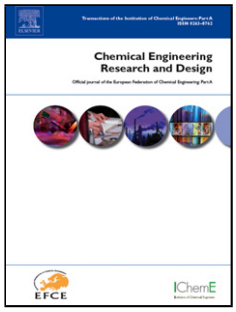

Title: The use of various organic solvents to tailor the properties of Ibuprofen-glucosamine HCl solid dispersions

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The use of various organic solvents to tailor the properties of Ibuprofen-glucosamine HCl solid dispersions

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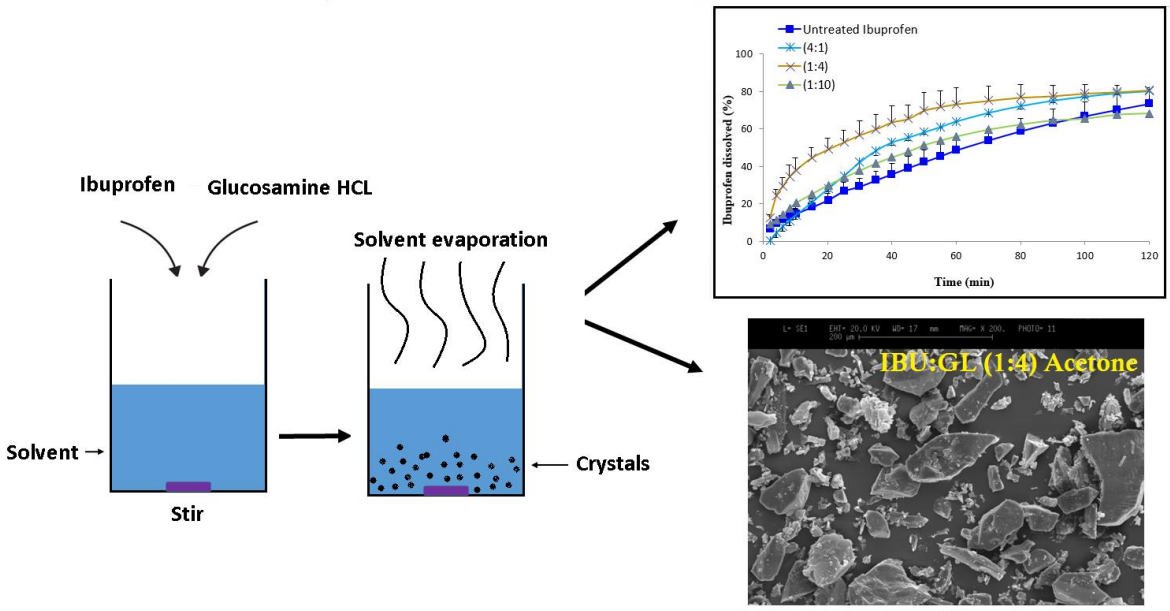
Graphical abstract



Highlights:

- Glucosamine is a potential carrier to enhance the dissolution of ibuprofen
- The type of solvent has a big impact on dissolution of ibuprofen-glucosamine
- The present of water in solid dispersion formulation altered the dissolution rate
- Solid state analyses ruled out any interaction between ibuprofen and glucosamine

Abstract

Ibuprofen is a Biopharmaceutical classification system class II drug that exhibits poor dissolution rate in the gastrointestinal tract. The aim of the present study is to enhance the dissolution of ibuprofen in presence of glucosamine. To this end, different ratios of ibuprofen:glucosamine were dissolved in various organic solvents to obtain the solid dispersions of ibuprofen-glucosamine mixtures. The solid state analysis of the samples (differential scanning calorimetry, Fourier infrared spectroscopy and x-ray powder diffraction) and the morphology (scanning electron microscope) were investigated. Particle size analysis and in vitro dissolution studies showed that the type of solvent has a significant influence on dissolution rate. Ibuprofen-glucosamine solid dispersions obtained from acetone produced better dissolution compared to that of other organic solvents. The effect of water in binary

mixtures of either acetone or ethanol was also explored and the results showed that when the ratio of acetone to water was 75:25, the highest dissolution was obtained. Solid state analysis ruled out any chemical interaction between the drug and carrier even in the presence of various organic solvents which indicates a good stability of the solid dispersions to enhance the dissolution rate of ibuprofen. It was also investigated via XRPD analysis that the ibuprofen retained its crystallinity without any adverse effect on the dissolution rates. In conclusion, the present study showed that a manipulation of the organic solvent:water ratio and a change in the type of organic solvent impacted on ibuprofen-glucosamine achieving very high dissolution rate without compromising its crystallinity and physical stability.

