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Compaction of recrystallised ibuprofen

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ABSTRACT

Ibuprofen (α-methyl-4-(isobutyl)phenylacetic acid) was recrystallised from a range of solvents. Particle morphology, crystallinity, melting points and powder flow properties were evaluated. Additionally, the compaction properties of the ibuprofen control and recrystallised samples were assessed at different compaction forces and speeds, before and after blending with an equal amount of lactose, using a Stylcam® 100R rotary press simulator. Recrystallised ibuprofen samples displayed equal or better tablet strength than the control, whilst ibuprofen recrystallised from acetone had improved flowability and ibuprofen recrystallised from 2-ethoxyethyl acetate exhibited lower levels of elastic energy during compaction. Additionally, when formulated with lactose, recrystallised ibuprofen samples displayed lower punch adhesion levels, particularly at a low compaction force.

1. Introduction

The common analgesic drug ibuprofen, a non-porous drug with poor compression properties, is readily prone to capping [1] and has tendencies to stick to tablet punches during compression [2]. The common crystal form of the drug displays poor powder flow properties due to the high cohesivity and adhesivity and bad dissolution behaviour because of its hydrophobic structure [2]. It has been shown that the morphology of ibuprofen is influenced by the polarity of recrystallisation solvent [3,4]. The aim of this study was to improve the particle morphology by recrystallisation from a range of solvents and investigate the subsequent influence on compaction properties.

2. Methodology

Ibuprofen, obtained from Albermarle, USA (Ibu-Con) was recrystallised from cyclohexane (Ibu-Cyc), acetone (Ibu-Ac), propan-2-ol (Ibu-Iso), and 2-ethoxyethyl acetate (Ibu-Eth) obtained from VWR, UK. Solutions of concentrations 45–110 g/100 ml were prepared by dissolving ibuprofen powder in a measured volume of solvent in a jacketed beaker connected to a thermostated, circulating water bath. The stirred solution was heated to 45 °C to ensure complete dissolution. Supersaturation was induced by cooling to 25 °C at which temperature crystallisation occurred within 1–8 h. The resulting solid was collected by filtration.

The solid product was examined using an Olympus optical microscope fitted with a digital camera and image capture software, and with an FEI Quanta 200 scanning electron microscope (SEM). Samples were analysed using a Perkin Elmer Pyris 1 differential scanning calorimeter (DSC) with samples heated from 20 °C to 100 °C at 10 °C min^{-1}. Powder X-ray diffraction patterns were collected using a Rigaku Miniflex at wavelength 1.542 Å using a scan range of 5–50° 2θ. Samples were ground with a pestle and mortar and packed into an aluminium sample holder.

The flowability of each ibuprofen sample was determined according to Carr's Compressibility Index (Eq. (1)):

$$\text{Carr's Compressibility Index} = \left[\frac{\text{tapped density} - \text{initial density}}{\text{tapped density}}\right] \times 100 \quad (1)$$

The compaction properties of the recrystallised ibuprofen and control samples were assessed using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) fitted with 11.28 mm flat-faced tooling. The effect of compaction force (5 or 25 kN) and speed (5 or 25 tablets min^{-1}) on tablet crushing strength (P) (6D tablet tester, Schleuniger, Germany) diameter (D) and thickness (T) was evaluated and tablet tensile strength [5] calculated using Eq. (2):

$$\text{tensile strength} = \frac{2P}{\pi DT} \quad (2)$$

Force–displacement profiles were plotted for both upper and lower punches allowing plastic and elastic compaction energies to be measured via the Analis® software (v. 2.01, Medel'Pharm, France). Additionally, the recrystallised ibuprofen and control samples were individually blended with an equal amount of lactose

