consisted of needle shaped individual cocrystals entangled or fused with each other to give spherical agglomerates (Fig. 8). Material morphology influences various pharmaceutical and biopharmaceutical parameters such as flowability, packing, compaction, compressibility, solubility and dissolution characteristic of drug powder. This is particularly advantageous for pharmaceuticals, as it improves the downstream processing. Formation of cocrystals and their subsequent agglomeration in a single step saves at least four operations involved in conventional size enlargement processes (granulation) for pharmaceuticals. Another advantage is the prevention of polymorphic changes, to which drugs can be susceptible during these unit operations (31).

Cocrystal agglomerates were also subjected to evaluation for improved mechanical properties. Compaction and Heckel plot studies were performed on cocrystal agglomerates using a compaction press. The crushing strength (hardness) of the tablets compressed using cocrystal agglomerates was significantly higher (10 kP) than the tablets compressed using ibuprofen alone (6 kP) at 5,000 N, indicating that the strength of cocrystal compact was much higher than ibuprofen compact. Furthermore, Heckel plot studies indicated lower mean yield pressure (Py) values for cocrystal agglomerates compared to ibuprofen, confirming the improved compressibility of the product. This highlights the directly compressible nature of the product negating the need for additional excipients. Sun and Hou have reported that cocrystal formation can modify mechanical properties of caffeine (7). Karki *et al.* have also improved mechanical properties of

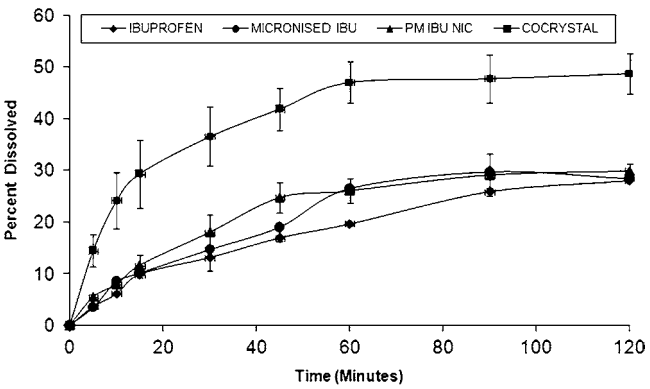

Fig. 9 Comparative dissolution profiles.

paracetamol by cocrystallization (6). It is also demonstrated that water of crystallization could significantly improve powder compaction properties by facilitating the formation of slip planes in the hydrate crystal (32). We have previously obtained directly compressible agglomerates by melt solidification (33) and melt granulation (34), where agglomeration was found to improve the tableting properties of drugs. Therefore, the improved compressibility and compactability of ibuprofen nicotinamide cocrystals may be attributed to cocrystallization or agglomeration of cocrystals or to both factors. The exact contribution of cocrystallization and agglomeration in enhancing the tableting properties is being further investigated in depth.

The release of ibuprofen from cocrystals was compared with pure drug, physical mixture and micronized ibuprofen. Ibuprofen shows pH-dependent solubility. Earlier reports and our experience suggest the dissolution of ibuprofen is sensitive to the dissolution medium (35). Attempts to establish the in-vitro-in-vivo correlation for ibuprofen using different dissolution mediums have also posed great challenges (36). These studies suggest the use of lower pH media have better discrimination compared to the higher pH solution. Therefore, dissolution of cocrystals was compared with ibuprofen and physical mixture in deionised water as a discriminating medium. The USP chromatographic purity method was adopted with slight modifications for separation and estimation of ibuprofen. Ibuprofen and nicotinamide have retention times of 7.52 min and 1.55 min, respectively. Cocrystals showed significant improvements in dissolution when compared to ibuprofen, PM and micronized ibuprofen (Fig. 9). Although PM and micronized ibuprofen showed faster dissolution compared to pure drug, this difference was not significant. The slight increment in dissolution from PM might be due to change in pH caused by nicotinamide (pH of medium after dissolution testing of PM was 0.25 units higher than after dissolution of ibuprofen alone), while increased dissolution of micronized ibuprofen is due to reduced particle size. This is in agreement with the previous study reporting improved solubility of ibuprofen by cocrystalization (37).

To evaluate the feasibility of the process at higher scale, 1 kg batch was produced at the optimum process conditions. Sampling was performed every 15 min and analyzed by XRPD. All samples showed consistent cocrystal purity, indicating the feasibility of commercializing the process. The samples were monitored for the physical stability using XRPD for 6 months at ambient conditions. No changes in the XRPD patterns were observed, indicating good storage stability. Recently, HME has gained popularity as a continuous granulation tool for wet, as well as solvent-free melt granulation of pharmaceuticals (38). Successful commercialization of various melt extrusion products, including Kaletra® (Ritonavir and Lopinavir in a solid solution) by Abbot laboratories, Gris-PEG® (Griseofulvin–polyethylene glycol-dispersion) and Cesamet® (Nabilone-PVP), has validated the commercial significance of the technology. Considering the advantages and commercial success of basic technology, continuous cocrystallization by HME has great potential.

CONCLUSION

Cocrystal agglomerates were successfully produced using a continuous, solvent-free, readily scalable HME technique. This technology offers tight control over the process with the flexibility for tailoring the cocrystal purity. Processing temperature and mixing intensity were found to be key parameters to produce high purity cocrystal. Cocrystallization and agglomeration were achieved in a single processing step, and the directly compressible nature of the extruded product negates the need for further size modification steps. HME is an established continuous and solvent-free technology readily addressing the regulatory demand of quality by design (QbD) and, hence, offers high potential for pharmaceuticals. Application of online analytics such as Raman and NIR spectroscopy to this technique is under investigation.

ACKNOWLEDGEMENTS

Yorkshire Concept, Proof of Concept Funding, Yorkshire Forward, UK. The authors gratefully acknowledge the technical assistance of Andy Baker, Thermo Scientific, UK.

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