The dissolution and solid state behaviours of coground ibuprofen-glucosamine HCl

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Abstract

The cogrinding technique is one of most effective methods for improving the dissolution of poorly water soluble drugs and it is superior to other approaches from an economical as well as an environmental stand point, as the technique does not require any toxic organic solvents. Present work explores the role of D-glucosamine HCl (GL) as a potential excipient to improve dissolution of a low melting point drug, ibuprofen (Ibu), using physical mixtures and coground formulations. The dissolution of the poorly soluble drug has been improved by changing the ratio of Ibu:GL and also grinding time. The results also showed that although GL can enhance the solubility of Ibu, it also reduces pH around the Ibu particles which led to poor dissolution performance when the concentration of GL is high. The effect of GL on the solubility of Ibu could be misleading if the pH of the final solution was not measured. Grinding reduced the particle size of GL significantly but in case of Ibu it was less effective. Solid state analysis (XRPD, DSC and FT-IR) showed that ibuprofen is stable under grinding conditions, but the presence of high concentration of GL in samples subjected to high grinding times caused changes in FT-IR spectrum of Ibu which could be due to intermolecular hydrogen bond or esterification between the carboxylic acid group in the ibuprofen and hydroxyl group in the GL.

Keywords: Cogrinding, Glucosamine HCl, Dissolution enhancement, Solubility, Solid state,

Introduction

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. Many potential drug candidates are characterized by a low oral bioavailability due to their low solubility or dissolution rate. This is the reasoning behind the enhancement of the dissolution or solubility of poorly water soluble drugs particularly Class II drugs. Researchers have applied several techniques to improve the drug dissolution, namely micronization,[1] solid dispersion,[2] solvent deposition,[3] ordered mixtures,[4] roll-mixing [5] and complexation.[6] The size reduction method has also been extensively utilised[7-8] because the increase in surface area can enhance the dissolution and consequently the bioavailability of pharmaceutical materials. Size reduction of pharmaceutical materials is often performed by the dry milling process, but the size reduction by dry milling is limited at around 3 μm due to aggregation between particles. Grinding is generally used for reducing particle size since the dissolution is strongly affected by particle size. It has been reported that a strong force (such as grinding) may increase the surface free energy and cause distortion of the crystal lattice as well as reducing particle size.[9] It has been reported that the size reductions in nanometer range can be carried out by other techniques such as salt-assisted milling.[10] Recent research has explored particle size reduction to the submicron region by cogrinding with additives.[11-14] Cogrinding is economically and environmentally desirable as, unlike other techniques, it does not require toxic solvents[15] and sophisticated equipment.[16] Although ibuprofen (Ibu) particle size is small enough to dissolve well, it is poorly soluble in an aqueous solution. It belongs to class II of the biopharmaceutical classification system (BCS) and is characterized by a high per-oral dose, low aqueous solubility and high membrane permeability. Therefore, the bioavailability of ibuprofen is limited by the poor dissolution.

Glucosamine (GL) is a naturally occurring, highly water soluble, non-toxic compound derived from the exoskeletons of arthropods. When it is given orally, it has been shown to decrease pain and improve mobility in osteoarthritic joints of humans.[17-18] This has led to its popular use as a nutritional supplement in both humans and dogs. This monosaccharide is one of a family of amino sugars and is a weak base. Due to the instability of glucosamine, its salts (either hydrochloride or sulphate) are used in therapy[19] but glucosamine HCl is more stable than glucosamine sulphate.[20] Our previous results showed the ability of glucosamine as a hydrophilic carrier to enhance the dissolution of CBZ in solid dispersion formulations [21] and ground formulations containing piroxicam.[22] Ibuprofen has a low melting point (around 76 ^{o}C) compared to carbamazepine (192 ^{o}C) and piroxicam (around 200 ^{o}C) and it is not clear that glucosamine could be a potential excipient to improve the dissolution of low melting points drugs such as ibuprofen from coground formulations as under grinding conditions ibuprofen might melt. In other words, the melting point of ibuprofen is fairly low compared to piroxicam and carbamazepine and during grinding the temperature can go up closer to the melting point of ibuprofen. Therefore, this work explores the use of D-glucosamine HCl as a potential excipient to improve the dissolution of drugs with low melting points such as ibuprofen in coground formulations. Meanwhile, the effect of the order of grinding on dissolution of ibuprofen was also investigated. The physicochemical characteristics and solid state of the prepared coground systems, morphology of particles and their solid state were also studied to investigate any interaction between drug and glucosamine HCl.

Materials and methods

Materials

Ibuprofen (Ibu) was purchased from Spectrum (USA). D-(+)-glucosamine hydrochloride (Sigma, USA) was used as a hydrophilic carrier. All materials were of analytical grade and used as obtained.

Preparation of coground mixtures of drug-carrier

Coground samples of different ratios of drug to carrier (4:1, 1:4, and 1:10) were prepared using ball mill (Fritsch, Germany). The total amount of drug: carrier was kept constant for all formulations (20 g). The volume of the ball mill chamber was 250 ml and eight steel balls were used with diameter of 20 mm occupying one third of volume of the chamber. The vibration rate was set to 400 rpm. The samples were subjected to different grinding times (1, 10 and 20 minutes). In order to investigate the effect of grinding process on dissolution behaviour of ibuprofen, the drug was ground separately in absence of glucosamine. Then the mixture of ground ibuprofen and un-ground D-glucosamine HCl were prepared by mixing them in a tubula blender for 10 min. Different ratios of drug: carrier (4:1, 1:4 and 1:10) were prepared for comparison purposes. After mixing, the powders were stored in a screw-cap glass vial at room temperature until used.

An attempt was also made to further investigate the effect of ibuprofen's particle size on dissolution by preparing different size fractions of ibuprofen (63-90, 90-125, 125-250 and >250 μm). Different source of ibuprofen with a wider particle size distribution was purchased from IMCD (UK) to get the different size fractions for this study.

Preparation of ground ibuprofen

Ibuprofen was ground on its own for different grinding times 1, 10 and 20 min. This was carried out to investigate the effect of grinding time on ibuprofen dissolution behaviour in the absence of any excipients.

Preparation of physical mixtures of drug-carrier

Physical mixtures of drug and carrier were prepared by mixing ibuprofen and D-glucosamine hydrochloride in a turbula blender for 10 min. The same ratios of drug: carrier (4:1, 1:4 and 1:10) were also used in the preparation of physical blends as used in the preparation of coground formulations. This was to ensure a comparison could be made with the ground Ibu-glucosamine formulations. The physical mixtures were stored in a screw-cap glass vial at room temperature until used.

Solubility studies

Solubility of ibuprofen was performed according to a previously published method.[22] Also, an excess of ibuprofen was added to 10 mL of phosphate buffer pH 7.4 containing different concentrations of D-glucosamine hydrochloride. The capped test tubes were shaken at 37 °C for 72 h in a water bath (Clifton, UK). Subsequently, the suspensions were filtered through a 0.45-μm membrane filter, and the filtrates were diluted with pH 7.4 phosphate buffer to get absorbance between 0.1 and 1.5 (a calibration curve was constructed for different concentrations of ibuprofen solutions at pH 7.4 with a correlation coefficient of 0.999). The diluted solutions were analyzed to determine the concentration of ibuprofen using a UV spectrophotometer (Shimadzu 160A) at 221 nm. The solubility results reported in Table 1 are the mean and standard deviation of at least three determinations. The preliminary results

showed that there was no interference between ibuprofen and glucosamine at this wavelength.

Dissolution studies

A USP dissolution apparatus no. 1 (basket method) was used to monitor the dissolution profiles of ibuprofen ground powders and physical mixtures. All formulations used to fill the capsules contained the same amount of ibuprofen drug content (200 mg). The dissolution medium was 900 mL pH 7.4 equilibrated to 37˚C and the baskets were rotated at 75 rpm according to USP XXVIII. From the dissolution flask, samples were withdrawn at selected time intervals (5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105 and 120 min) using a peristaltic pump and the concentrations of ibuprofen in the samples were determined by UV spectrophotometer at 221 nm. A minimum of three determinations for each sample was carried out. For comparison purposes, dissolution testing was carried out for all the physical mixtures.

Dissolution parameters

Various dissolution parameters, namely dissolution efficiency (DE), mean dissolution time (MDT) and mean dissolution rate (MDR), were used to quantify the dissolution performance of ibuprofen formulations. The DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to the time, t, expressed as the percentage of the area of the rectangle.[23]

$$DE = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

Where y is the percent of drug dissolved at time t.