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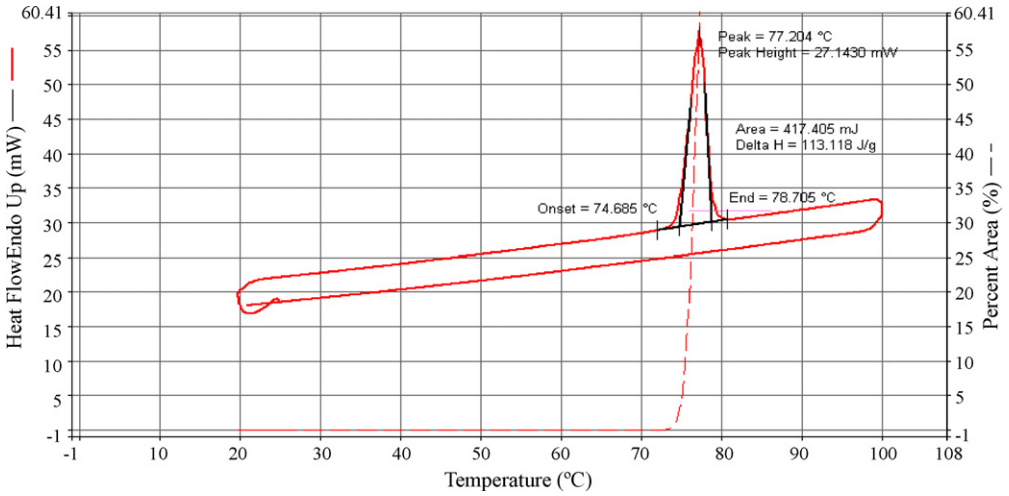

Fig. 1. Thermal analysis of ibuprofen control material showing a single melting isotherm at 77 °C. Recrystallised samples showed similar traces.

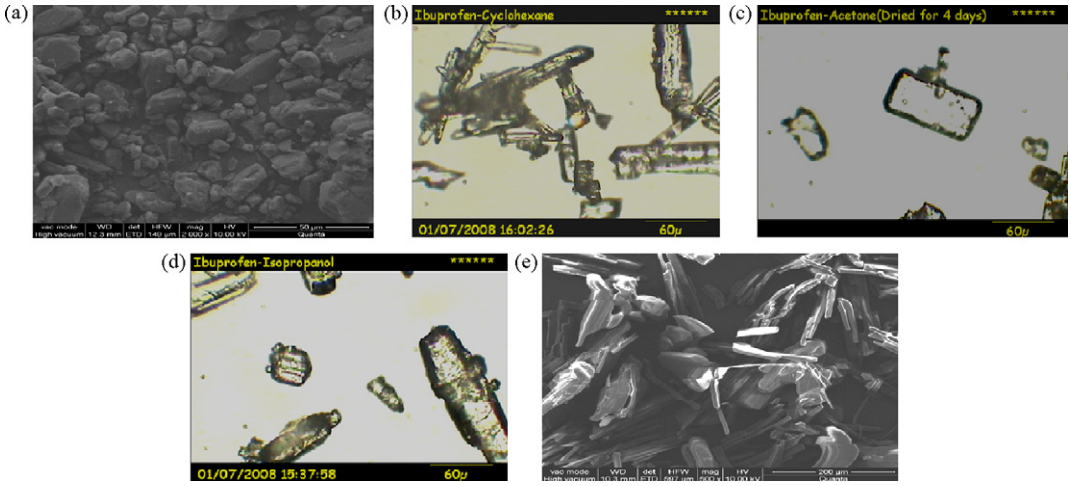

Fig. 2. Optical and SEM images of powder samples showing the morphology and particle size of samples: (a) control material, as purchased, and recrystallised from (b) cyclohexane, (c) acetone, (d) propan-2-ol, and (e) 2-ethoxyethyl acetate.

(Tablettose® 80, Meggle, Germany) in a turbula mixer (Type 2B, WAB, Switzerland) for 5 min before being passed through a 500 μm aperture sieve (Endecotts, UK). Each mixture was then lubricated by adding 0.5% (w/w) of magnesium stearate (BDH, UK) and mixed for a further 2 min. Tablets of each ibuprofen–lactose blend were produced under the same conditions as described for the individual ibuprofen samples. Adhesion of ibuprofen to the upper punch was assessed by immersing the punch face in a known volume of 96% ethanol following each compaction run and the UV absorbance of the subsequent solution was determined at 264 nm (Genesys 10, Thermo Scientific, USA).