Keywords: Solid dispersion, Ibuprofen, Glucosamine HCl, Dissolution rate, Organic solvents, Solid state analysis

1. Introduction

The first step for an oral solid dosage form such as tablet or capsule after administration is the release of the active pharmaceutical ingredient (API) from the dosage form and its dissolution in the gastrointestinal (GI) fluids before the absorption. This indicates that the bioavailability of many poorly water soluble drugs can be restricted by their dissolution rates [1]. Ibuprofen (IBU) is classified as a non-steroidal anti-inflammatory drug (NSAID) and is commonly used in the treatment of pain and fever. The analgesic effect of IBU has been reported to be dependent on the serum/plasma concentrations of the drug in the body. Therefore, in order to achieve a fast onset of therapeutic action; IBU should be available for rapid absorption. IBU is a BCS Class II drug, therefore has high membrane permeability and could achieve almost 100 % absorption, if it was not poorly soluble in the aqueous medium. This indicates that the fast

dissolution of IBU in the GI tract following oral administration is highly desirable in terms of formulation design and delivery [2-4]. Even though several formulations such as prodrugs [5], inclusion complexes [6], microcapsules [7], etc. have been developed for IBU, the dissolution rates and the oral bioavailability of IBU from these formulations have not been consistent. In addition, the methods used to prepare those formulations were time consuming and costly. Furthermore, some formulations were quite bulky with poor flow properties, which in question may raise some regulatory concerns.

An increase in the dissolution rate of poorly water-soluble drug has become a major challenge in drug formulation. Solid dispersion (SD) technique [8,9] has therefore been used to improve dissolution of poorly water-soluble drugs such as IBU [10,11] and piroxicam [12,13]

Various polymers such as polyvinylpyrrolidone [14,15], hydroxypropyl methylcellulose [14], ethylcellulose [16] and polyethylene glycol [17] are common polymeric carriers used in such systems. However, the mechanisms underpinning the observed improvements in dissolution rate of solid dispersions when various organic solvents are used is not fully understood. The foregoing completely relies on a thorough understanding of the dissolution behaviour of both components (drug and carrier) to form the solid dispersion. Although, a lot of hydrophilic carriers have been used to improve the rate of dissolution of poorly soluble drugs, the use of glucosamine-HCl (GL) as a hydrophilic carrier can prove advantageous over other carriers. This is due to the fact that GL is used in pain relief and to improve mobility in osteoarthritic joints of humans [18, 19] Glucosamine is a naturally occurring monosaccharide from a family of amino sugars, which is highly water soluble and non-toxic. It is a weak base and due to its instability, only GL salts (either hydrochloride or sulphate) are used in therapy [20]. The use of GL as a hydrophilic carrier in solid dispersions of IBU can provide better benefits for the patients suffering from osteoarthritis as they do not need to administer two different formulations. Furthermore, the addition of GL might improve the rate of dissolution of IBU

formulations. Generally, ethanol is the common solvent in the preparation of solid dispersion and to the best of knowledge; there are no studies in the literature to show the impact of the type of organic solvent on the properties of solid dispersions. Therefore, the aim of this study was to prepare solid dispersion formulations of IBU-GL for dissolution enhancement using different organic solvents. The morphology and physico-chemical characteristics of the prepared solid dispersions were studied. In addition, any interaction between IBU and GL were also investigated.

2. Materials and Methods

2.1 Materials

IBU and GL were purchased from Spectrum (USA) and Sigma (USA), respectively. Acetone, ethanol, methanol, dichloromethane and acetonitrile were obtained from Fisher Scientific, UK. All materials were of analytical grade and used as obtained.

2.2. Preparation of solid dispersions of drug-carrier

The solid dispersions were prepared according to the method of Al-Hamidi et al. 2010 [21] with some variations. Briefly, solid dispersions of IBU and GL were first prepared using the solvent evaporation technique in weight ratios of IBU:GL - 4:1, 1:4 and 1:10. Both the drug and carrier were dispersed in acetone (50 mL) in a beaker. The solvents were then evaporated at 40 ˚C over a period of 48 h under constant agitation at 200 rpm. The prepared solid dispersions were then ground using a mortar and pestle, and stored in a desiccator at room temperature until used. In order to investigate the effect of solvent type on the physicochemical properties of the solid dispersions, this entire process was repeated with ethanol, methanol, acetonitrile and dichloromethane as the solvent instead of acetone.

In the second series of the formulations, IBU and GL were dissolved in acetone (30 mL) and distilled water (30 mL), respectively. The GL solution was added to the IBU solution under the same conditions described above. Agitation of the drug-carrier mixture continued until the solvents evaporated and a dry powder was obtained (approximately after 48 h at 40 ˚C). This procedure was also used for solid dispersions obtained from ethanol (a safe solvent) and water as the solvent for IBU and GL, respectively. The dispersions were ground and stored under the same conditions as described above.

2.3 Preparation of physical mixtures of drug-carrier

For comparison purposes, physical mixtures of IBU-GL with different ratios of 4:1, 1:4 and 1:10 were prepared by mixing IBU and GL in a Turbula blender (TF2, Basel, Switzerland) for 10 min. The physical mixtures were stored in a screw-cap glass vial at room temperature until used.

2.4. Particle size analysis

Particle size of ibuprofen-glucosamine crystallized from the different organic solvents was determined using a Sympatec laser diffraction particle size analyzer (Clausthal-Zellerfeld, Germany). In this technique, approximately 2 g of the sample was introduced and a laser beam is passed through the sample. Different size particles diffract the light at different angles to produce a particle size distribution (volume based distribution). All the data was analysed using the software provided by the company (WINDOX) to calculate $D_{10\%}$, $D_{50\%}$ and $D_{90\%}$. The data reported regarding particle size analysis are the mean and standard deviation of three determinations.

