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Crystal engineering of ibuprofen using starch derivatives in crystallization medium to produce promising ibuprofen with improved pharmaceutical performance

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Ibuprofen exhibits poor flow, poor compaction and dissolution behaviour, and it is prone to capping after ejection from the die. Therefore, the aim of the present research was to engineer ibuprofen crystals in the presence of two disintegrants (starch and sodium starch glycolate) in order to improve its flow, compactibility and dissolution behaviour simultaneously. To this end ibuprofen and different concentrations of disintegrant (0.25 to 10% w/w in case of starch and 0.25 to 7% w/w in case of sodium starch glycolate) were dissolved in ethanol and water respectively. The ibuprofen solution was then added to the aqueous solutions containing the different concentrations of disintegrant. Ibuprofen precipitated within 10 min and the crystals were separated and dried for further studies. The obtained crystals were characterized in terms of flow, density, tablet hardness, dissolution behaviour and solid state. The results showed most of engineered ibuprofen to have better flow with a high compactibility. The results also showed that an increase in the concentration of starch in the crystallization medium resulted in a reduction in the hardness of ibuprofen tablets, but this was not the case for ibuprofen samples engineered in the presence of sodium starch glycolate. It is interesting to note that although engineered ibuprofen showed superior dissolution as compared to untreated ibuprofen, the highest concentration of starch (10%) or sodium starch glycolate (7%) slowed down the release remarkably due to an increase in the viscosity of the dissolution medium around drug particles. Solid state analysis (FT-IR, XRPD and DSC) ruled out the presence of different polymorphic forms and also any interaction between these disintegrants and ibuprofen. In conclusion, the engineering of ibuprofen in the presence of disintegrant showed how properties such as flow, compaction and dissolution behaviour can be simultaneously manipulated to suit a desired application.

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1. Introduction

In previous years many attempts have been used to change the morphology of drug crystals using different crystallization procedures. This is done in order to improve their compression and flow properties so that they are suitable for direct compression as this is the fastest, simplest, and least expensive way in manufacturing tablets. Examples of crystallization procedures are spherical crystallization which transforms crystalline drugs into agglomerated forms,[1–4] crystallization from different solvents to produce different crystal habit[5–7] and incorporation of additives by co-precipitation.[8–10]

Ibuprofen, 2-(4-isobutylphenyl)-propionic acid is a widely used analgesic and antirheumatic drug. It is a drug which is well known to exhibit poor flow properties and poor compression ability due to its high cohesive and viscoelastic properties respectively. A great problem in manufacturing is its high tendency of sticking to the punches.[11]

Moreover ibuprofen is also known as a poor water soluble drug. It is classified as class II according to the Biopharmaceutics Classification System (BCS) which means that it has high intestinal permeability and low water solubility. Therefore, dissolution of ibuprofen in gastrointestinal tract is a rate limiting factor for oral absorption and as such increasing

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the dissolution rate could increase the oral bioavailability of this drug. On the other hand, rapid drug release is preferable, especially for analgesic drugs.

Apart from acting as a disintegrating agent, starch has been widely used as a binder and also as a diluent in oral solid dosage formulations.[12,13] Sodium starch glycolate is mainly used as a modern super disintegrant in oral dosage forms.[14] Swain *et al.* (2015) used sodium starch glycolate in oral dispersible tablets to enhance the dissolution of ibuprofen through faster disintegration of tablets but no attempt was made to change the crystal properties of the ibuprofen.[15] In another study solid dispersions of ibuprofen with starch 1500 was designed through factorial design to enhance the dissolution rate of ibuprofen, but stability of solid dispersions might be an issue in solid dispersion formulation due to the presence of amorphous structure.[16]

Many attempts have been made in the past to improve the properties of ibuprofen using different crystallization techniques or additives.[7,17–20] An improvement of the flow characteristics and the compressibility of drug crystals have been observed, but not of dissolution at the same time, which is what this study is aiming to do. Therefore the aim of this project is to use a non-toxic solvent in a simple crystallization technique in the presence of starch and sodium starch glycolate to improve flow, hardness and dissolution of ibuprofen tablets simultaneously with no significant interaction between ibuprofen and starch derivatives. This piece of work will open up a new window for the possibility of enhancing these three important parameters simultaneously.

2. Experimental

2.1. Material

Ibuprofen and sodium starch glycolate were purchased from spectrum chemical MFG, Corp (USA), and starch from Fisher Scientific (UK). The solvent used in this study was ethanol which was also obtained from Fisher Scientific (UK). All solvents and chemicals were of analytical reagent grade used as obtained.

2.2. Preparation of ibuprofen crystals

Nine different modified crystals of ibuprofen were prepared and labelled as Ib1 to Ib9 (Table 1). Ibuprofen was dissolved in ethanol to produce 30% w/v solution. In all crystallization process 10 ml of the ethanolic solution of ibuprofen (30% w/v) was added to 100 ml of distilled water containing appropriate amount of disintegrant (Table 1) under continuous stirring with a magnetic stirrer at approximately 500 rpm for 20 minutes at room temperature. The precipitated crystals from each solution were collected after 20 minutes by filtration under vacuum (the pore size was 0.45 μm). The obtained crystals were spread on a petri-dish and dried in an oven at 50 °C for 24 hours. The obtained crystals were stored in a screw capped glass vial at room temperature before use for further studies.

2.3. Scanning electron microscopy (SEM)

The morphology of crystals (their habit and surface features) was examined using a scanning electron microscope (Leica Cambridge S360, UK) operating at 15 kV. The samples were coated under vacuum with gold in an argon atmosphere prior to observation.

2.4. Powder flow measurement

Flowability of the treated and untreated ibuprofen samples was assessed by a determination of Carr's Index (CI). The CI was calculated according to eqn (1):[21,22] three grams of the samples were gently poured into 10 ml measuring cylinders and the bulk volume of the particles was recorded. The measuring cylinder was tapped 100 times using a tapping machine (model, Erweka, Germany) to achieve tapped volume. Then bulk and tapped density was calculated using mass over the volume. The obtained densities were incorporated into the following equation to calculate the Carr's index value.

$$\mathrm{CI} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100 \qquad (1)$$

2.5. Particle size analysis

Particle size analysis distribution of all formulations (unground formulations) was conducted using a Sympatec (Clausthal-Zellerfeld, Germany) laser diffraction particle size analyzer using the liquid method. Small amount of the ibuprofen samples were added to an aqueous saturated ibuprofen solution under sitting conditions and the mean particle size was calculated automatically using the software provided.

2.6. Differential scanning calorimetry (DSC)

DSC (Mettler Toledo, Switzerland) was used to study the thermal behaviour of all the samples. Samples of ibuprofen crystals (4–5 mg) were heated ranging from 20 to 150 °C at a scanning rate of 10 °C min^{-1} in crimped aluminium pans under a nitrogen gas. The enthalpy of fusion, onset temperatures and melting points of the samples were automatically calculated using the software provided (Mettler-Toledo, Switzerland).

2.7. X-ray powder diffraction (XRPD)

The XRPD patterns of untreated ibuprofen, starch, Na starch, ibuprofen crystallized without disintegrant and ibuprofen crystallized with the two disintegrants at different concentrations were obtained using a Bruker D2 Phaser XRPD diffractometer. The samples were scanned from 5° to 55° 2θ at a rate of 1.5° min^{-1}.