The MDT is the most likely time for a molecule to be dissolved from a solid dosage form. This is calculated using the following equation:

$$\text{MDT} = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

Where j is the sample number, t_j is the midpoint of the $_j$th time interval (easily calculated with ((t + t-1)/2) and ΔM_j is the additional amount of drug dissolved between t_j and t-1.

The MDR can be calculated according to the following equations.

$$\text{MDR} = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n}$$

Where *n* is the number of dissolution sample times, Δt is the time at midpoint between t and t-1, easily calculated with [t + (t-1)/2].

Scanning electron microscopy

Electron micrographs of ibuprofen ground mixtures were obtained using a scanning electron microscope (Leica Cambridge S360, UK) operating at 15 kV. The samples were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were taken to study the morphology of the ground mixtures.

Fourier transform infrared (FT-IR) studies

FT-IR spectra (range 650-4000 cm^{-1}) of ibuprofen ground mixtures or physical mixtures were recorded using ATR with an FT-IR spectrophotometer (PerkinElmer, UK). A few milligrams of sample were placed on the middle of the sample stage using a micro spatula

and force applied by twisting the top of the arm of the sample stage. The spectra were the result of averaging 4 scans at 1 cm^{-1} resolution.

Differential scanning calorimetery (DSC) studies

Samples of ground or physical mixtures of ibuprofen-glucosamine (3-6 mg) were placed in standard aluminium pans (40 µl) sealed with a lid. The crimped aluminum pans were heated from 20 to 350 ˚C at a scanning rate of 10 ˚C/min under nitrogen gas. The enthalpy, onset temperatures and melting points of the samples were automatically calculated using the software provided (Mettler-Toledo, Switzerland).

Results and discussion

Dissolution studies

The release profiles of ibuprofen from mixtures of ibuprofen-glucosamine with different ratios ground for different times (1, 10 and 20 min) are shown in Figures 1a to 1c. It is clear from Figure 1a that the dissolution of untreated ibuprofen is not as good as coground samples. When ibuprofen-glucosamine mixture with the ratio of 4:1 was subjected to different grinding times an improvement in the dissolution was observed. Figure 1a shows that grinding time has an impact on the dissolution of ibuprofen from ground samples. When the ratio of drug:carrier was 4:1, 1 min grinding was sufficient to produce the fastest dissolution. For the samples containing a high glucosamine concentration (ratio of drug to carrier 1:4 and 1:10, Figures 1b, 1c), a reduction in dissolution was observed with most of the coground samples of the ibuprofen-glucosamine giving a lower dissolution than that of the untreated ibuprofen. This could be due to a reduction in the pH of the dissolution medium around ibuprofen particles at high concentration of glucosamine. Glucosamine is a weak base which can reduce the pH of the dissolution medium around ibuprofen particles when it

dissolves (the pH of 1, 5, 10 and 15 %w/v of glucosamine HCl in phosphate buffer in absence of ibuprofen with nominal pH of 7.4 measured immediately was reduced to 6.4, 5.8, 5.3 and 3.4 respectively). Therefore, as the solubility of ibuprofen is pH dependent,[24] the dissolution rate of ibuprofen is expected to decline when pH reduces due to the presence of an increasing content of glucosamine in the samples.

Figure 1a also shows that an increase in the grinding time from 1 min to 20 min caused a reduction in the dissolution of ibuprofen samples. This reduction with an increase in grinding time was still an improvement over that of the untreated ibuprofen samples. This is an advantage for high dose drugs such as ibuprofen and carbamazepine as generally the final weight of the mixtures of these drugs with carrier to produce high dissolution rate can exceed 1 g and it is often difficult to accommodate more than 1 g powder in a capsule. The results presented here showed that glucosamine could be an ideal carrier to enhance the dissolution rate of ibuprofen at low concentration of glucosamine and low grinding times. In addition, the presence of glucosamine in ibuprofen would be of extra benefit as it has been proved that glucosamine is a useful chemical in osteoarthritis.[25] Comparing all dissolution profiles in Figure 1 shows that the effect of grinding time is dependent on the ratio of Ibu:GL used in the formulation.

These results indicated that there is an optimum level for glucosamine to increase the dissolution of ibuprofen and beyond this optimum, the drug dissolution decreases which could be due to a reduction in the pH of the solution as more glucosamine was used. This is consistent with solid dispersion data previously reported for carbamazepine,[21] where the dissolution rate of CBZ was improved by the presence of glucosamine but there was an optimal concentration of the carrier to have a maximum dissolution

The above conclusion was supported by DE, MDT, and MDR reported in Table 1. On the basis of these dissolution parameters the highest DE_{120min} (69.0%) and MDR (1.14 % min^{-1}) and the lowest MDT (27.7 min) was observed for the sample with the ratio of drug to carrier 4:1 ground for 1 min. This indicated that the cogrinding of ibuprofen with GL can significantly improve dissolution efficiency of ibuprofen samples. DE data showed that cogrinding of ibuprofen-glucosamine above 1 min at 4:1 ratio did not improve or change the DE remarkably (Table 1).

Dissolution of ibuprofen from physical mixtures showed that the presence of glucosamine was unable to increase the dissolution of ibuprofen (Figure 2), even in case of 4:1 and 1:4 a reduction in dissolution efficiency of the samples was observed (in Table 1, grinding time 0 is an indication of physical mixture). An increase in DE of physical mixtures of ibuprofen-glucosamine from 31.5% (Ibu:GL, 4:1, concentration of GL is 20%) to 46.9% (Ibu:GL, 1:10, concentration of GL is 91%) occurred. However, there was no significant difference ($p>0.05$) between the 1:10 ratio with untreated ibuprofen (DE was 45.4%) indicating that the presence of glucosamine in the physical mixtures of ibuprofen was unable to enhance the dissolution rate of ibuprofen significantly (Figure 2).

To investigate the effect of grinding on untreated ibuprofen on its dissolution, the second series of experiments was designed. In this series the untreated ibuprofen was ground for 1, 10 and 20 min in the absence of glucosamine. The dissolution profiles and dissolution parameters for this series of experiments are shown in Figure 3 and Table 1 respectively. Table 1 showed that the ground ibuprofen caused a significant reduction in the dissolution of the untreated ibuprofen (as from manufacturer) (ANOVA test, $p< 0.05$). The reduction in the

dissolution of ibuprofen could be due to the presence of larger ibuprofen particles as a result of agglomeration (Table 2). The presence of very fine and large ibuprofen particles caused an increase in span values, indicating wider particle size dissolution. However, enhancing the dissolution of poorly water soluble drugs by grinding such as griseofulvin[26] and naproxen[27] has been reported.

Although Table 2 shows that the coground samples demonstrated different average particle sizes, no relationships between particle size and dissolution was established. For example, high grinding time reduced the average particle size of coground samples from 20.0±1.1 (ratio of drug:carrier 1:10, ground for 1 min) to 1.9±0.04 µm when grinding time was increased to 20 min (Table 2). On the basis of particle size, one would expect to see a significant increase in the dissolution of the ground sample for 20 min. There was however a slight increase in the dissolution efficiency of this sample (around 5% increase compared to the sample ground for 1 min) (Table 1) though this increase was not statistically significant ($p>0.05$). This suggests that a reduction in the particle size of coground samples may not be the solution to improving the dissolution of ibuprofen. The authors believe that due to the presence of high surface energy for smaller particles these particles might aggregate when exposed to the dissolution medium whereas this is not the case for larger particles. This could be a reason for coground formulations with very fine articles in some formulations showed slower dissolution (see Tables 1 and 2).

On the basis of the above conclusion, the effect of ibuprofen's particle size (63-90, 90-125, 125-250 and >250 µm) on dissolution was carried out and the results were shown in (Figure 4) (a different source of ibuprofen with a wider particle size distribution was purchased from IMCD (UK) to get the different size fraction for this study). The figure shows the smaller

particles (63-90 µm) to have the slowest dissolution behaviour compared to the larger particles (>250 µm) which could be due to the aggregation of smaller particles as a results of high surface energy. The other fractions showed slightly faster dissolution than the smallest and the largest size fractions. This indicates that the presence of agglomerated drug particles can reduce the drug dissolution.

Although Figure 3 showed that the grinding of pure ibuprofen did not enhance the dissolution efficiency (Table 1), it was decided to explore whether pure ground ibuprofen can show similar behaviour in the mixture of ground ibuprofen with unground glucosamine (Figure 5 and Table 1). The results showed that, in contrast to pure ground ibuprofen samples (Figure 3), all samples containing ground ibuprofen (ground for 10 or 20 min) mixed with unground glucosamine produced the highest dissolution efficiency except the ratio of drug to carrier 1:4. This indicates that the dissolution behaviour of ground ibuprofen in the presence of carrier is different to the dissolution behaviour of pure ground ibuprofen *per se*. The dissolution of ground ibuprofen alone cannot dictate the dissolution of ibuprofen in the mixtures with glucosamine. The authors believe that the ground ibuprofen can be easily dispersed and attached to the surface of the larger glucosamine particles (ordered mixture, Figure 6). This in turn reduces the agglomeration tendency of the fine ground ibuprofen particles when exposed to the dissolution medium. This shows that when untreated ibuprofen was ground alone for 10 or 20 min and mixed physically with the carrier, higher carrier is needed to produce faster drug dissolution.