3. Results and discussion

Thermal analysis of the recrystallised samples showed no significant difference with the control sample. The melting point was confirmed to be 76–78 °C for all samples, in agreement with literature [6] with no other thermal transitions observed, showing that no significant changes were made to the crystal form by the recrystallisation process. An example DSC trace is shown in Fig. 1. Similarly, the X-ray patterns obtained showed agreement with published data [7] and no changes to the diffraction pattern following recrystallisation. All samples showed good crystallinity with well-defined peaks, and no changes to peak positions.

Examples of the particles obtained from each crystallisation solvent are shown in Fig. 2. Ibu-Cyc showed an elongated morphology, as did Ibu-Eth. In contrast, Ibu-Ac and Ibu-Iso displayed plate like morphologies of rectangular shape.

Recrystallised ibuprofen samples displayed equivalent flowability to the ibuprofen control, except the ibuprofen recrystallised from acetone that displayed excellent flow properties (Table 1).

Recrystallised ibuprofen samples were found to have equal or better tablet strength than the control (Fig. 3). However, Ibu-Cyc displayed a considerable decrease in tablet strength when compressed at high compaction force and speed. Generally, the strength of tablets increased at 30 kN (probably due to increased inter-particulate bonding as a result of the higher compaction force), and decreased at the higher compaction speed, due to the reduction in the dwell time of the tablet punches and associated decrease in

Table 1
% Carr's index and corresponding flowability of ibuprofen samples.

	Carr's index (%)	Flowability
Ibu-Con	25.3	Poor
Ibu-Iso	25.5	Poor
Ibu-Cyc	23.7	Poor
Ibu-Ac	11.62	Excellent
Ibu-Eth	30.0	Poor

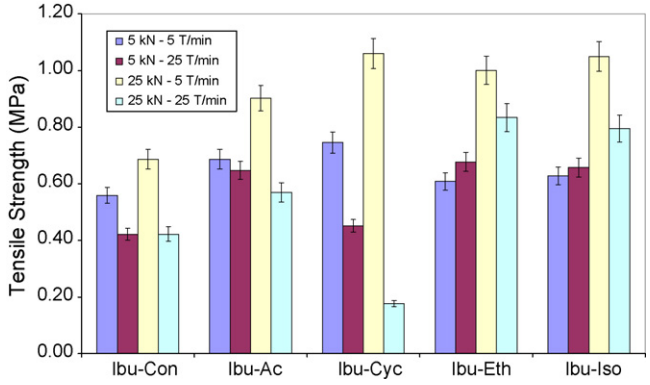

Fig. 3. The effect of compaction force and speed on the tensile strength of ibuprofen tablets.

inter-particulate bonding. Marshall et al. [8] found that the compaction of ibuprofen was a balance between plastic and elastic deformation and the predominating mechanism was determined by punch velocity. In the present study, most recrystallised ibuprofen samples exhibited comparable elastic and plastic energies of compaction to the control sample (Fig. 4). However, ibuprofen recrystallised from 2-ethoxyethyl acetate demonstrated lower levels of elastic energy, which could be beneficial during high-speed tablet production where ibuprofen is prone to capping [1]. Capping occurs when the upper layer detaches itself from the main body of the tablet and is caused by elastic recovery of the compressed particles. Pedersen [9] explained that on decompression elastic recovery occurs axially and the tablet is weakened. During ejection from the die, gradual radial recovery also occurs, which results in capping because of failure at the points of low density and bonding within the tablet.

Tablets of recrystallised ibuprofen samples blended with lactose were found to have better (Ibu-Ac, Ibu-Cyc and Ibu-Eth) or comparable (Ibu-Iso) strengths to those of ibuprofen control at a low compaction force (Fig. 5) and whilst all samples showed an increase in tablet strength at the higher compaction force Ibu-Con exhibited the greatest improvement in tablet strength. This suggests that robust tablets comprising recrystallised ibuprofen could be produced at lower compaction forces thus preventing wear and tear of the compression tooling.