2.8. Determination of the amount of disintegrant adsorbed to ibuprofen

Ibuprofen samples (100 mg) were weighed accurately and dissolved in 10 ml ethanol. This was then dispersed in 1000 ml of water, such that any drug would have dissolved and the disintegrant would have remained dispersed. 5 ml of the dispersion was then filtered through a 0.45 μm membrane filter to separate the ibuprofen solution from the disintegrant. The filtered samples were then analyzed spectrophotometrically at a wavelength of 221 nm using a 2100 Perkin Elmer UV

Table 1 Composition of the different formulations and the amount of disintegrant attached to ibuprofen crystals after crystallization

Sample	Drug : disintegrant (g)	Ibuprofen[a]	Starch[b] (w/v)	Sodium starch glycolate[b] (w/v)	%disintegrant attached[c] (theoretical %disintegrant)
Ib1	3 : 0	10 ml	—	—	—
Ib2	3 : 0.25	10 ml	0.25%	—	0.8 (7.8)
Ib3	3 : 1	10 ml	1%	—	12.2 (25)
Ib4	3 : 5	10 ml	5%	—	42.9 (62.5)
Ib5	3 : 10	10 ml	10%	—	70.25 (76.9)
Ib6	3 : 0.25	10 ml	—	0.25%	7.9 (7.8)
Ib7	3 : 1	10 ml	—	1%	16.7 (25)
Ib8	3 : 5	10 ml	—	5%	18.9 (62.5)
Ib9	3 : 7	10 ml	—	7%	33.29 (70)

[a] The amount of ibuprofen dissolved in 10 ml solvent was 3 g for all samples. [b] These are the percentages of disintegrants in 100 ml of the solution. [c] Values in parenthesis show the theoretical %w/w of disintegrant added to the crystallization medium.

spectrophotometer. The drug content was determined by reference to a standard solution. The amount of disintegrant was taken as the difference between the absorbance of the standard and the spectrophotometrically determined absorbance of the sample. In addition the percentage of ibuprofen was also determined by DSC study. For this purpose the enthalpy of each sample was divided to enthalpy of crystallized ibuprofen (Ib1).

2.9. Preparation of ibuprofen tablets

The compacts were prepared directly from the sieved fraction of the ground crystals (45–250 μm) using an 8 mm flat-faced punch (model MTCM-1, Globe Pharma, US). The manual tablet compression machine, model MTCM-I, is designed for compaction of powders into tablets one at a time. The press has the capability to compress tablets from 1 kN to around 15 kN. The material for each tablet was weighed (100 mg), introduced into the die and compacted at increasing compression pressures of 35, 70, 105, 140 and 175 MPa, using a single punch press. The compaction surfaces were lubricated with 1% w/v magnesium stearate in acetone before compaction. The compacts were held under load for 20 seconds, ejected and stored in screw-capped bottles for 24 hours before using, to allow for possible hardening and elastic recovery. For comparison purposes, tablets were also made from physical mixtures.

2.10. Porosity calculation

In order to calculate the total porosity of each tablet, the dimension of tablets (diameter and thickness) were measured using an electronic digital calliper (Fisher Scientific, UK) immediately before hardness testing. The true density of powders was determined using Ultrapycnometer 1000 (Quantachrome Instruments, UK). Tablet porosity was then calculated according to the following equation.

$$\text{Tablet porosity} = \left[1 - \frac{\left(\frac{\text{tablet weight}}{\text{tablet volume}}\right)}{\text{true density of powder}}\right] \times 100 \qquad (2)$$

2.11. Crushing strength and capping tendency of tablets

Tablets diameter and thickness was measured first using a digital micrometer (Fisher Scientific, UK) and recorded. The crushing strength of tablets was determined from the force required to fracture the compacts on a motorized tablet hardness tester (Dr SCHLEUNIGER Tablet tester 8M). A minimum of 3 tablets were selected for hardness measurements. Tablets were assessed visually for capping by observation of the final tablets for horizontal striations. For comparison purposes, a hardness test was also conducted for physical mixtures.

2.12. Dissolution studies

A USP dissolution test apparatus no. 2 (rotating paddle method, Erweka, Germany) was used to monitor the dissolution profiles of the tablets made from the different samples. All tablets used were 100 mg in weight. The dissolution medium was 900 ml of phosphate buffer (pH 7.2) equilibrated to 37 ± 0.5 °C and the paddles rotating at 50 rpm. Samples were taken at predetermined intervals using a peristaltic pump and assayed for drug content by a UV spectrophotometer at 221 nm. Each sample was determined in triplicate. Dissolution studies were only conducted for the compacts produced at 105 MPa only.

3. Results and discussion

It should be kept in mind in the present manuscript the percentages of disintegrant mentioned in the figures or tables are the percentages that are dissolved in the 100 ml crystallization medium not the percentages of disintegrant attached to ibuprofen samples after crystallization and drying (see Table 1 for more details).

3.1. Scanning electron microscopy (SEM)

As morphology of drug particles do have an impact on micrometric properties and dissolution behaviour, the morphology of the engineered ibuprofen samples was investigated using SEM.

It has already been shown that the crystal habit of ibuprofen depends on crystallization conditions such as the type of

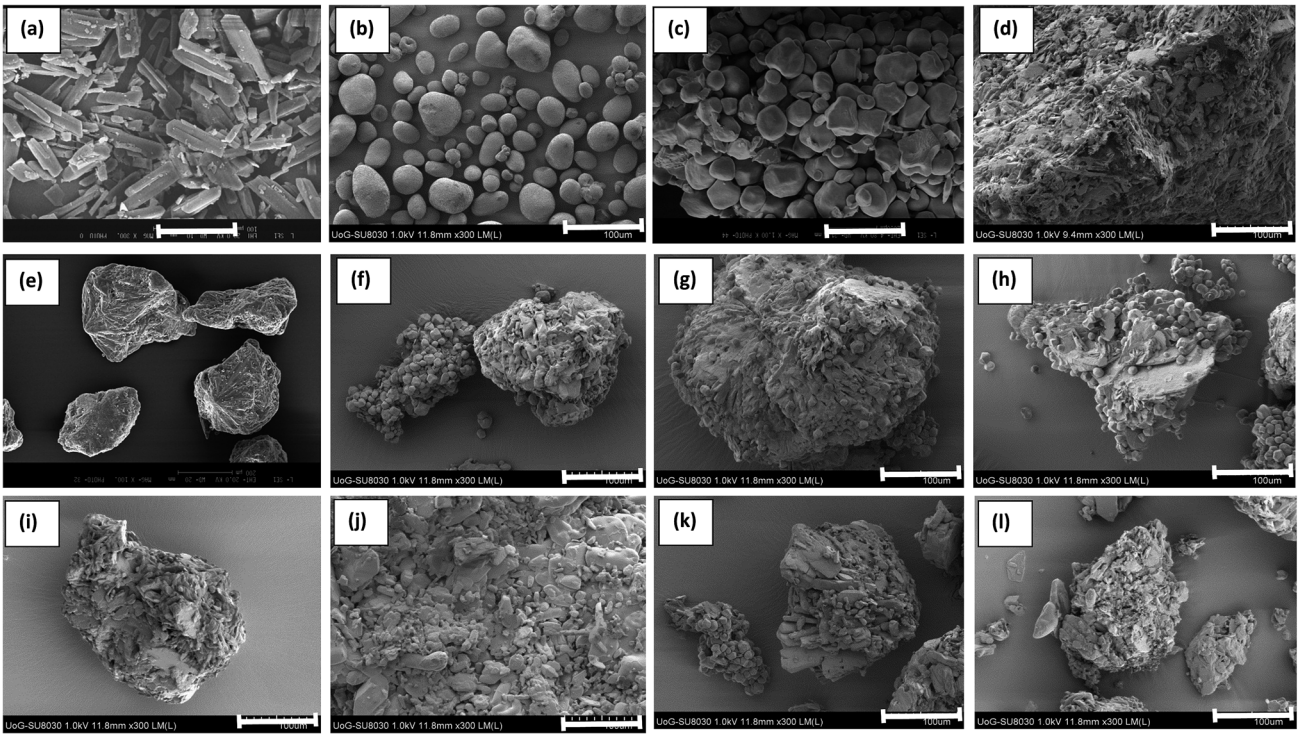

Fig. 1 SEM images of (a) ibuprofen, (b) Na starch glycolate, (c) maize starch, and ibuprofen crystallized in the presence of (d) 0% disintegrant, (e) 0.25% starch, (f) 1% starch, (g) 5% starch, (h) 10% starch, (i) 0.25% Na starch, (j) 1% starch, (k) 5% Na starch, (l) 7% Na starch (scale on each graph is 100 μm).