It is obvious from the above explanation the coground samples of ibuprofen: glucosamine showed conflicting effect of the micronization technique on the dissolution of ibuprofen samples (e.g., the effect of size of particles, concentration of carrier and micronization time).

These contradictory results do not align with the normal effect of micronization technique on the dissolution of different coground mixtures. It is believed that the higher micronization time might cause the agglomeration of particles which has direct relationship to high surface energy of particle. The increase or reduction in the dissolution of ibuprofen might be attributed to the increase in wettability or reduction in pH of the dissolution medium by the presence of glucosamine which is discussed later in the manuscript.

In summary, all dissolution profiles generally showed that the fastest dissolution was obtained when ground ibuprofen (ground for 10 or 20 min) was mixed with unground glucosamine (ratio of drug:carrier 1:10). This was closely followed by cogrinding of ibuprofen with glucosamine for 1 min when the ratio of Ibu:GL was 4:1. This shows that practically it is impossible to embed 2200 mg ibuprofen-glucosamine (1:10) into a capsule whereas in the case of 4:1 ratio the final weight of the samples would be 240 mg. On the basis of this coground formulation of ibuprofen-glucosamine at the ratio of 4:1 is preferable.

Different parameters, such as the ratio of glucosamine, grinding time, and the type of grinding (alone or cogrinding) affected the dissolution of ibuprofen. Each parameter either enhanced or reduced the dissolution of ibuprofen by practicing one or more of the positive or negative effects, respectively. The positive effects include enhancement of ibuprofen by exerting one or more of the following: reduction of ibuprofen particle size, dispersion of glucosamine between ibuprofen, adsorption of fine particles of ibuprofen on the surfaces of glucosamine particles, and improved ibuprofen wettability by glucosamine.

Several studies have reported that an increase in the dissolution of coground samples is due to an enhancement in solubility of drugs in the presence of hydrophilic carrier.[28] The presented

results show that an increase in the concentration of GL up to 5% w/v increased the solubility of ibuprofen, but further increase in the concentration of GL caused a reduction in the solubility from 21.2 mg/ml to 12.3 mg/ml which could be due to a reduction in the actual pH of the solution at the end of the solubility testing procedure due to the use of HCl salt of glucosamine instead of glucosamine base (Table 3). For example the pH of the solution containing 1% GL after 72 h in the presence of ibuprofen in the solubility test was 6.4 whereas in case of 15% GL it was 2.2. As the solubility of Ibu reduces remarkably by a reduction in pH, therefore, this could be the reason for poor solubility of coground samples containing high concentration of GL.

Effect of grinding on the morphology of Ibu-GL formulations

SEM images of untreated Ibu, untreated GL and some of formulations mixtures of Ibu-GL are shown in Figure 6. The figure shows that untreated ibuprofen is elongated in shape whereas GL particles are prismatic crystals. The SEM images of ground GL showed that under grinding larger particles were broken down into smaller particles as the grinding time increased (Figure 6). This was supported by the particle size analysis listed in Table 2. The table shows that when the grinding time increased from 0 to 20 min the mean particle size ($D_{50\%}$) was reduced from 259.3±0.4 to 12.8±0.5 µm (around 20 times reduction in particle size). Whereas in case of pure ibuprofen the mean particle size was reduced 3 times as the grinding time was increased from 0 (29.1±0.6 µm) to 20 min (9.8±0.3 µm) (Table 2). Comparing SEM images of coground samples for ratio of Ibu:GL 4:1 ground for 1 min (Figure 6) and 20 min (Figure 6) showed that there was still a number of original ibuprofen crystals present after 1 min grinding. In the case of the high concentration of GL (Ibu:GL 1:10) smaller average particles (Figure 6 and Table 2) were obtained for 20 min grinding

time (1.9±0.04 µm) compared to 1 min grinding (20.0±1.1 µm). This could be attributed to the fragile nature of GL crystals as discussed for grinding of pure GL.

SEM images of the physical mixtures of ground ibuprofen with unground GL shows that the ground ibuprofen particles adhered to the surface of large unground GL particles (Figure 6) when the concentration of GL is very high. This is less obvious for the samples containing 80% Ibu and 20% GL (Ibu:GL 4:1). The dispersion of ground ibuprofen on large unground GL particles could be a reason for better dissolution of these samples.

Solid state characterization

FT-IR analysis was carried out on all samples to confirm any structural changes at the molecular level. FT-IR spectra for ibuprofen samples ground for different grinding times are shown in Figure 7(I). Bands characteristic of ibuprofen were found at 1710 cm^{-1} and 2955 cm^{-1}, due to carbonyl and hydroxyl stretching vibration respectively. It is apparent from the FT-IR spectra that the samples of ibuprofen subjected to different grinding times exhibited similar IR spectra as the same peaks at the same wavenumber are seen for ground ibuprofen. This indicates that ibuprofen is stable under grinding conditions on its own and no structural changes at the molecular level were associated with it.

In order to investigate the effect of grinding on Ibu in the presence of GL, the lowest and highest grinding times for different ratios of Ibu:GL (4:1, 1:4 and 1:10) were selected and their FT-IR spectra are shown in Figure 7(II). All coground samples showed the same characteristic band for the presence of GL (3288 cm^{-1}) in the samples. Whereas the characteristic band at 1710 cm^{-1} was shifted to higher wavenumbers when the ratio of Ibu:GL decreased. For example at ratio of 4:1 (Ibu:GL) the wavenumber was 1710 cm^{-1} (similar to

unground Ibu) whereas at ratios of 1:4 and 1:10 this wavenumber was shifted to 1714 and 1717 cm^{-1} respectively when the samples were ground for 20 min. The FT-IR shows that grinding time increased the extent of the shift. For example the wavenumber for Ibu:GL 1:10 ratio ground for 1 and 20 min was 1713 and 1717 cm^{-1} respectively. In case of physical mixtures of Ibu:GL for ratios 4:1 and 1:4 the same wavenumber (1710 cm^{-1}) was observed but when the concentration of GL increased (Ibu:GL 1:10) the band was slightly shifted towards higher wavenumber (1712 cm^{-1}, FT-IR spectrum was not shown). This indicates that grinding is the main factor to cause this shift which could be attributed to the formation of intermolecular hydrogen bond or esterification between the carboxylic acid group in the ibuprofen and hydroxyl group in the GL.

DSC was used to investigate any changes in the thermal behaviour of ibuprofen or glucosamine samples subjected to grinding. The DSC traces of untreated ibuprofen and ibuprofen ground for different times are shown in Figure 8. The results showed that the untreated ibuprofen had a sharp endothermic peak around 79 °C with an enthalpy of fusion around 128 J/g (Table 4). Table 4 shows that as the grinding time increased for the untreated ibuprofen, the enthalpy slightly decreased. This could be attributed to the amorphization of ibuprofen as a result of grinding. Comparing the enthalpies between grinding time 0 (127.8 J/g) and 20 min (124.7 J/g) shows that the amorphization did not occur to a large extent. This indicates that ibuprofen is stable under grinding conditions of up to 20 min. Similar results were reported for glipizide[29] where 3 h grinding did not produce a significant amount of amorphous content in the samples, whereas in case of clarithromycine, grinding for 30 min produced a high content of amorphous region.[30]

As all DSC traces for all formulations showed only one peak around the melting point of ibuprofen, therefore, we did not include their DSC traces but their melting points and

enthalpies were listed in Table 4. It is obvious from Table 4 that there is no significant shift in the melting peak of ibuprofen when the ratio of Ibu:GL in the simple physical mixtures was reduced from 4:1 (78.9±0.9 ^{0}C) to 1:10 (77.6±0.2 ^{0}C). The intensity of peak reduces due to a reduction in the concentration of drug in the samples as the ratio of drug:carrier reduces. This indicates ibuprofen did not interact with glucosamine in the physical mixtures.

The coground samples with the ratio of Ibu:GL 4:1 ground for 1, 10 and 20 min showed similar enthalpy and almost similar melting point. When the ratio of ibuprofen:glucosamine reduced to 1:4 or 1:10 the same pattern was obtained regarding the melting point of ibuprofen, but there were changes in the enthalpy of the samples which could be due to lack of high homogeneity of the samples when the concentration of drug is very low.