2.5 Scanning electron microscopy (SEM)

In order to obtain the micrographs of the samples, they were mounted on a metal stub layered with a double-sided adhesive tape. The samples were coated under vacuum with gold in an argon atmosphere prior to observation using a scanning electron microscope (Leica Cambridge S360, UK) operating at 15 kV. Images with different magnifications were obtained to study the morphology of the solid dispersions.

2.6 Fourier transform infrared (FT-IR) studies

The FT-IR spectra (range 650-4000 cm^{-1}) of physical mixtures of IBU-GL and their respective solid dispersions were recorded using an FT-IR spectrophotometer (PerkinElmer, UK). The sample was mounted on the sample stage and pressure applied by turning the top of the arm of the sample stage to create a flat surface and maintain intimate contact between the sample and the stage. The spectra obtained were the average of 4 scans at 1 cm^{-1} resolution.

2.7 Differential Scanning Calorimetry (DSC) studies

Samples of physical mixtures of IBU-GL or corresponding solid dispersion formulations (3 - 6 mg) were weighed in standard aluminium DSC pans (40 µl). The crimped sample pans were heated at a scanning rate of 10 ˚C/min under dry nitrogen gas. The enthalpies, onset and melting temperatures of the samples were calculated using the STARe software (Mettler-Toledo, Switzerland).

2.8 X-ray powder diffraction studies (XRPD)

The XRPD patterns of unprocessed IBU, GL, their physical mixtures and the manufactured solid dispersions were obtained using a Bruker D8 Advance (Germany) in theta-theta mode. The diffraction analysis was performed using a Cu anode at 40kV and 40 mA, parallel beam Goebel mirror, 0.2 mm exit slit, LynxEye Position Sensitive Detector with 3° opening

(LynxIris at 6.5 mm) and sample rotation was set at 15 rpm. Each of the samples was scanned over the 5 to 50° diffraction angle (2θ) range with a step size of 0.02° 2θ and a counting time of 0.1 seconds per step.

2.9 Dissolution studies

An assessment of the dissolution properties of IBU both from the solid dispersions and physical mixtures was conducted using the USP dissolution apparatus I (basket method). Each formulation was filled into the capsules containing equivalent amounts of IBU (200 mg). The capsules were placed in baskets which were set to rotate at 75 rpm according to USP XXVIII in a phosphate buffer (900 mL, pH 7.4) dissolution medium equilibrated to 37 ± 0.5 °C. Sample media were withdrawn from the dissolution vessels at pre-set time intervals (5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105 and 120 min) and the concentrations of drug in the samples were determined by UV spectrophotometric analysis at 221 nm. A minimum of three determinations was carried out for each dispersion sample and for purposes of comparison; dissolution tests were also carried out for all the corresponding physical mixtures.

2.10 Dissolution parameters

In this study, three main dissolution parameters namely dissolution efficiency (DE), mean dissolution time (MDT) and mean dissolution rate (MDR) were calculated. DE is defined as the area under the dissolution curve up to the time, t, expressed as the percentage of the area of the rectangle; MDT is the most likely time for a molecule to be dissolved from a solid dosage form while MDR is the average dissolution rate for the whole dissolution profile. The details about these parameters and their relevant equations are described elsewhere [22-25].

3. Results and Discussion

3.1 Dissolution

The dissolution profiles of IBU from solid dispersions of IBU-GL with different ratios prepared from various organic solvents are shown in Figures 1 (a-e). It is clear from these profiles that the type of solvent had a significant impact on the dissolution performance of IBU from the various solid dispersions. This could be due to the difference in polarity associated with these different solvents. The polarity of solvents used to prepare the solid dispersion of IBU-GL can be ranked as follows: acetonitrile > ethanol > acetone = methanol > dichloromethane.

As observed from Figure 1(a) the fastest dissolution rate was obtained for the samples when the ratio of IBU:GL was 1:4 with acetone as the solvent. As the proportion of GL increased from 1:4 to 1:10 (IBU:GL), a significant decrease in IBU dissolution occurred. This indicates that the ratio of drug to carrier in the solid dispersion is one of the main parameters controlling the dissolution rate of these solid dispersions. A direct relationship between the amount of GL in the formulation and IBU dissolution could not be established, however a reduction in the dissolution rate was observed for the samples with high proportion of carrier compared to those with low proportion of carrier. In addition, all the solid dispersion formulations had higher dissolution rates compared to that of untreated IBU samples. Figure 1(a) shows that increasing the amount of carrier from 80 % (ratio of drug to carrier 1:4) to 90.9 % (ratio of drug: carrier 1:10) did not cause any further improvement in dissolution of IBU. These results correlated with those obtained from the DE, MDT and MDR data listed in Table 1.