Tablet adhesion, more commonly termed picking or sticking, refers to removal of material from the surface of the tablet and its subsequent adhesion to the punch tip [9]. The magnitude of this problem can range from minor punch filming, where a thin layer of powder adheres to the punch face, to major picking, where large amounts of the tablet surface are removed and stick to the punch

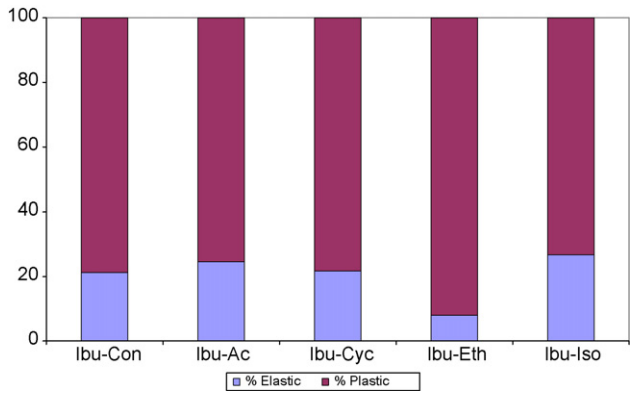

Fig. 4. Mean % elastic and plastic compaction energies of ibuprofen tablets.

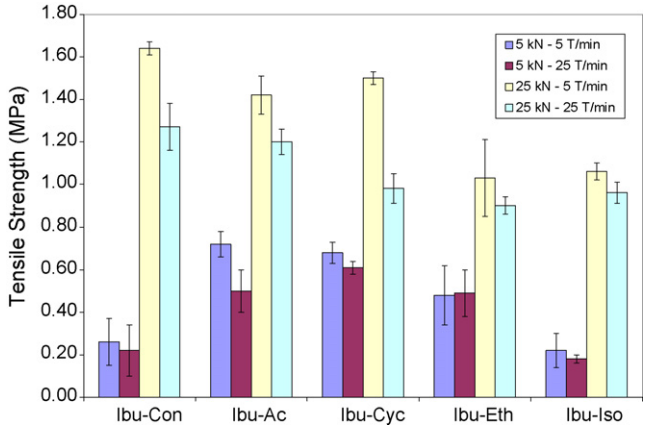

Fig. 5. The effect of compaction force and speed on the tensile strength of ibuprofen–lactose tablets.

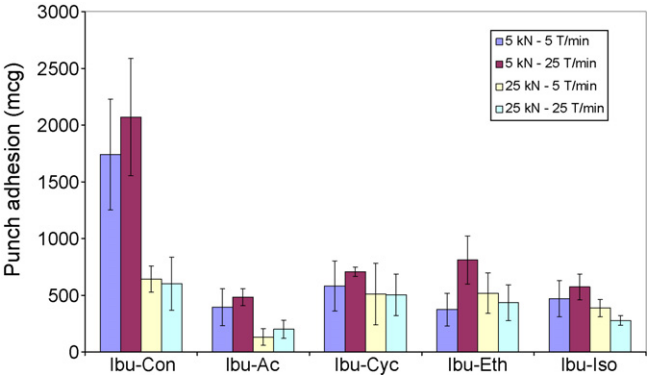

Fig. 6. The effect of compaction force and speed on the punch adhesion of ibuprofen.

face. Punch filming affects the appearance of the tablet, whilst larger occurrences of sticking can lead to unacceptable tablets and even damage to the tablet tooling or machinery. Previous research has shown that adhesion of ibuprofen to the tablet punches during tabletting is influenced by the type of tooling used [10,11] and the type and level of lubricant in the formulation [12]. When formulated with lactose, recrystallised ibuprofen samples displayed lower punch adhesion levels, particularly at a low compaction force (Fig. 6), which may be accredited to a change in the interaction between the punch face and particle surface as result of the different morphology following recrystallisation. In the control sample, a greater interaction at the punch–particle interface resulted in higher levels of adhesion. A higher compaction force was required to achieve a reduction in punch adhesion of the control sample, possibly due to the increased force overcoming the interaction between the punch face and ibuprofen particles during compaction [10]. However, reduced adhesion levels were achieved with the recrystallised samples at the low compaction force. This could be of benefit during tablet manufacture where lower compaction forces are favoured to reduce wear and tear of tooling.

4. Conclusion

The results indicate that ibuprofen recrystallised from various solvents can offer advantages in terms of particle morphology, flowability and compaction properties. Recrystallised samples produced tablets of equal or better tensile strength compared to the control, even at low compaction force. Additionally, a reduction in punch adhesion may be attained thus aiding tablet manufacture.

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