Thermal behaviour of coground ibuprofen-GL was compared to the thermal behaviour of ground ibuprofen mixed with unground GL. The results did not show big differences in the melting peak of ibuprofen between coground formulations and ground ibuprofen-unground glucosamine. All these indicated that ibuprofen can be ground and physically mixed with glucosamine without any significant interaction between them. Generally coground formulations showed slightly higher enthalpies compared to the physical mixtures of ground Ibu with unground GL. The difference and variations could be due to the lack of a high homogeneity between the samples but it seems coground samples showed better uniformity as the difference between the enthalpies for the same ratio for Ibu:GL with the different grinding times is less.

Conclusion

The present study showed that the role of glucosamine HCl in coground formulations containing ibuprofen is complex. This amino sugar has the capability to enhance the

solubility and hence the dissolution of ibuprofen. The results showed that ibuprofen is stable under grinding condition and can be mixed with glucosamine to improve the dissolution. Care must be taken when ibuprofen is ground in the presence of glucosamine as high concentration of glucosamine at high grinding time caused slight changes in FT-IR of ibuprofen. No changes were reported for coground formulations contacting low concentration of glucosamine subjected to low grinding time. The results showed that glucosamine can be used as a potential excipient in coground of ibuprofen to enhance the dissolution.

Declaration of interest

All authors report no declaration of interest.

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Table 1. Effect of cogrinding time on dissolution parameters of physical mixtures

Drug: carrier ratio	Cogrinding time[a]	DE_{120min} (%)	MDT (min)	MDR (%.min^{-1})
Ibuprofen	0	45.4 ± 5.7	45.8 ± 1.4	0.79 ± 0.10
Ibuprofen	1	32.6 ± 2.9	46.7 ± 8.9	0.55 ± 0.07
Ibuprofen	10	38.9 ± 4.7	48.9 ± 6.7	0.67 ± 0.05
Ibuprofen	20	39.2 ± 11.8	53.3 ± 10.1	0.71 ± 0.10
4:1	0	31.5 ± 7.8	45.5 ± 5.7	0.50 ± 0.14
4:1	1	69.0 ± 0.1	27.7 ± 3.2	1.14 ± 0.02
4:1	10	64.5 ± 7.1	33.5 ± 3.2	1.09 ± 0.14
4:1	20	64.8 ± 12.3	39.7 ± 10.2	1.10 ± 0.20
1:4	0	37.3 ± 8.4	52.1 ± 2.4	0.65 ± 0.16
1:4	1	45.8 ± 7.3	30.3 ± 1.9	0.90 ± 0.14
1:4	10	37.7 ± 5.8	51.6 ± 6.7	0.66 ± 0.08
1:4	20	43.8 ± 5.9	49.3 ± 2.8	0.70 ± 0.08
1:10	0	49.6 ± 1.0	40.9 ± 5.1	0.87 ± 0.04
1:10	1	27.9 ± 5.2	31.1 ± 2.1	0.53 ± 0.11
1:10	10	37.6 ± 4.1	54.4 ± 3.0	0.62 ± 0.03
1:10	20	32.6 ± 4.0	46.1 ± 6.7	0.56 ± 0.06
Mixtures of ground Ibu-Unground GL				
4:1	1	44.9 ± 4.5	49.4 ± 2.6	0.76 ± 0.07
4:1	10	59.5 ± 6.4	33.7 ± 2.7	1.00 ± 0.10
4:1	20	59.7 ± 4.2	26.8 ± 4.6	0.98 ± 0.08
1:4	1	54.0 ± 10.5	34.3 ± 6.7	0.90 ± 0.20
1:4	10	44.2 ± 7.9	18.3 ± 4.5	0.92 ± 0.20
1:4	20	52.7 ± 3.9	35.5 ± 1.7	0.90 ± 0.08
1:10	1	45.8 ± 5.7	32.0 ± 6.5	0.80 ± 0.12
1:10	10	69.2 ± 6.6	13.8 ± 6.6	1.50 ± 0.12
1:10	20	68.0 ± 0.5	13.1 ± 4.2	1.40 ± 0.04

[a]Cogrinding time 0 min is the physical mixture for 10 min simple mixing

Table 2. Particle size analysis of formulation samples subjected to various processes

Formula	Grinding Time (min)	$D_{10\%}$ (µm)	$D_{50\%}$ (µm)	$D_{90\%}$ (µm)	Span
IBU	0	5.9 ± 0.3	29.1 ± 0.6	83.9 ± 1.5	2.68
IBU	1	2.5 ± 0.1	16.0 ± 0.2	87.6 ± 3.5	5.31
IBU	10	1.2 ± 0.1	9.1 ± 0.7	128.3 ± 1.3	14.00
IBU	20	1.3 ± 0.1	9.8 ± 0.3	125.5 ± 2.0	12.60
Glucosamine	0	96.4 ± 3.3	259.3 ± 0.4	328.5 ± 0.2	0.89
Glucosamine	1	1.5 ± 0.1	22.7 ± 0.2	126.2 ± 0.2	5.50
Glucosamine	10	0.8 ± 0.1	5.2 ± 0.8	120.6 ± 8.9	23.00
Glucosamine	20	1.5 ± 0.1	12.8 ± 0.5	140.7 ± 0.7	10.80
PM of Ibu:GL					
(4:1)		5.5 ± 1.1	30 ± 1.8	103.6 ± 2.6	3.27
(1:4)		5.7 ± 0.5	47.6 ± 1.9	145.2 ± 0.3	2.93
(1:10)		8.4 ± 0.7	88.9 ± 2.6	152.3 ± 0.7	1.62
Coground Ibu:GL					
(4:1)	1	2.6 ± 0.2	19.7 ± 0.8	117.6 ± 0.6	5.83
(1:4)	1	1.7 ± 0.1	18.6 ± 0.1	116.6 ± 0.1	6.17
(1:10)	1	1.5 ± 0.1	20.0 ±1.1	127.1 ± 1.0	6.28
(4:1)	10	1.3 ± 0.1	11.3 ± 0.1	120.4 ± 0.1	10.60
(1:4)	10	0.7 ± 0.1	2.4 ± 0.02	12.4 ± 0.0	4.83
(1:10)	10	0.7 ± 0.1	2.07 ± 0.2	13.2 ± 1.4	6.04
(4:1)	20	1.2 ± 0.2	13.7 ± 0.2	122.3 ± 0.8	8.83
(1:4)	20	0.7 ± 0.1	3.6 ± 0.2	116.5 ± 3.5	32.30
(1:10)	20	0.7 ± 0.0	1.9 ± 0.1	12.5 ± 0.5	6.13
Ground Ibu:Unground GL					
(4:1)	1	2.0 ± 0.2	16.7 ± 0.7	121.9 ± 0.6	7.17
(1:4)	1	4.3 ± 0.5	80.9 ± 0.4	151.6 ± 1.2	1.82
(1:10)	1	3.6 ± 0.3	81.9 ± 9.0	151.7 ± 0.9	1.82
(4:1)	10	1.7 ± 0.4	14.6 ± 0.2	140.7 ± 1.3	9.53
(1:4)	10	4.1 ± 0.2	101 ± 0.3	154.7 ± 1.2	1.49
(1:10)	10	2.7 ± 0.2	85.1 ± 5.2	152.1 ± 0.6	1.76
(4:1)	20	1.2 ± 0.1	10.9 ± 1.3	138.2 ± 1.2	12.50
(1:4)	20	1.5 ± 0.1	28.1 ± 8.5	144.5 ± 1.6	5.09
(1:10)	20	2.3 ± 0.1	87.6 ± 2.1	152.8 ± 0.4	1.72

[a]These formulations are subjected to 10 min simple physical mixture in turbula blender

Table 3. Solubility of ibuprofen in presence of different concentrations of glucosamine after 72 h

Formulation	pH nominal/final	mg/ml
Untreated Ibuprofen	7.4/6.4	6.6 ± 0.8
Untreated Ibuprofen in presence of:		
1% carrier	7.4/6.1	10.5 ± 2.8
5% carrier	7.4/4.2	21.2 ± 1.0
10% carrier	7.4/2.7	15.5 ± 1.1
15% carrier	7.4/2.2	12.3 ± 0.5

Table 4. Enthalpy and fusion or transition temperature of various Ibuprofen samples containing glucosamine