Figures 1(b) shows that when the solvent was changed from acetone to ethanol no significant improvement ($p>0.05$) in the dissolution was observed with regards to different ratios of IBU:GL. In some cases, the reported DE values for the solid dispersions were less or similar to that of untreated IBU (Table 1). Similar results were obtained when methanol (Figure 1c), dichloromethane (Figure 1d) or acetonitrile (Figure 1e) were used. This indicates that not all types of solvents used in the preparation of solid dispersions can improve the dissolution rate

of IBU significantly. In other words, the type of solvent used to prepare solid dispersions plays an important role in the dissolution enhancement of IBU and the selection of the right solvent to achieve the maximum dissolution is pivotal to the dosage forms design and delivery. All these results were also supported by DE, MDT and MDR results as reported in Table 1. This general decrease in drug release as a result of increased GL levels was also observed by Al-Hamidi et al. 2015 [26]. They attributed this to the fact that IBU dissolution was pH dependent and the increasing amount of GL decreased the pH of the dissolution medium thereby reducing the dissolution rate of IBU from the samples [27].

The particle sizes of all the samples were determined ($D_{10\%}$, $D_{50\%}$ and $D_{90\%}$) to find a correlation between the dissolution data and the average particle sizes of the samples (Table 1I). A comparison between all DE data and the mean particle size revealed that there was no correlation between the dissolution rates and particle sizes of the samples (Figure 1f). This indicates that particle size does not play a key role in the dissolution enhancement of the IBU from the solid dispersions prepared using this method.

Among all the formulations studied, it can be concluded that solid dispersion samples obtained using acetone as a solvent followed by ethanol showed better dissolution performances regardless of the ratio of drug to carrier compared to the samples obtained from the other solvents studied, therefore, these solvents were selected for further investigations.

In the next series of formulations, GL which is highly water soluble up to 320 mg/mL [28] was dissolved in water, while, IBU was dissolved in either acetone or ethanol (refer to preparation of solid dispersions) rather than dissolving or dispersing both IBU and GL in a single organic solvent. The dissolution profiles of IBU from these solid dispersion samples prepared from binary mixtures of acetone-water and ethanol-water are shown in Figures 2 (a) and (b), respectively. IBU dissolution rate increased significantly ($p<0.05$) with binary mixtures of

acetone/water when the ratio of drug to carrier was 1:10 (Figure 2a), while the other ratios showed a reduction in dissolution rate. This shows that when water was added as the second solvent with the aim of improving the dissolution rate for IBU, the proportion of hydrophilic carrier had increased to achieve this effect, relative to when a single organic solvent is used. In the case of the ethanol/water samples, an increase in DE values (from 33.2 to 49.5 %) was observed (Table 1) when the concentration of GL was increased from 4:1 to 1:10 (IBU:GL).

Particle size analysis of all solid dispersion formulations showed that there was no clear trend between the dissolution rate and the $D_{50\%}$ of the samples. It was obvious in most cases that the presence of a high concentration of the GL increased the average size of the solid dispersion particles (Table 2). In other words, the solid dispersion formulations with the ratio of 1:10 IBU:GL showed the largest particle size. Therefore, these results showed that particle sizes of solid dispersion particles did not have a significant impact on dissolution profile of IBU formulations.

In order to determine the effect of GL on the dissolution profile of IB, the physical mixtures of IBU:GL at different ratios were prepared and their dissolution profiles and dissolution parameters obtained as shown in Figure 2(c) and Table 1 respectively. The results showed that the presence of GL did not improve the dissolution performance of IBU significantly ($p>0.05$) even when the concentration of GL was high (IBU:GL 1:10). A comparison of all the DE values of the solid dispersions relative to the physical mixtures demonstrated that the solid dispersions prepared from acetone performed better than the physical mixtures (see the average DE values in Table 1 regardless the ratio of drug:carrier).

The highest dissolution rate was obtained when the ratio of IBU:GL was 1:10 and acetone/water was used as the solvent with a DE of 60.1 %. As this value was the highest among all formulations studied so far, the effect of % proportion of acetone in the acetone/water binary mixture used in the preparation of the solid dispersion of IBU:GL ratio 1:10 was further

investigated. Figure 3(a) shows that the percentage of acetone used in the acetone/water binary mixture had a significant effect ($p<0.05$) on the dissolution performance (Table 3). The results showed that the highest DE (71.2%) was obtained when 75% acetone-was used. and DE was the lowest (49.7 %) when 100% acetone was used. This indicates that the presence of water is essential to achieve the highest dissolution performance for solid dispersions of IBU:GL (1:10) when acetone is used but the proportion of water should be optimized to achieve the highest dissolution performance.

Similar processes were carried out for the ethanol formulations and the results showed that the percentage of ethanol did not significantly ($p>0.05$) change the dissolution rate of IBU-GL solid dispersion remarkably (Figure 3b) and this was supported by the data reported in Table 3.

3.2 SEM studies

SEM images of all solid dispersions (21 formulations in total) were taken but not all are shown in manuscript as other images do not provide any further information. Only SEM images of solid dispersions obtained from acetone and ethanol with a ratio of IBU:GL 1:4 (Figure 4), and samples obtained through acetone-water with different percentages of acetone are shown (Figure 5). It is interesting to note that when IBU-GL solid dispersions were obtained from ethanol, the sample particles aggregated (Figure 4) unlike the discrete particles observed when acetone was used. This could be one of reasons for the poor dissolution of the ethanol samples due to the reduced surface area available for dissolution relative to the acetone samples. (Table 1).