solvent and the presence of additives.[23–26] The common crystal form of ibuprofen (Fig. 1) appears as fine acicular crystals with high cohesion tendency (Fig. 1a), which is reflected in its obvious poor flow which is discussed later. Starch and sodium starch glycolate showed almost similar morphology (rounded shape with smooth surfaces, Fig. 1b and c respectively). When ibuprofen was crystallized in the absence of any disintegrant, a different morphology was obtained with the crystals having rough surfaces comprising of flat-shaped ibuprofen particles sticking together to make bigger particles (Fig. 1d). Similar flat-shaped particles for ibuprofen were also reported when ibuprofen was crystallized in the presence of 5% PEG 8000.[23] The presence of starch in the crystallization medium showed similar surfaces to ibuprofen crystallized in the absence of disintegrant but with lots of starch particles adhered to ibuprofen surfaces particularly at high concentration of starch (Fig. 1f–h). The presence of sodium starch glycolate in the crystallization medium changed the surface of the obtained particles. The presence of sodium starch glycolate particles on particle surfaces are not clearly seen (Fig. 1i–l). It was observed that ibuprofen particles crystallized in the presence of 7% sodium starch glycolate (Fig. 1l) were fairly large with stiff surfaces.

Table 2 Powder properties obtained of the different ibuprofen formulation

	Powder properties				
Formulation	True density (g cm^{-3})	Bulk density (g cm^{-3})	Tapped density (g cm^{-3})	Carr's index (%)	Hausner ratio
Pure Ib	1.14 ± 0.05	0.22 ± 0.08	0.31 ± 0.04	29.7 ± 0.5	1.42 ± 0.09
Ib1	1.10 ± 0.06	0.46 ± 0.09	0.51 ± 0.05	9.8 ± 1.0	1.11 ± 0.10
Ib2	1.17 ± 0.05	0.46 ± 0.05	0.50 ± 0.06	8.0 ± 0.9	1.09 ± 0.09
Ib3	1.18 ± 0.09	0.43 ± 0.03	0.50 ± 0.02	14.0 ± 0.1	1.16 ± 0.04
Ib4	1.33 ± 0.08	0.38 ± 0.02	0.53 ± 0.02	28.3 ± 0.1	1.39 ± 0.04
Ib5	1.40 ± 0.07	0.38 ± 0.03	0.50 ± 0.03	24.0 ± 0.1	1.32 ± 0.03
Ib6	1.17 ± 0.05	0.43 ± 0.05	0.50 ± 0.01	14.0 ± 0.1	1.16 ± 0.02
Ib7	1.19 ± 0.09	0.43 ± 0.04	0.52 ± 0.05	17.3 ± 1.0	1.21 ± 0.11
Ib8	1.42 ± 0.02	0.40 ± 0.04	0.51 ± 0.06	21.6 ± 1.0	1.23 ± 0.10
Ib9	1.45 ± 0.04	0.36 ± 0.01	0.50 ± 0.02	28.0 ± 0.1	1.39 ± 0.03

3.2. Density and flowability

Powder density and flowability are closely related parameters because particles that are denser generally show better flow tendency.[27] The Hausner ratio and the Carr's index have been widely used to estimate the flow properties of powders. According to Carr's index a value between 5–15%, 12–16%, 18–21%, and 23–28% indicates excellent, good, fair, and poor flow properties of the material, respectively.

Table 2 shows that the true density of crystallized ibuprofen in the presence of additives is higher than the true density of ibuprofen in the absence of additives. This is due to the presence of starch and sodium starch glycolate with higher true density in the samples as the true density of starch (1.48 g cm^{-3}) and sodium starch glycolate (1.56 is g cm^{-3}) is higher than the true density of ibuprofen (1.10 g cm^{-3}) crystallized in the absence of disintegrants (see Tables 2 and 3).

Comparing the flowability (Carr's index value) of the various recrystallized samples (Table 2) showed that ibuprofen samples recrystallized in the presence of low concentration of disintegrants (starch 0.25% (Ib2) and 1% (Ib3), sodium starch glycolate 0.25% (Ib6) and 1% (Ib7)) had lower Carr's index compared to those samples crystallized in the presence of high concentration of disintegrants (5% above). These CI values are also less than the CI value of untreated ibuprofen (CI of 29.7%). Such a decrease in CI indicates that there were great improvements in flow and packing ability of the powder mass in comparison to the commercial ibuprofen powder. This could be due to the existence of less elongated particles compared to the untreated ibuprofen which is obvious from SEM micrographs (Fig. 1). The changes in flow should be discussed under the context of the effect of particle size and shape. The flow properties of dissimilar materials with the same particle size have been investigated using permeability and shear cell[28] indicating particle shape might have significant effects on powder flow. Recently Fu *et al.*[29] carried out an extensive study on the effect of particle shape and size on the flow behaviour of various lactose powders. They showed that two lactose samples with identical shapes (SpheroLac® 100 and InhaLac® 230) but different particle sizes showed different Carr's index values. The lowest Carr's index (better flowability) was for Spherolac 100 reflecting its more efficient particle packing when in a conditioned and low stress state, due to having larger particle size and lower cohesivity. They also showed that two lactose samples with similar particle size distribution but different particle shape (SpheroLac® 100 and FlowLac® 100) showed less efficient packing for Spherolac 100 due to its irregular shape as compared to FlowLac®. The shear properties of 8 different powders, which varied in particle size and shape using an annular shear cell was also reported.[30] They showed that needle shaped particles exhibited high angle of internal friction leading to poor flow. The above information can be applied to the engineered ibuprofen samples as discussed in the manuscript. It is generally believed that the flowability of powders decreases as the shapes of particles become more irregular.[30] It can be noted that generally as the amount of disintegrant in the samples increases flowability seems to decrease. For example when starch concentration was increased from 1% (Ib3) to 5% (Ib4) the Carr's index also increased from 14% to 28.3%. Similarly when sodium starch glycolate concentration increased from 1% (Ib7) to 5% (Ib8) CI increased from 17.3% to 21.6%. The results generally showed that high concentration of disintegrant is not in the favour of good flow for the engineered ibuprofen powder. The improved flowability observed from the results may also be due to the higher bulk densities observed for the modified ibuprofen samples (Table 2) being in the range of 0.36–0.46 g cm^{-3} compared to 0.22 g cm^{-3} for untreated ibuprofen. Recently Jallo *et al.*[31] made an attempt to enhance the bulk density of pharmaceutical powders by dry coating to modify the surface of the particles in order to improve the flow. They showed that the coated particles showed higher bulk density and their flow moved from a poorer to a better flow classification. Ibuprofen engineered in the absence of any disintegrant also showed lower CI which is an indication of excellent flow which could be due to the rounded shape of these particles. Hausner ratio also confirmed a similar pattern where untreated ibuprofen showed the highest Hausner's ratio (1.42). According to Wells[32] a Hausner ratio value of less than 1.20 is indicative of good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow display by the material. It can be concluded that engineering ibuprofen particles in absence or presence of low concentration of disintegrant enhances the flow properties of ibuprofen powders.