Formula	Grinding Time (min)	Melting peak (^{o}C)	Enthalpy (J/g)
Untreated Ibuprofen	---	78.6 ± 0.1	127.8 ± 4.4
Untreated Ibuprofen	1	77.9 ± 0.2	127.2 ± 2.1
Untreated Ibuprofen	10	77.4 ± 0.2	126.9 ± 5.9
Untreated Ibuprofen	20	76.6 ± 0.4	124.7 ± 4.1
Physical mixtures Ibu:GL			
(4:1)	0	78.9 ± 0.9	99.1 ± 2.2
(1:4)	0	77.5 ± 0.2	22.3 ± 1.4
(1:10)	0	77.1 ± 0.02	8.2 ± 1.9
Coground Ibu:GL			
(4:1)	1	77.3 ± 0.3	98.1 ± 6.0
(4:1)	10	76.8 ± 0.2	99.9 ± 0.8
(4:1)	20	76.6 ± 0.1	99.0 ± 3.5
(1:4)	1	77.1 ± 0.1	26.2 ± 1.4
(1:4)	10	76.4 ± 0.1	28.1 ± 2.8
(1:4)	20	76.2 ± 0.1	25.6 ± 1.4
(1:10)	1	76.9 ± 0.1	10.4 ± 0.1
(1:10)	10	76.1 ± 0.1	11.3 ± 1.5
(1:10)	20	76.3 ± 0.1	11.6 ± 0.4
Ground Ibu:Unground GL			
(4:1)	1	77.6 ± 0.3	100.5 ± 8.6
(4:1)	10	77.8 ± 1.1	100.4 ± 4.0
(4:1)	20	76.8 ± 0.3	94.5 ± 6.9
(1:4)	1	77.3 ± 0.1	17.9 ± 4.2
(1:4)	10	76.5 ± 0.2	14.1 ± 2.1
(1:4)	20	76.5 ± 0.3	21.8 ± 0.6
(1:10)	1	76.5 ± 0.1	9.3 ± 1.0
(1:10)	10	77.1 ± 1.2	9.8 ± 0.4
(1:10)	20	76.3 ± 0.3	10.4 ± 0.4

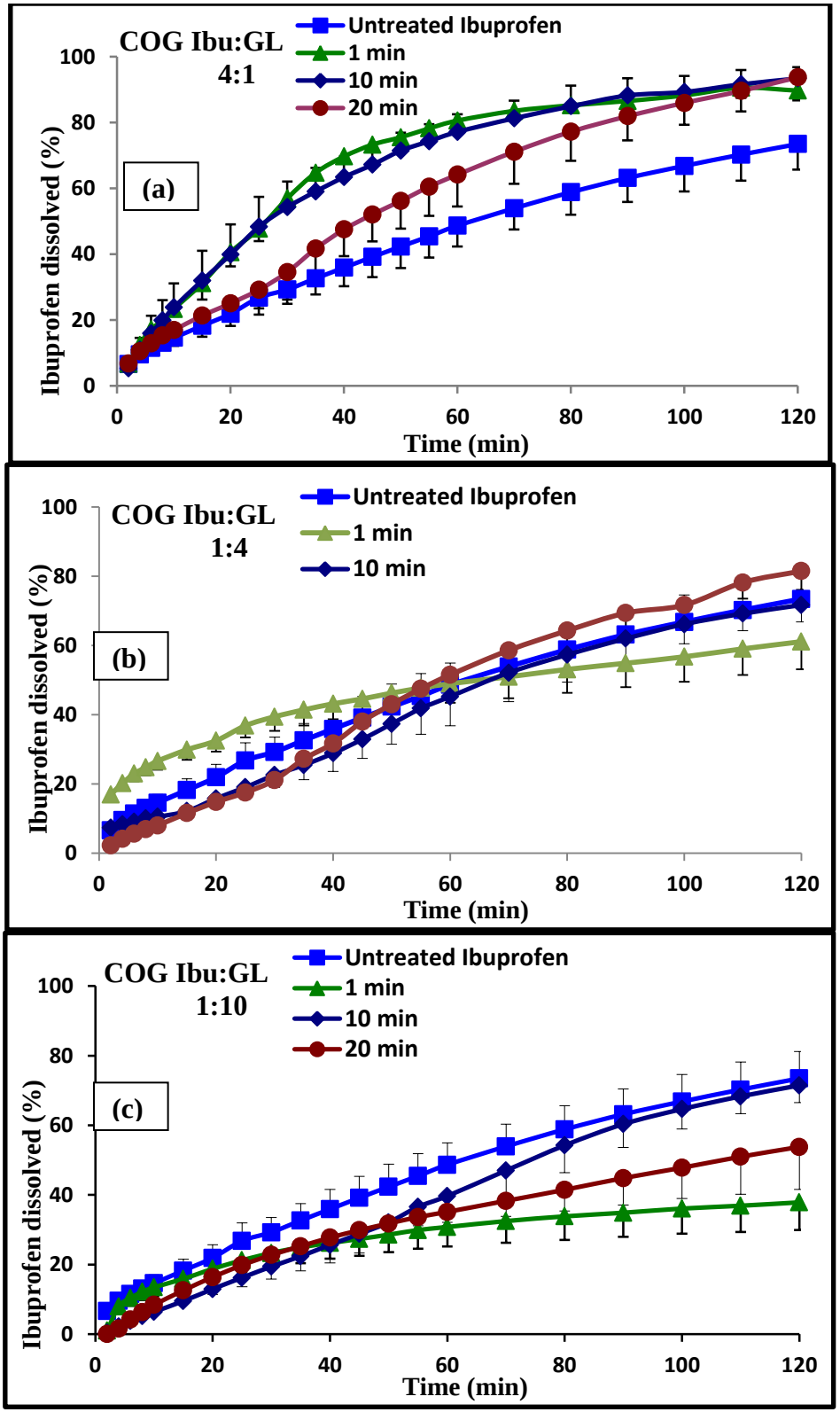


Figure 1. The effect of grinding time on dissolution rate of ibuprofen from coground formulations with different ratios of Ibuprofen:glucosamine (drug:carrier): (a) 4:1; (b) 1:4; (c) 1:10 (COG=coground).

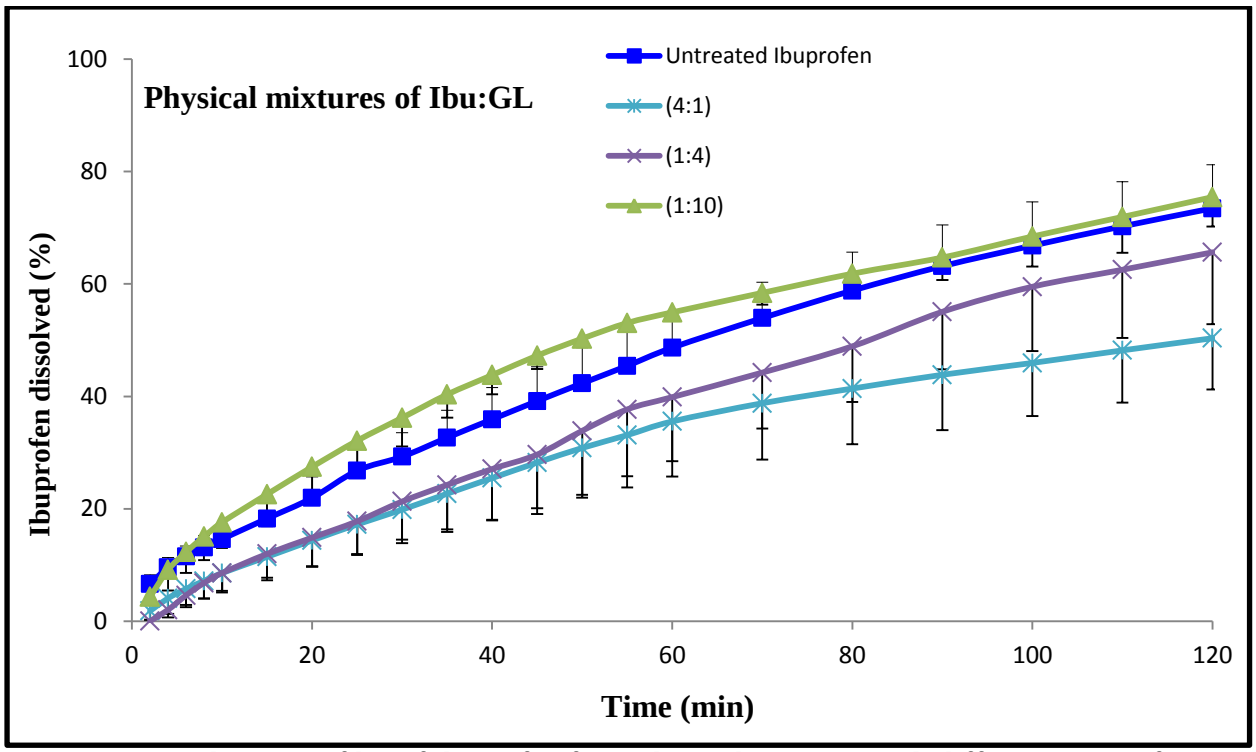


Figure 2. Dissolution profiles of Ibuprofen from physical mixtures with different ratios of drug-glucosamine.