As solid dispersion samples obtained from acetone:water (50:50) showed the best dissolution efficiency (Table 1; DE of 60.6 %), SEM images of the solid dispersions were obtained from binary mixtures at other ratios (100, 75, 50 and 40% acetone) and depicted in Figure 5. SEM

shows that the size of obtained particles gets bigger as the proportion of acetone decreased or as the proportion of water increased.

3.3 DSC studies

DSC was used to investigate any thermal changes in the IBU-GL solid dispersions. Only the thermal behaviour of solid dispersions obtained through acetone and acetone:water (75:25) were investigated as these samples showed the fastest dissolution (See Tables 1 and 3 to compare DE values). The DSC traces of untreated IBU, GL and IBU-GL solid dispersions are shown in Figures 6a and b. Untreated IBU had a sharp endothermic peak at approximately 79 °C with an enthalpy of fusion of approximately 128 J/g (Table 4). The intensity of the peak and the enthalpy of fusion reduced due to a decrease in the proportion of drug in the samples as the ratio of the carrier increases in the formulations.

All the DSC thermograms for the formulations showed a single peak around the melting point of IBU, therefore the melting points and enthalpies are listed in Table 4. It is apparent from Table 4 that there was no significant ($p>0.05$) shift in the melting peak of IBU when the amount of IBU was reduced in IBU:GL mixtures from 4:1 (78.9 ± 0.9 °C) to 1:10 (77.1 ± 0.1 °C). This indicates that there was no interaction between IBU and GL in the physical mixtures.

When the enthalpies of different solid dispersions of IBU-GL obtained using different organic solvents at the same ratio of drug: carrier were compared, it was noticed that their enthalpies were slightly different from each other (compared to the enthalpies of the samples at the same ratio of IBU-GL) which could be due to differences in the homogeneity of IBU in the samples. A similar study on solid dispersions of IBU-GL was carried out by Wahab et al. (2013) using only ethanol as a solvent [29]. DSC results from their study showed the presence of amorphous content in solid dispersion samples when the proportion of GL was high. The authors believe that the conclusion by Wahab et al (2013) could be misleading as the reduced intensity of the

melting peak for IBU could have been due to the presence of low concentrations of IBU and high GL content and not due to the presence or formation of amorphous contents in the solid dispersions.

3.4 FT-IR studies

FT-IR analysis of GL, IBU, solid dispersions obtained from acetone (ratio of IBU:GL 1:4 and 1:10), acetone/water (ratio of IBU:GL 1:10) was carried out to indicate any chemical changes/interactions at the molecular level (Figure 7). IR peaks characteristic of IBU were observed at 1710 cm^{-1} and 2955 cm^{-1}, due to carbonyl and hydroxyl stretching vibration, respectively. Solid dispersions of IBU obtained from acetone or acetone/water exhibited similar IR spectra as the same peaks were observed at the same wavenumbers for both sample sets. This shows that IBU was stable during the preparation of solid dispersion and no chemical changes/interactions at the molecular level occurred during the process. A similar pattern was obtained when other organic solvents or different ratios of IBU:GL were used in the preparation of IBU-GL solid dispersions (Figures not shown).

3.5 XRPD studies

It has been reported that IBU XRPD has characteristic peaks at 2θ of around 12°, 16.40°, 17.5°, 20°, 22° as shown in Figure 8 which is an indication of the highly crystalline nature of IBU. Comparing all XRPD for solid dispersion samples showed that all diagnostic peaks for IBU were present in all the samples, demonstrating that IBU retained its crystalline nature in these samples. . In some cases, the intensity of the peaks were higher than those of pure IBU and GL which could be due to their highly crystalline nature after recrystallization. All these information indicate that an increase in the dissolution of IBU could not be due to the presence of amorphous samples, but could be due to the hydrophilic nature of GL.

4. CONCLUSION

The results obtained showed that the dissolution of ibuprofen can successfully be enhanced by choosing the right organic solvent when glucosamine HCl is used as a carrier. The results demonstrated that acetone and ethanol could be the best solvents in the preparation of solid dispersions of Ibuprofen using glucosamine as a hydrophilic carrier. In addition, the results showed that the dissolution rates of ibuprofen can further be enhanced by changing the proportion of water when binary solvents such as acetone/water are used in solid dispersion formulations. The solid state analysis confirmed that glucosamine HCl can be used as a potential carrier in solid dispersion formulations of ibuprofen to enhance the dissolution without compromising its crystalline nature and stability.

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Figures caption list

Fig. 1 Dissolution profiles of IBU-GL solid dispersions with different ratios of drug: carrier where (a) acetone, (b) ethanol, (c) methanol, (d) dichloromethane and (e) acetonitrile were used as solvent (data are presented as mean and standard deviations of 3 determinations); (f) Relationship between particle size and dissolution efficiency (DE) of solid dispersions

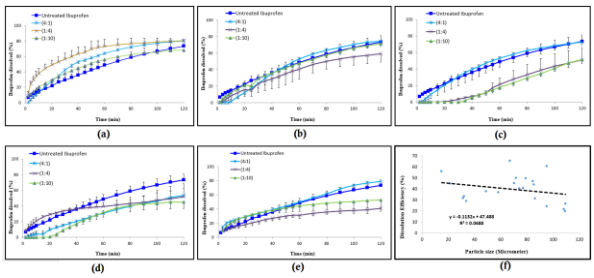

Fig. 2 Dissolution profiles of IBU-GL solid dispersions with different ratios of drug : carrier where (a) acetone/water, (b) ethanol/water was used as solvents; (c) dissolution profiles of IBU-GL physical mixtures with different ratios of drug : carrier (data are presented as mean and standard deviations of 3 determinations).