Table 3 Particle size distribution for various ibuprofen samples

	Particle size (μm)			
Sample	$X_{10\%}$	$X_{50\%}$	$X_{90\%}$	Span $(X_{90\%} - X_{10\%})/X_{50\%}$
Pure ibuprofen	48.1	131.7	435.6	2.90
Ib1	35.4	134.5	504.7	3.49
Ib2	55.2	257.8	708.3	2.53
Ib3	40.6	196.3	443.7	2.05
Ib4	42.8	170.9	348.4	1.79
Ib5	25.8	138.0	337.1	2.25
Ib6	47.4	245.8	654.6	2.47
Ib7	27.9	121.5	379.2	1.82
Ib8	29.2	107.7	225.0	1.82
Ib9	30.9	113.5	237.9	3.49

3.3. Particle size analysis

Table 3 shows the average range of particle size for various engineered ibuprofen samples. Taking $X_{50\%}$ (50% undersize of the particles) as a parameter for comparing the particle size of the samples, it can be seen that the average particle size has increased in comparison to the untreated ibuprofen sample. It is interesting to note that the presence of starch increased the average particle size compared to ibuprofen sample crystallized in the absence of starch. However, further increases in the concentration of starch decreased the $X_{50\%}$ and also the span value decreased accordingly (Table 3). This indicates that the presence of starch produced smaller span values which are an indication of narrower particle size distributions (Table 3). It

can be seen that an increase in the concentration of disintegrant generally leads to a reduction in crystal size (compare Ib2 with Ib5 and Ib6 with Ib9). Reported studies have suggested that adsorption of polymers on the surface of nuclei leads to the formation of a diffusional boundary layer, which inhibits nucleation and growth, resulting in smaller crystal size.[33] This however was not the case here as these disintegrants could act as binders[34] and stick ibuprofen particles together to make ibuprofen–disintegrant granules. This could be the main reason for the presence of bigger particles in the presence of 0.25% disintegrants compared to the particle size of ibuprofen crystallized in the absence disintegrant (Table 3). In addition it was also observed that ibuprofen samples crystallized in absence of disintegrant (Ib1) were fragile and under the particle size measurement process are highly likely broken down to smaller particles when they are being stirred for the particle size measurement leading to a wider particle size distribution then a higher span value (Table 3). A reduction in the particle size with increasing disintegrant concentration could be due to the presence of individual excess of disintegrant particles in the samples which do not take part in making ibuprofen granules (SEM images showed that disintegrants have very smaller particles compared to ibuprofen granules). The presence of separate disintegrant particles is obvious in some of SEM images (Fig. 1). This is supported by the presence of bimodal particle size distribution where the first peak is an indication of separate disintegrant particles which do not take part in making ibuprofen granules (Fig. 2). In case of ibuprofen samples crystallized in the presence of sodium starch glycolate, a general, similar pattern was obtained, where bigger particles were observed when the concentration of sodium starch glycolate was low (Ib6 and Ib7). These results can be correlated well with CI values as larger particles have small surface area then less van der Waals forces and better flow.

Table 3 also shows that the presence of disintegrants in crystallization medium produced narrower particle distribution (smaller value of span indicates narrower particle size distribution). It has been investigated that fine particles having high surface to mass ratios are more cohesive than coarser particles, which results in inappropriate flow properties.[35]

3.4. Mechanical properties of modified ibuprofen crystals

Good compactibility and compressibility are essential properties of directly compressible crystals. Compactibility of samples was evaluated based on the hardness of the tablets compressed at different compaction pressures. Fig. 3 shows the effect of two disintegrants in the crystallization medium of ibuprofen on the hardness of ibuprofen tablets when compressed at different compaction pressures. It can be seen from Fig. 3 that the compaction pressure played a major role on the mechanical strength of all ibuprofen tablets. Results showed that in most cases the hardness of tablets increased as the compression loads increased until a certain value was reached, after which a higher compression load resulted in a reduction in hardness of

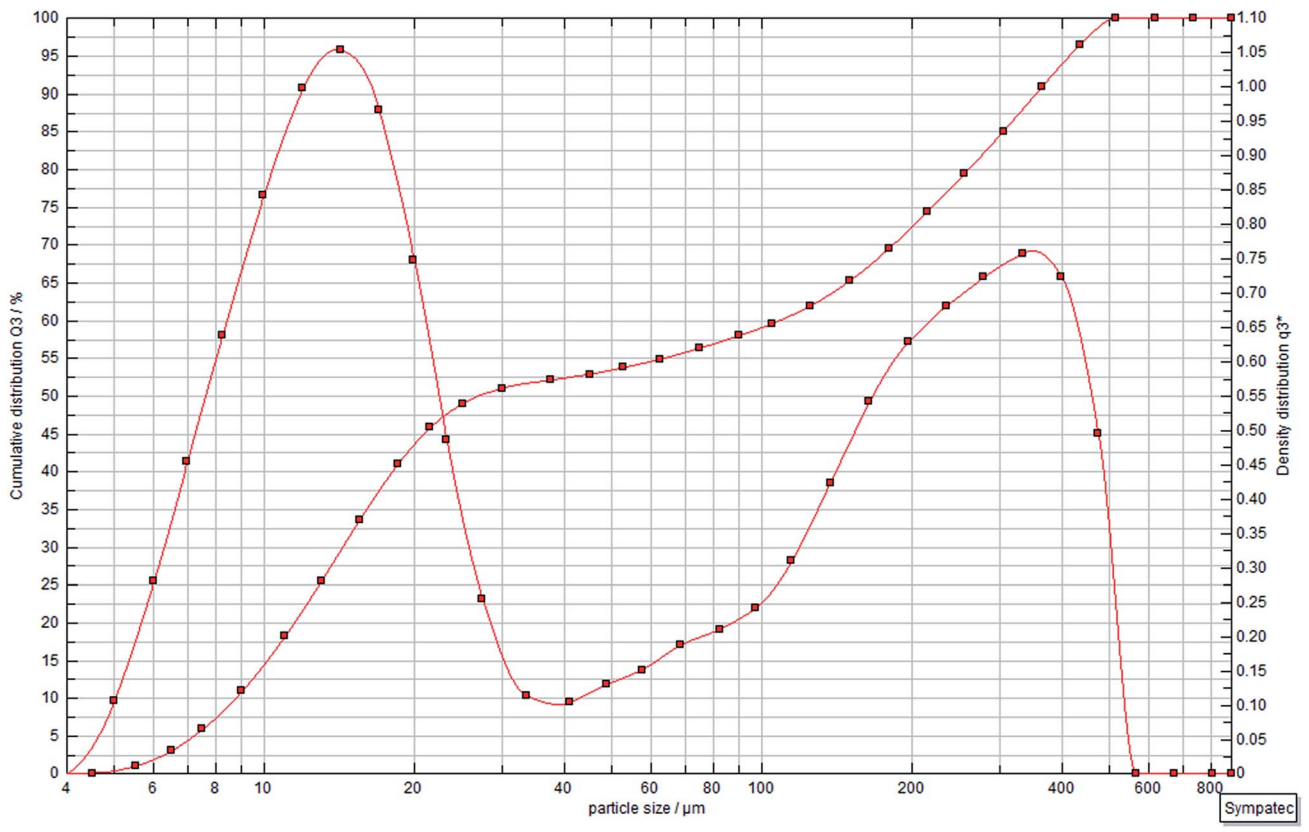

Fig. 2 Particle size distribution of ibuprofen sample crystallized in the presence of 10% starch.

tablets (Fig. 3). For example, when compression pressure was increased from 105 to 140 MPa the hardness of ibuprofen tablets made from crystallized ibuprofen in absence of starch and in the presence of 0.25% starch was reduced from 50 to 42 N and from 45 to 38 N respectively. In some cases a similar pattern was obtained when ibuprofen samples crystallized in the presence of different concentration of sodium starch glycolate was compressed at different pressures (Fig. 3B).