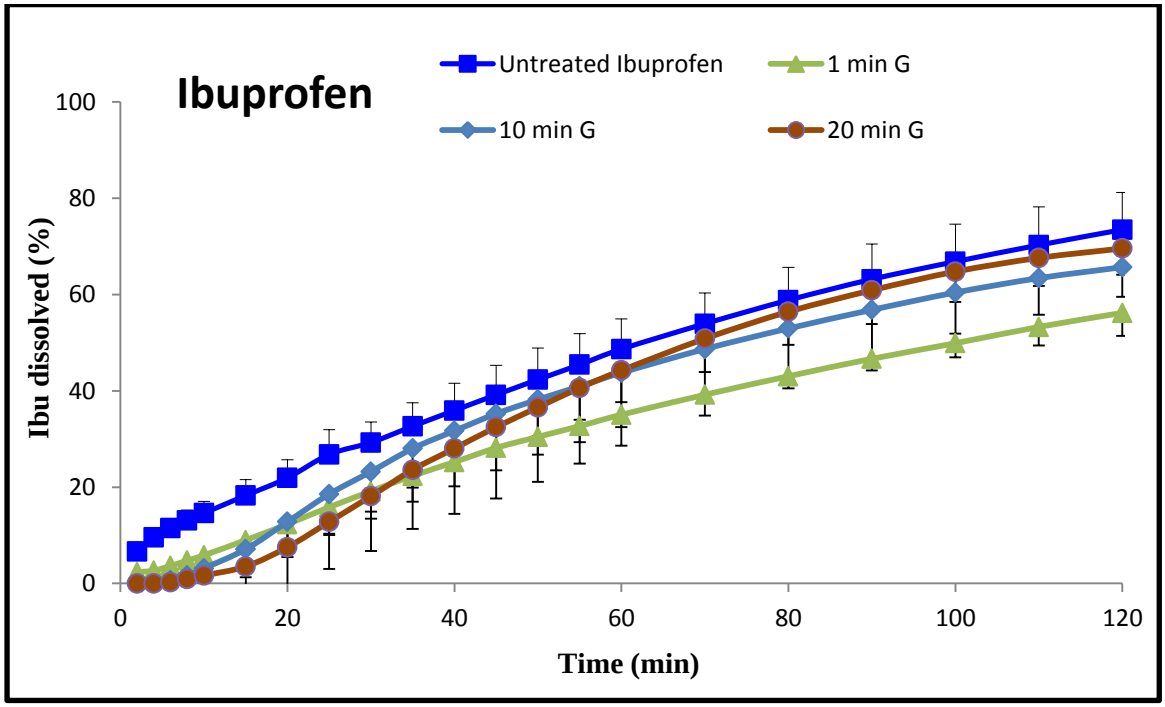


Figure 3. The dissolution behaviour of pure Ibuprofen subjected to different grinding times (G=grinding).

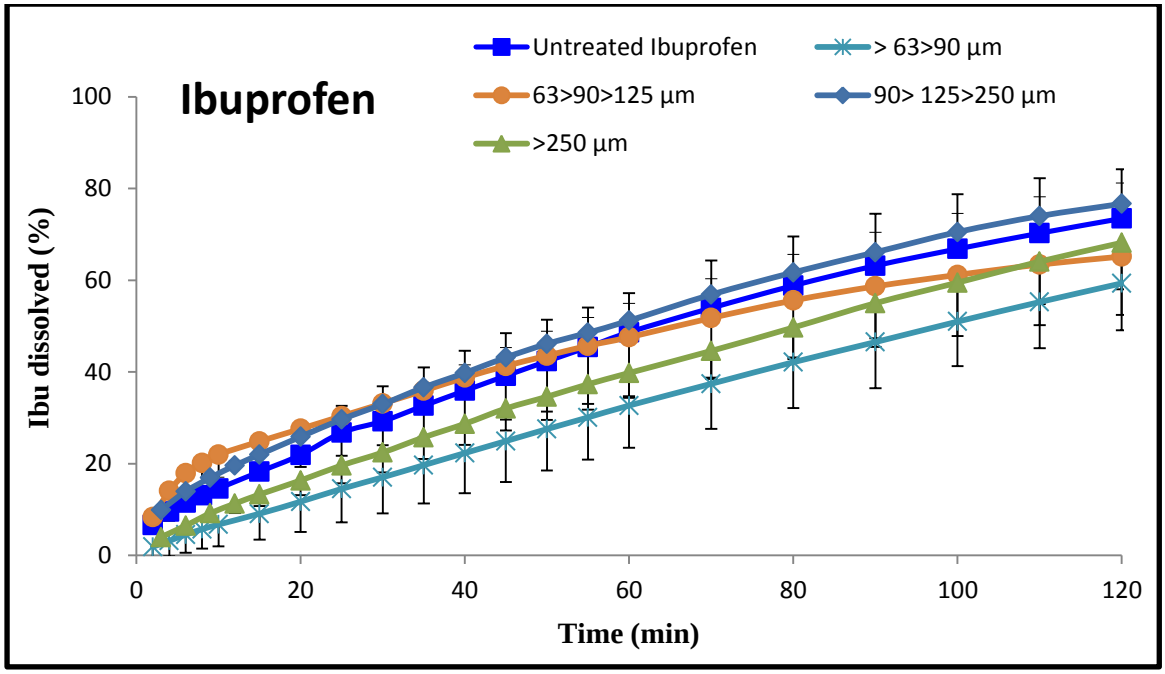


Figure 4. Dissolution profiles of untreated Ibuprofen with different particle size (data are mean and standard deviations of minimum 3 determinations).