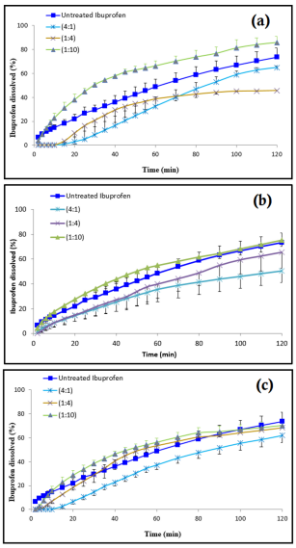

Fig. 3 Effect of the % (a) acetone in acetone-water mixtures and (b) ethanol in ethanol/water mixtures used to prepare solid dispersions of IBU-GL on the dissolution profile on IBU--GL solid dispersions (data are presented as mean and standard deviations of 3 determinations).

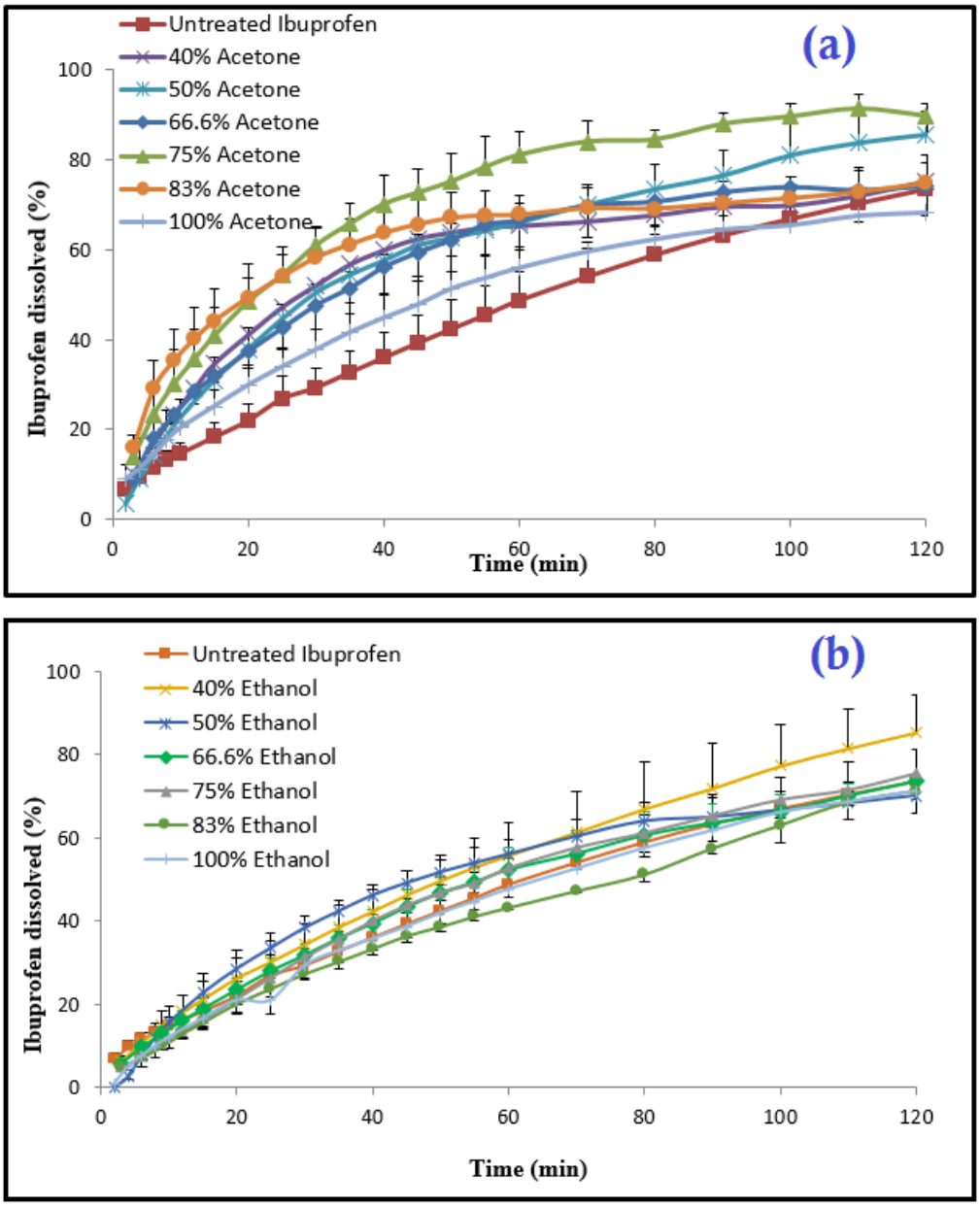

Fig. 4 SEM images of untreated IBU, GL and solid dispersions of IBU-GL (1:4) obtained from acetone and ethanol