Generally, poor compactibility of powders could be due to a poor or lack of plastic deformation during compaction or lower elastic moduli of powders which is accompanied by high elastic recovery. When the pressure is removed the stored elastic energy is released which leads to a volume expansion of the particles and the tablet. This in turn can break (or weaken) the bonds between particles (at atomic distances) formed during the compaction process which leads to an increase in the porosity of tablets and reduction in the tablet hardness.[36] The authors believe that in the present study at optimum compaction pressure, the tablets can retain their integrity much better (low tablet porosity) compared to the tablets compressed at high pressures. For example the porosity of tablets made from crystallized ibuprofen without any additives was 22.0 ± 1.2, 17.2 ± 2.1 and 20.0 ± 1.1% at compaction pressures of 35, 105 and 175 MPa respectively. This indicates that the maximum hardness was obtained when the porosity was the least. Similar patterns were observed for ibuprofen samples crystallized in the presence of 5 and 10% starch. The tablet porosities for 5% starch samples were 30.1 ± 1.0, 25.4 ± 1.4 and 35.5 ± 1.5% and for the 10% starch samples it was 37.1 ± 0.9, 32.0 ± 1.8 and 36.2 ± 2.1% at compaction pressures of 35, 105 and 175 MPa respectively. A similar conclusion was reported for caffeine tablets where the tensile strength of caffeine tablets compressed at low pressure was much higher than those tablets compressed at very high pressures.[37] A reduction in the mechanical strength of tablets could be due to high elastic deformation which is a common sign of over-compaction. The reduced tablet hardness of some formulations in the present study suggest that the detrimental effect of porosity as a result of elastic recovery on tablet mechanical strength may have outplayed the bonding strength acquired due to elevated pressures. It has been reported that these alterations in hardness of tablets with compaction load changes could be due to changes in the elasticity of starch and sodium starch glycolate which changes the bonding between particles under compaction.[38]

Fig. 3 also showed that in most cases treated ibuprofen samples (with or without disintegrant) showed higher mechanical strength compared to untreated ibuprofen samples particularly in case of ibuprofen engineered without the

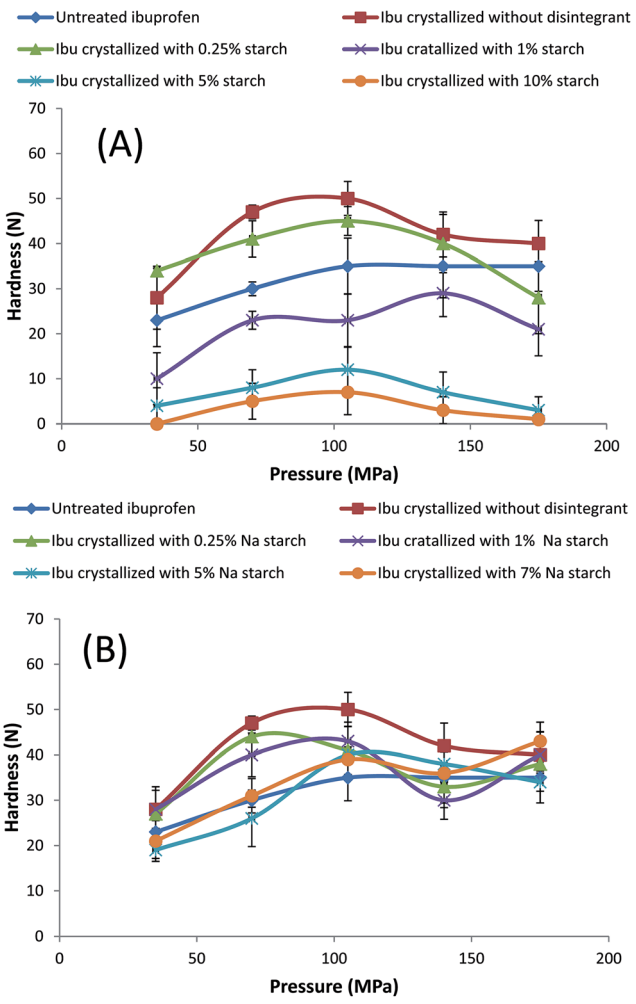

Fig. 3 Hardness–pressure profiles of various engineered ibuprofen tablets in presence of starch (A) and sodium starch glycolate (B).

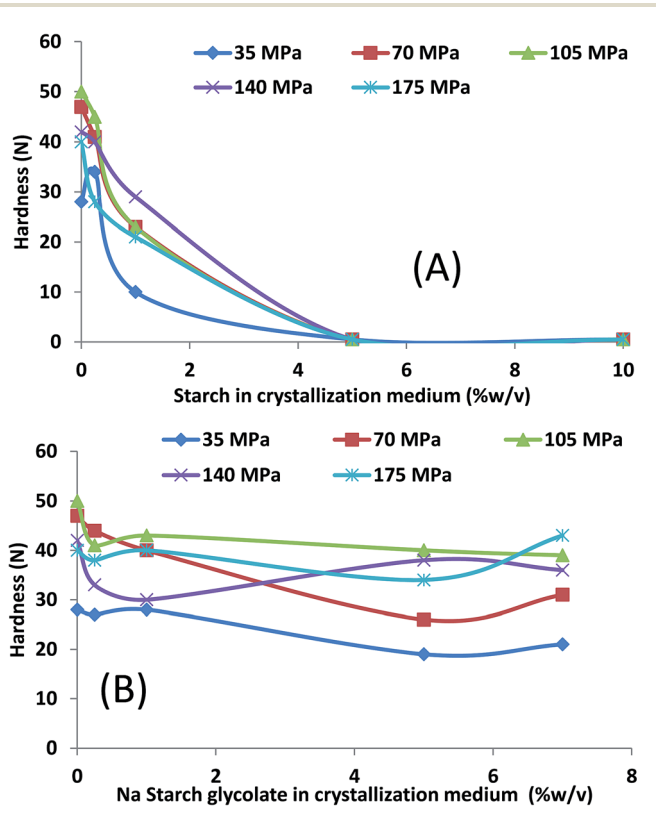

Fig. 4 The effect of %disintegrant (starch (A) and sodium starch glycolate (B)) used in the crystallization medium on hardness of ibuprofen tablets.

presence of additives. But the presence of additives is essential to get improved dissolution which is discussed later in the dissolution section. In order to have a better visualization of the effect of concentration of disintegrant on hardness of ibuprofen tablets the concentration of disintegrant used in the crystallization medium *versus* hardness was plotted (Fig. 4). It can be seen from Fig. 4A that as the concentration of starch in the crystallization medium increases the hardness seems to decrease remarkably. The tablets made from the samples Ib4 and Ib5 (starch 5% and 10% w/v respectively) were very weak under any compaction pressure used in the present study (Fig. 4A) which might be due to poor bonding properties of starch which tends to increase capping leading to very poor mechanical strength particularly at high concentration of starch.[39] This was not the case for ibuprofen samples crystallized in the presence of sodium starch glycolate. It has been reported that Na starch glycolate was successfully used in direct compaction formulations.[40] It is obvious from SEM images in the cases of 5 and 10% starch that the surface of the ibuprofen crystals were covered mostly by starch particles and as such during the compaction process, bonding occurs only between starch particles (Fig. 1) which are weaker than the bonding between ibuprofen–starch particles. It has been reported that this bonding between starch–starch particles is weak which could be the main reason for the poor mechanical strength of tablets obtained for these two formulations when high concentration of starch was used.[39]

In case of sodium starch glycolate less sensitivity of the hardness of ibuprofen tablets against the concentration of sodium starch glycolate was observed (Fig. 4B). It was interesting to note that at high compaction pressures (140 and 175 MPa), higher concentration of sodium starch glycolate produced harder tablets. This might be due to the better compactibility of sodium starch glycolate in comparison with starch. The higher hardness values of the tablets are indicative of stronger interparticulate bonding between the agglomerates compared to the untreated crystals.