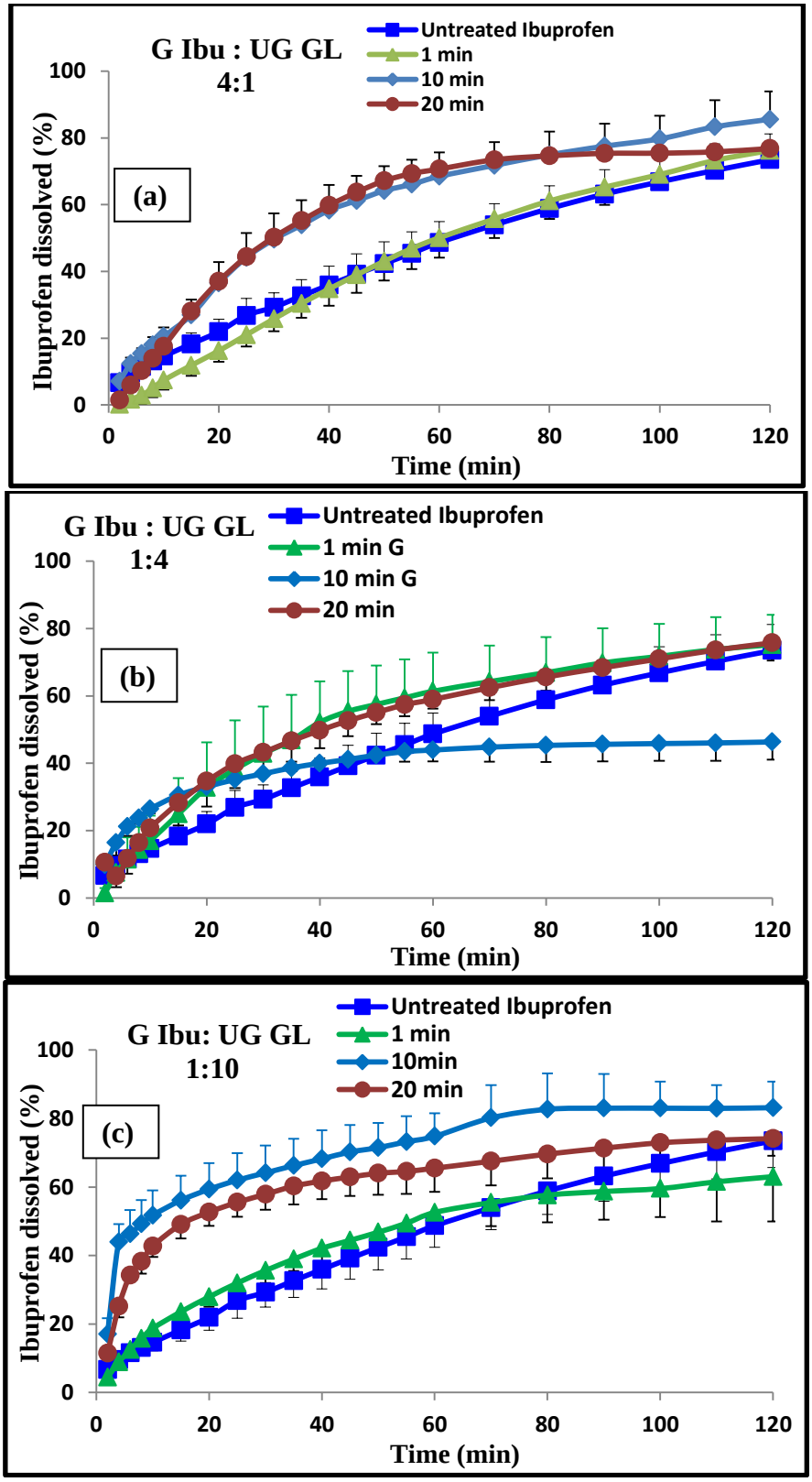
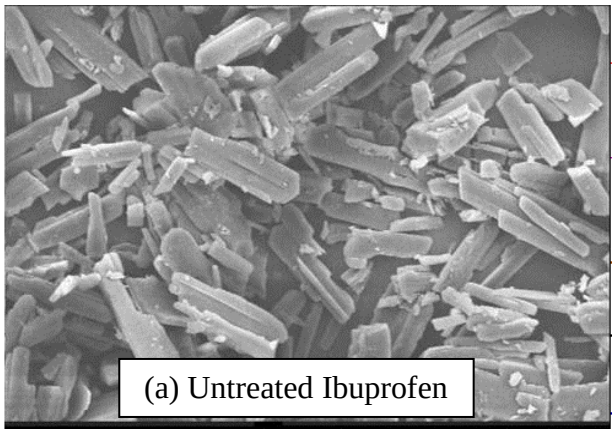
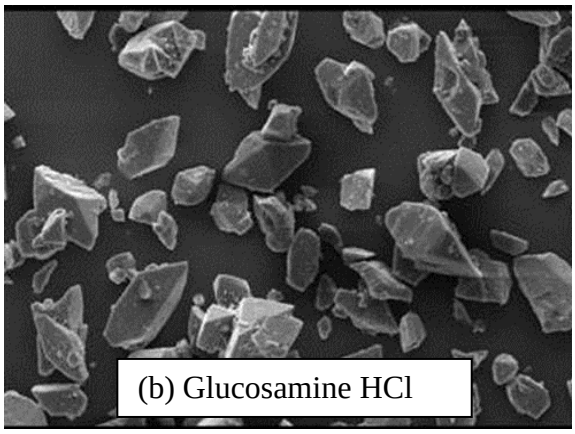
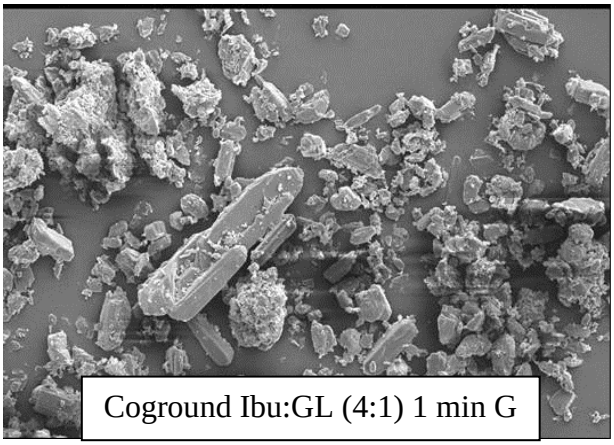
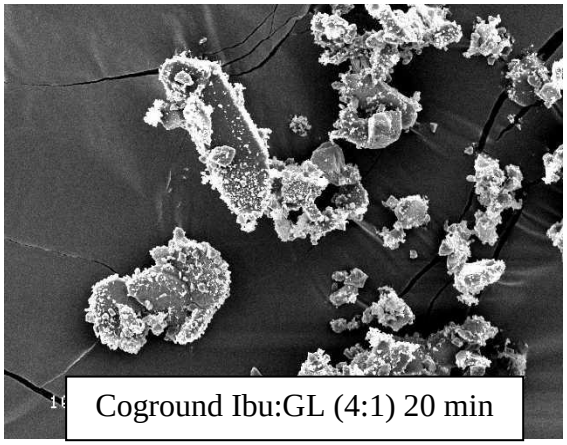


Figure 5. Dissolution behaviour of Ibuprofen-glucosamine mixture where ibuprofen subjected to different milling times followed by mixing with glucosamine for 10 min with different ratios of ibuprofen:glucosamine (drug:carrier): (a) 4:1; (b) 1:4; (c) 1:10 (G=ground; UG=unground).

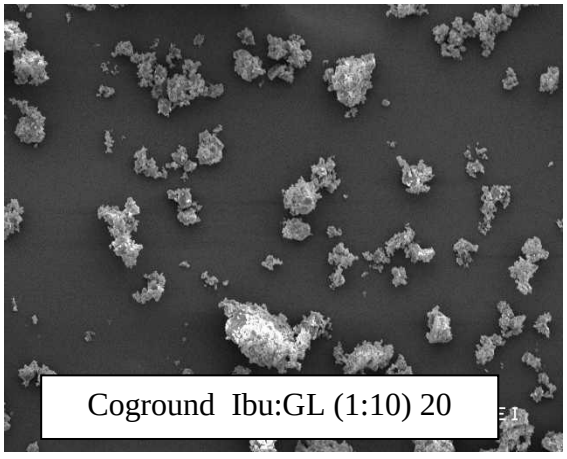

(a) Untreated Ibuprofen


(b) Glucosamine HCl


Coground Ibu:GL (4:1) 1 min G


Coground Ibu:GL (4:1) 20 min


Coground Ibu:GL (1:10) 1 min


Coground Ibu:GL (1:10) 20

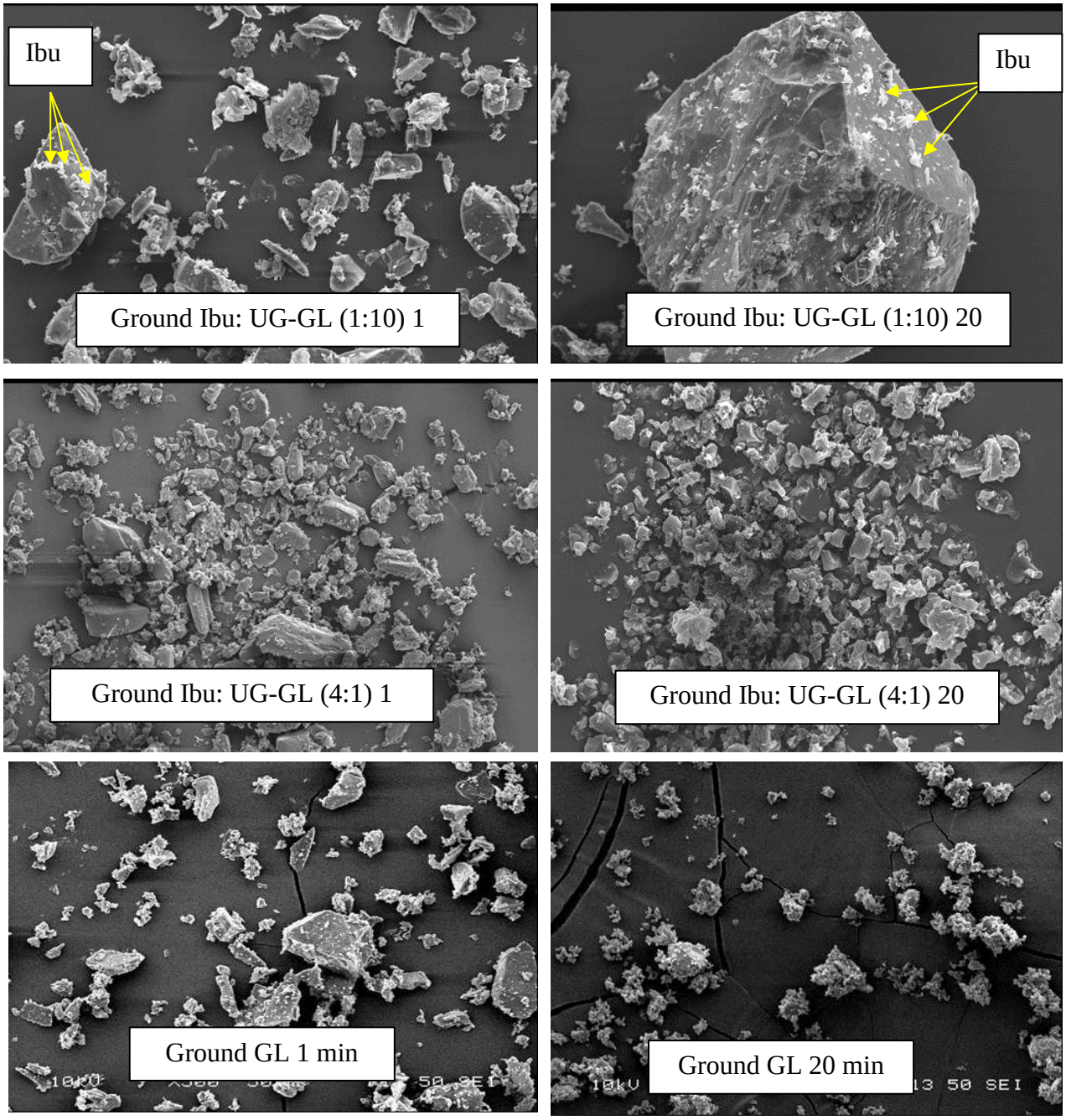


Figure 6. SEM images of ibuprofen, glucosamine and various coground formulations (Ibu=ibuprofen; GL=glucosamine; G=grinding; UG=unground)