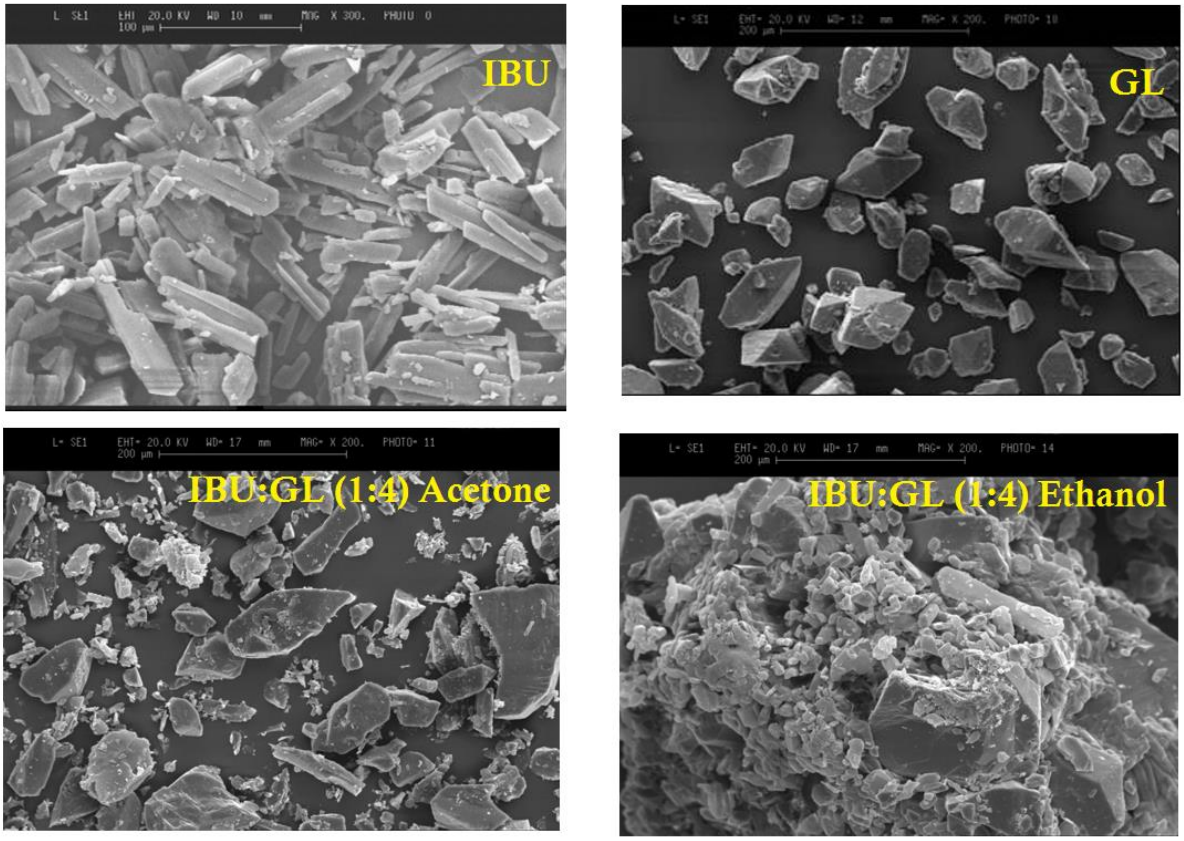

Fig. 5 The effect of % acetone on the morphology of IBU-GL solid dispersions (ratio of IBU:GL was 1:10).