For a better comparison between untreated ibuprofen and treated ibuprofen in the presence of disintegrants, physical mixtures of ibuprofen–disintegrant which have identical composition to the treated samples were prepared (only 0.25 and 1% disintegrants were prepared as higher concentration of starch 5 and 10% gave tablets with very poor mechanical strength). The hardness values of the physical mixtures and treated ibuprofen–starch were shown in Fig. 5A. The results showed that in most cases treated samples in absence or

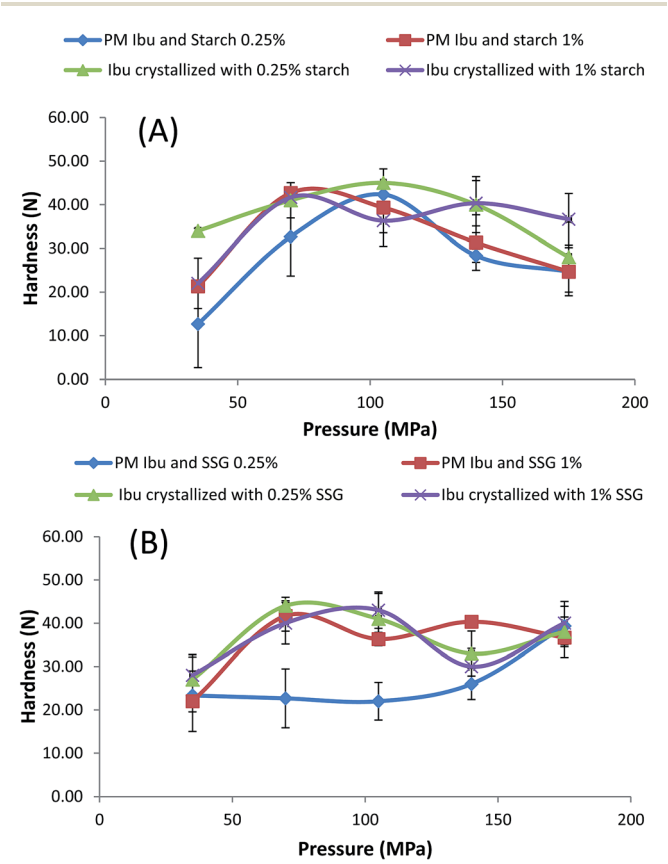

Fig. 5 Comparing hardness–pressure profiles between crystallized ibuprofen and their physical mixture counterparts (SSG = sodium starch glycolate; PM = physical mixture; Ibu = ibuprofen).

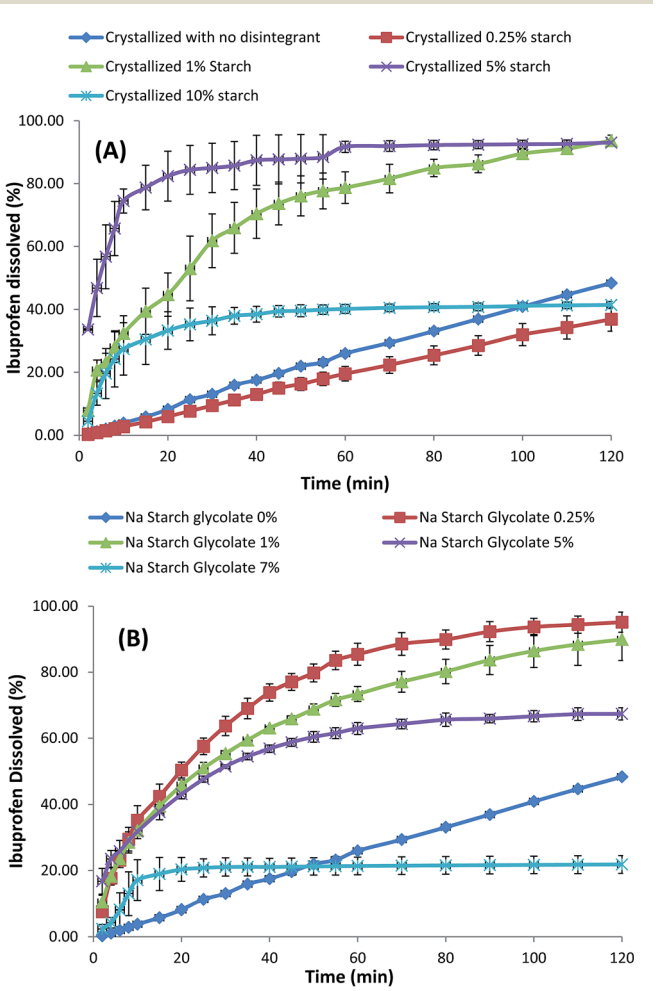

Fig. 6 Dissolution profiles of various crystallized ibuprofen from tablets made at 105 MPa compaction pressure ((A) samples containing starch and (B) samples containing sodium starch glycolate).

presence of additives showed better mechanical strength compared to their counterpart physical mixtures. It has been reported that poor compactibility of drug crystals can be attributed to the presence of crystal faces that give poor adhesion to other crystals and the absence of the faces that are required for optimal adhesion.[7] Here, for the ibuprofen crystals, the relative abundance of the different faces within the crystals was modified. This can affect the interparticulate bonding between these crystals, resulting in different compression properties.

It is known that there is a high affinity of the ibuprofen powder to stick to the tablet punches.[11] The common crystals stick to the punches due to its high cohesivity. A sticking to the punches was not observed for ibuprofen that was crystallized in the presence of starch or sodium starch glycolate. This indicates that differences concerning the surface structure of the crystals occur during the employed crystallization process. Previous research has shown that adhesion of ibuprofen formulated with 29.5% lactose monohydrate (Tablettose®) to the tablet punches during tableting is influenced by the type of tooling used and the type and level of lubricant in the formulation.[41] The adhesion of ibuprofen to the upper punch was determined by removing the upper punch and dissolving the powders stuck to the punch in ethanol after each compaction. The amount of ibuprofen in the solution was spectrophotometrically determined. Roberts *et al.*[41] showed that all ibuprofen formulations adhered to the punches with the highest being around 8 μg mm^{-2}, whereas this was not the case for the recrystallized ibuprofen in the absence and presence of starch derivatives used in the present study and there was no need to incorporate a direct compression filler such as Tablettose®. This may be accredited to a change in the interaction between the punch face and particle surface as a result of the different morphology obtained following recrystallization as compared to untreated ibuprofen.

3.5. Dissolution studies

Dissolution behaviour of all ibuprofen samples are shown in Fig. 6. It is obvious from Fig. 6A that ibuprofen crystallized in the presence of 1 and 5% starch showed superior dissolution compared to ibuprofen samples crystallized in the presence of 0.25% and 10% starch in the crystallization medium. It was observed that the low concentration of starch was not sufficient to disintegrate ibuprofen tablets thus leading to a slow dissolution profile (only 0.8% w/w starch associated with ibuprofen particles when the ratio of ibuprofen : starch in the crystallization medium was 3 : 0.25 w/w). In the case of the highest

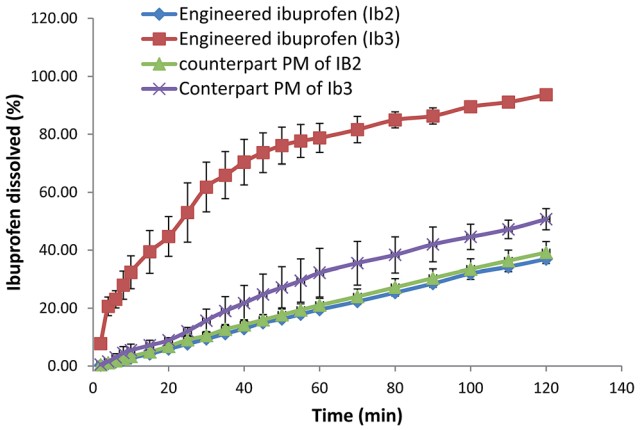

Fig. 7 Comparing the dissolution profiles of crystallized ibuprofen and their physical mixture counterparts compressed at 105 MPa (PM = physical mixture; Ib2 and Ib3 contained 0.25 and 1% starch in their crystallization medium respectively).