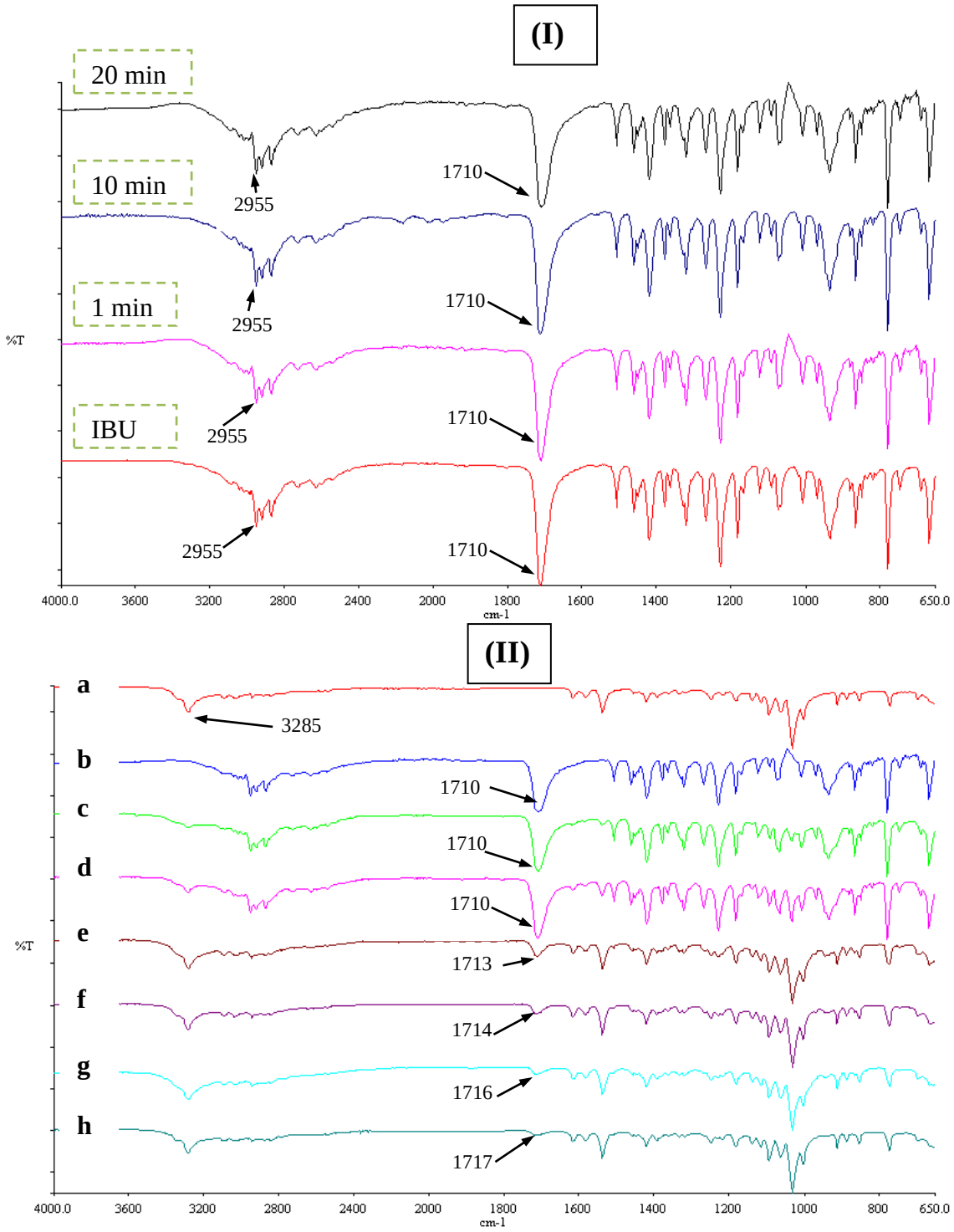


Figure 7. FT-IR spectra of ibuprofen ground for (I) 1, 10 and 20 min; and II: (a) glucosamine, (b) ibuprofen; and coground Ibu-GL ground for 1 min: (c) 4:1, (d) 1:4 and (e) 1:10 ; and ground for 20 min: (f) 4:1, (g) 1:4 and (h) 1:10.

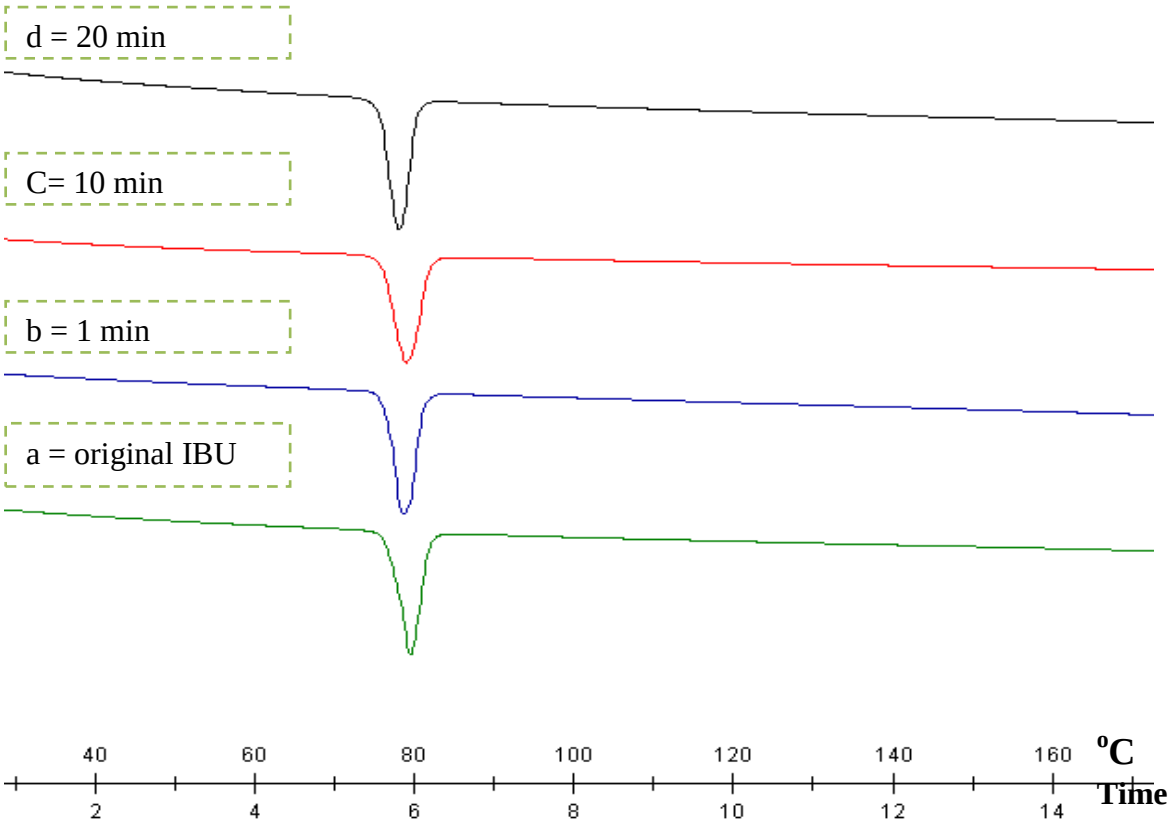


Figure 8. DSC traces of (a) original ibuprofen, ground Ibuprofen (b) 1 min, (c) 10 min, (d) 20 min scanned at 10 ^{o}C/min.