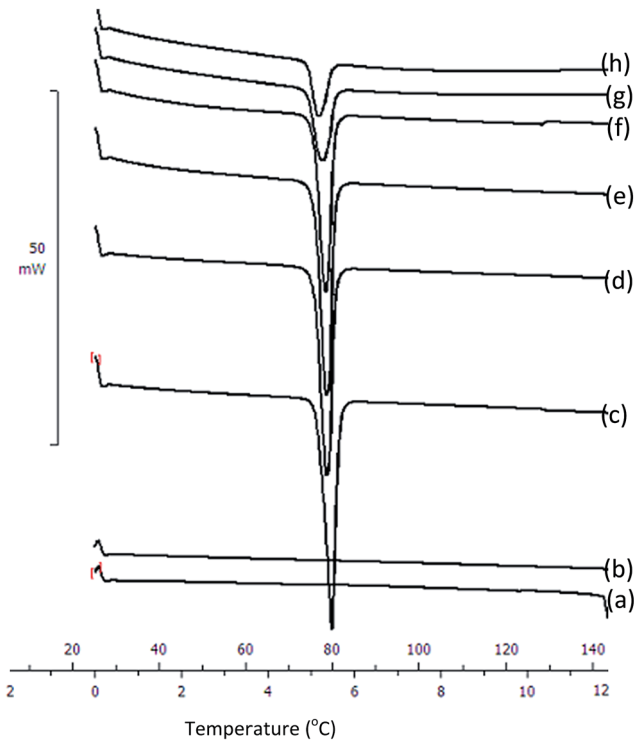

Fig. 8 DSC traces (a) Na starch glycolate, (b) maize starch, (c) untreated ibuprofen, and ibuprofen crystallized in presence of (d) 0% disintegrant, (e) 0.25% starch, (f) 1% starch, (g) 5% starch, (h) 10% starch (the mentioned percentages are the percentage of disintegrants in the crystallization medium).

Table 4 DSC and assay data obtained for various formulations[a]

Formulation	Peak (°C)	Enthalpy (J g^{-1})	%Ib (obtained from UV)
Pure ibuprofen	78.97 ± 0.23	119.8 ± 19.4	100
Ib1	77.59 ± 0.09	113.9 ± 1.6	99.4 ± 1.9
Ib2	77.63 ± 0.03	114.7 ± 0.5	99.2 ± 0.1
Ib3	77.57 ± 0.07	103.2 ± 1.5	87.8 ± 3.1
Ib4	77.12 ± 0.25	53.1 ± 0.1	57.1 ± 7.5
Ib5	76.35 ± 0.07	29.2 ± 3.3	29.8 ± 2.7
Ib6	77.59 ± 0.14	110.2 ± 2.3	92.1 ± 2.4
Ib7	77.66 ± 0.03	100.3 ± 2.2	83.3 ± 0.2
Ib8	77.76 ± 0.22	92.5 ± 0.2	81.1 ± 1.2
Ib9	77.85 ± 0.23	71.2 ± 1.8	66.6 ± 4.5

[a] Values are represented as mean SD, $n = 3$.

concentration of starch (ibuprofen : starch 3 : 10 w/w; theoretically contains 76.9% starch) used in the crystallization medium, it was shown that after crystallization this sample contains around 70% starch therefore, during the dissolution process, the presence of such high concentrations of starch around ibuprofen particles generates a very viscose solution around ibuprofen particles leading to a slow penetration of dissolution media into the tablet hence poor dissolution. Similar conclusion was suggested by Homayouni *et al.* when PVP and soloplus were used to improve the dissolution of celocoxib.[42,43]

Table 1 shows that in the case of sodium starch glycolate, more disintegrant attached to ibuprofen particles compared to starch when the ratio of ibuprofen : disintegrant was 3 : 0.25 w/w (this formulations contained around 8% sodium starch glycolate) (Table 4) therefore faster dissolution was expected for this formulation (Fig. 6A). But, as more Na starch glycolate was incorporated, the dissolution rate became slower due to the formation of a very viscose gel around ibuprofen particles during the dissolution process making it difficult for the dissolution medium to penetrate into the tablet or granules thereby retarding the diffusion of the drug solution from the tablet to the dissolution medium. Similar findings were found and reported for methylprednisolone and phenylbutazone when high concentration of sodium starch glycolate was incorporated in their tableting formulations.[44] For example at very high concentration of disintegrant (ibuprofen : disintegrant 3 : 7 w/w; contains 70% disintegrant) during the crystallization process around 33% Na starch glycolate will be associated with the ibuprofen particles which is high enough to make a viscose gel around the particles (see Tables 1 and 4).

For better comparison of the dissolution performance of crystallized ibuprofen in the presence of disintegrants, further dissolution tests were carried out only on starch samples as this disintegrant is the most commonly used disintegrant and also it is very cheap. To this end two ratios of ibuprofen : starch (3 : 0.25 and 3 : 1 w/w) were selected and their physical mixture counterparts were prepared (exactly the same composition as crystallized samples). Crystallized ibuprofen in the presence of starch (1% formulation) showed a remarkably faster dissolution as compared to its physical mixture counterpart (Fig. 6). Ibuprofen crystallized with a low concentration of starch

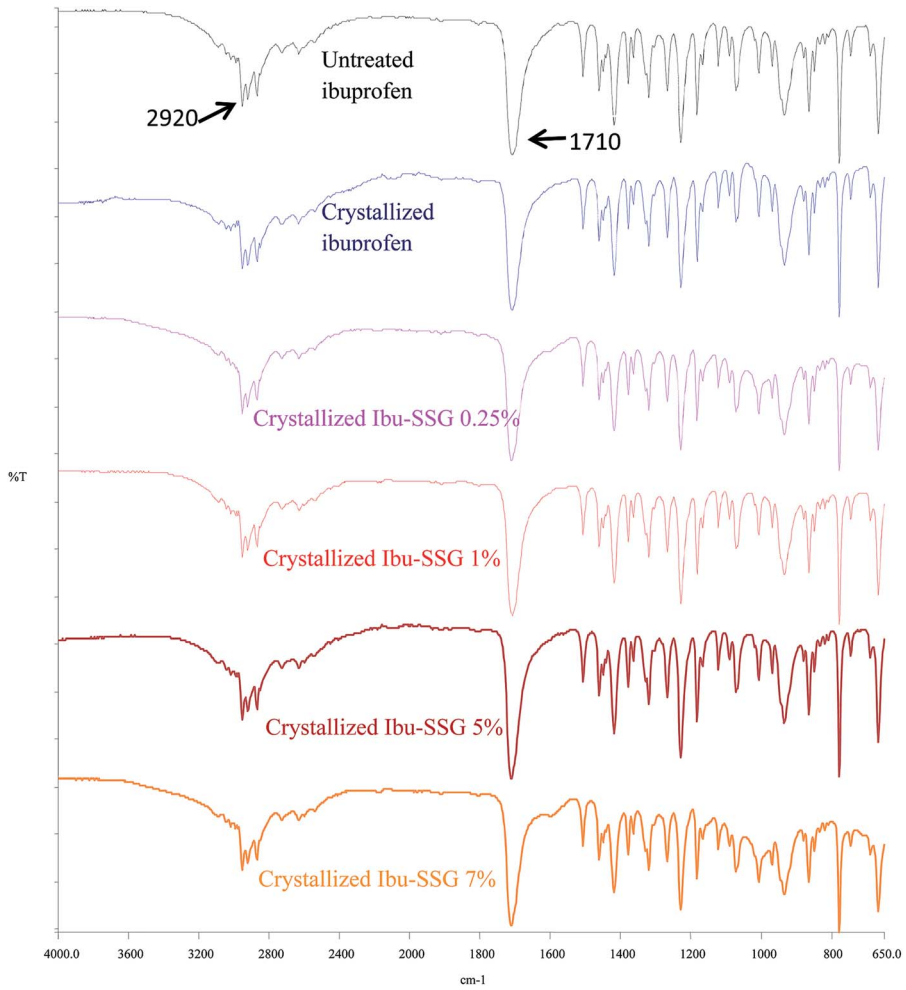

Fig. 9 FT-IR of some of crystallized ibuprofen samples and the excipients used in the crystallization medium (Ibu = ibuprofen; SSG = sodium starch glycolate).

(0.25%) did not show any significant difference with its physical mixture counterpart (Fig. 7).

3.6. Differential scanning calorimetry (DSC)

DSC can be used to determine the polymorphic composition of pharmaceutical powders, if two or more polymorphs are present. As it was shown in Fig. 8 all samples, irrespective of disintegrant type and concentration, showed a sharp melting point (single exothermic peak) which indicates that the modified ibuprofen samples are isomorphic with the starting material (ibuprofen). The results showed that there was no significant difference between melting points of untreated ibuprofen sample 78 °C and agglomerated samples ranging from 77.12 to 77.85 °C ($P > 0.05$) (Table 4). These results are in agreement with previous reports indicating that ibuprofen exists as a stable crystalline solid exhibiting a typical melting range of 75–77 °C.[7]

Table 4 shows a slight reduction in the enthalpy of ibuprofen crystallized in the absence of disintegrant (Ib1) compared to untreated samples which could be due to differences in their particle sizes. These changes in DSC data may be an effect of crystal size (crystal habit) and the amount of disintegrant contained in the sample.[6,45] A significant reduction in enthalpy of the treated samples in the presence of disintegrant is due to the presence of disintegrant in the samples. These enthalpies can be well correlated to the amount of disintegrant associated with the samples after crystallization (Table 4). A reduction in the enthalpy of crystals has been reported for other drugs as the presence of dissolved impurities (additives) may change the rate of crystallization and crystal habit by adsorbing the surface-active agents to the nuclei or growing crystals.[46]

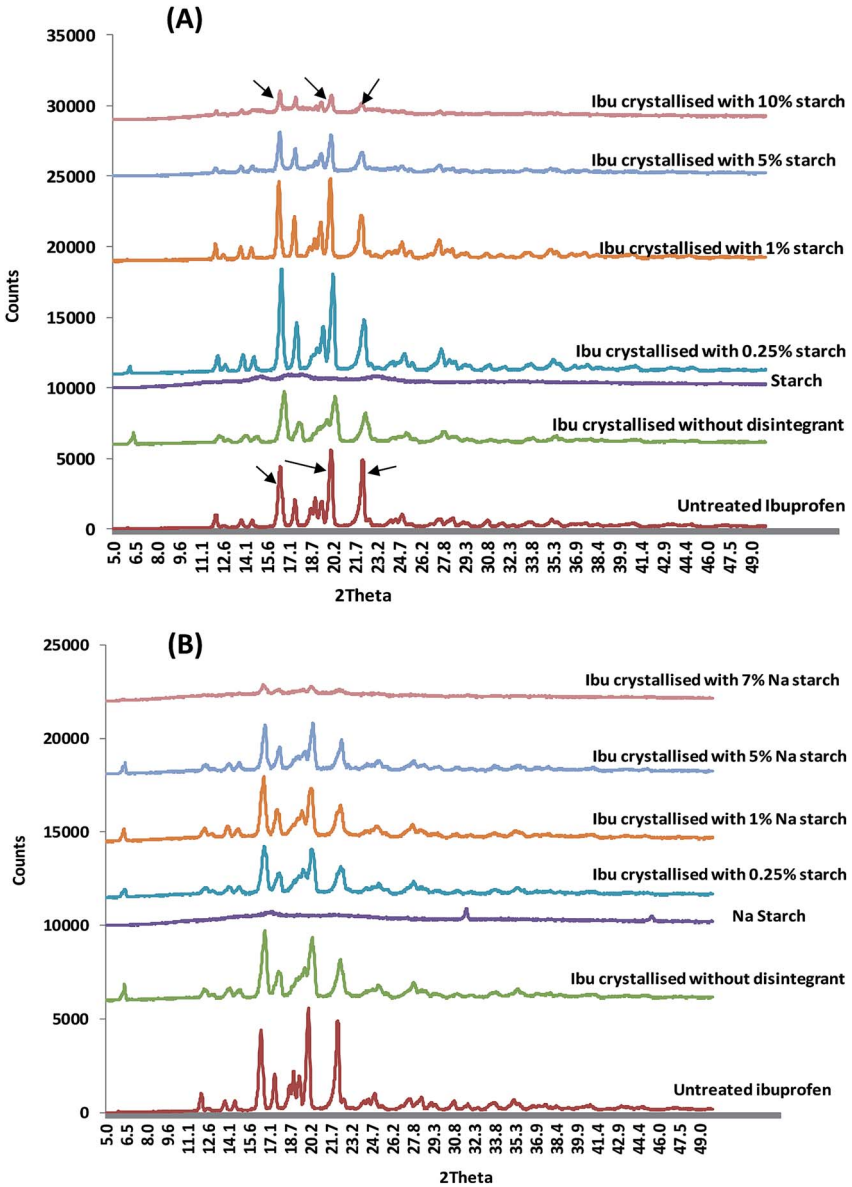

Fig. 10 XRPD of various ibuprofen crystallized in the presence and absence of starch (A) and sodium starch glycolate (B).

The assay results presented in Table 4 show that the value of ibuprofen assay is higher than expected value. This indicates that during the crystallization process some of the disintegrants were lost leading to high contribution of ibuprofen in the samples.

3.7. FT-IR

The FT-IR spectra of ibuprofen showed characteristic peaks at 1710 cm^{-1} and 2920 cm^{-1} due to carbonyl and hydroxyl stretching respectively (Fig. 9). These characteristic peaks appeared in all FT-IR spectra of crystallized ibuprofen samples indicating no changes in molecular level of ibuprofen when it is recrystallized in the presence of sodium starch glycolate (as ibuprofen–starch samples showed the same pattern, thus, their FT-IR spectrum were not included). The DSC results also confirmed that the chemical structure had not changed. Therefore the procedure used for the preparation of modified ibuprofen crystals involved only physical interactions of particulate materials, rather than chemical interactions. Comparison of FT-IR spectrum of original drug with that of crystallized ibuprofen did not reveal any distinctive changes. Both original and crystallized ibuprofen powders showed identical FT-IR spectra. All samples exhibited the same characteristic crystal intensity peaks and excluded any amorphous form.

To confirm the above findings XRPD was carried out on all samples including pure ibuprofen and disintegrants used in the present study (Fig. 10). It has been reported that ibuprofen characteristics peaks are in 2θ of around 16, 20 and 22.[47] These peaks are shown in Fig. 10 using black arrows. All XRPD shown (except pure starch and sodium starch glycolate) in Fig. 10a and b contained all these three diagnostic peaks showing the crystalline nature of the ibuprofen in these formulations. The smaller intensity of the samples crystallized in the presence of additives could be due to amorphous nature of starch and sodium starch glycolate associated with the ibuprofen. In case of ibuprofen crystallized in absence of additives the difference in the relative intensity of the peaks is due either to the variation of the crystal habit, because the relative abundance of the planes exposed to X-ray source is altered, or to differences in the size of the crystals.

4. Conclusion

Ibuprofen was successfully engineered in the absence and presence of two disintegrants namely; starch and Na starch glycolate. The crystallisation process changed the morphology of the ibuprofen crystals. DSC and FT-IR analysis however showed that all interactions were on the physical level and not chemically induced. There were no polymorphic changes either to the ibuprofen with Na starch glycolate improving the compaction properties of the ibuprofen especially at high pressures. Although, ibuprofen crystallized in the presence of Na starch glycolate produced harder tablets compared to the samples recrystallized in the presence starch, tablets made from the crystallized ibuprofen without any additives exhibited the highest tablet hardness. Dissolution properties were significantly improved for ibuprofen crystallised in both 1 or 5% starch and 0.25–5% Na starch glycolate. The highest concentration (10% starch and 7% Na starch glycolate) of disintegrant proved detrimental to dissolution due the formation of a viscous layer around the ibuprofen particles thereby slowing down dissolution. The engineering of ibuprofen thus proved beneficial in reducing the sticking on punches and improving compaction and dissolution behaviour.

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