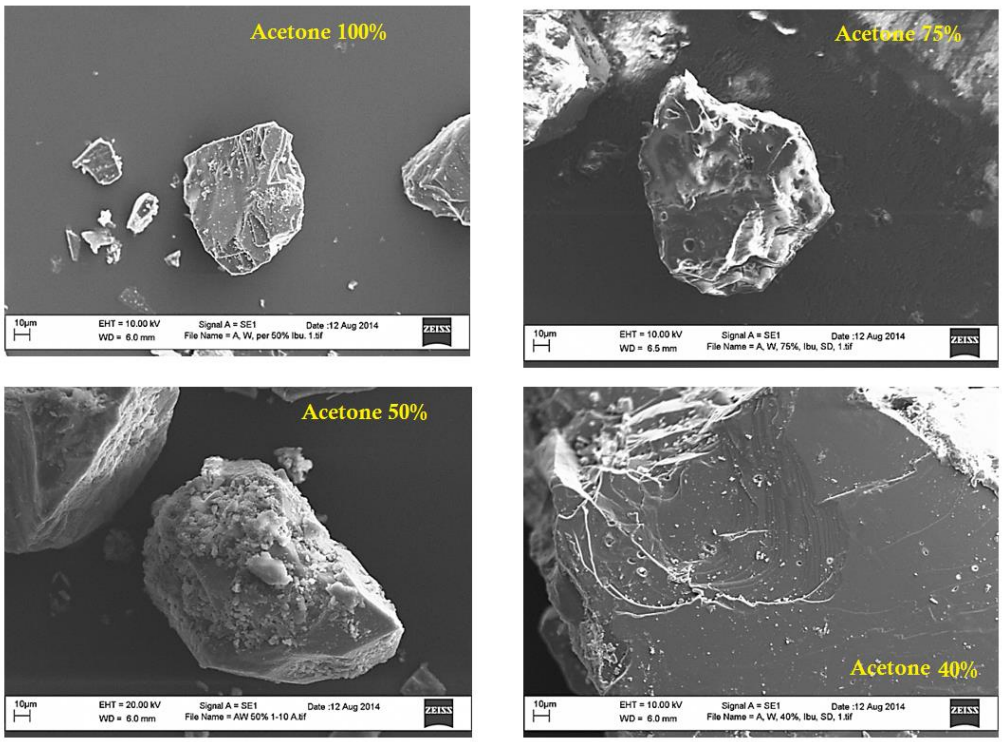

Fig. 6 DSC traces of unprocessed ibuprofen and solid dispersion of IBU:GL with different ratios obtained from (a) acetone and (b) acetone/water as solvents

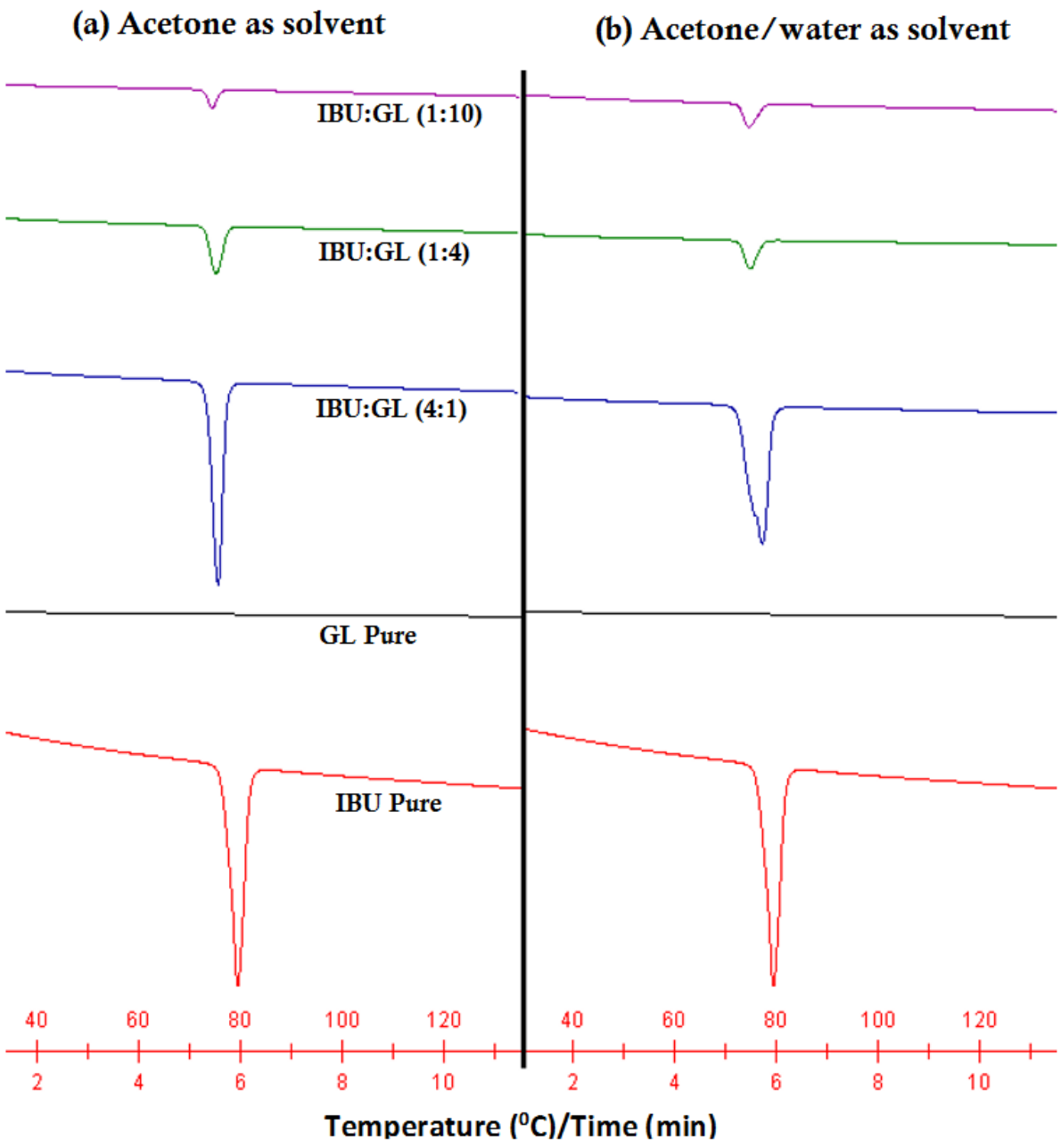

Fig. 7 FT-IR of (a) glucosamine HCl; (b) unprocessed ibuprofen; solid dispersions of IBU:GL obtained from (c) acetone (IBU:GL 1:10); (d) acetone/water 1:10 (IBU:GL 1:10) and (e) acetone (IBU:GL 1:4).

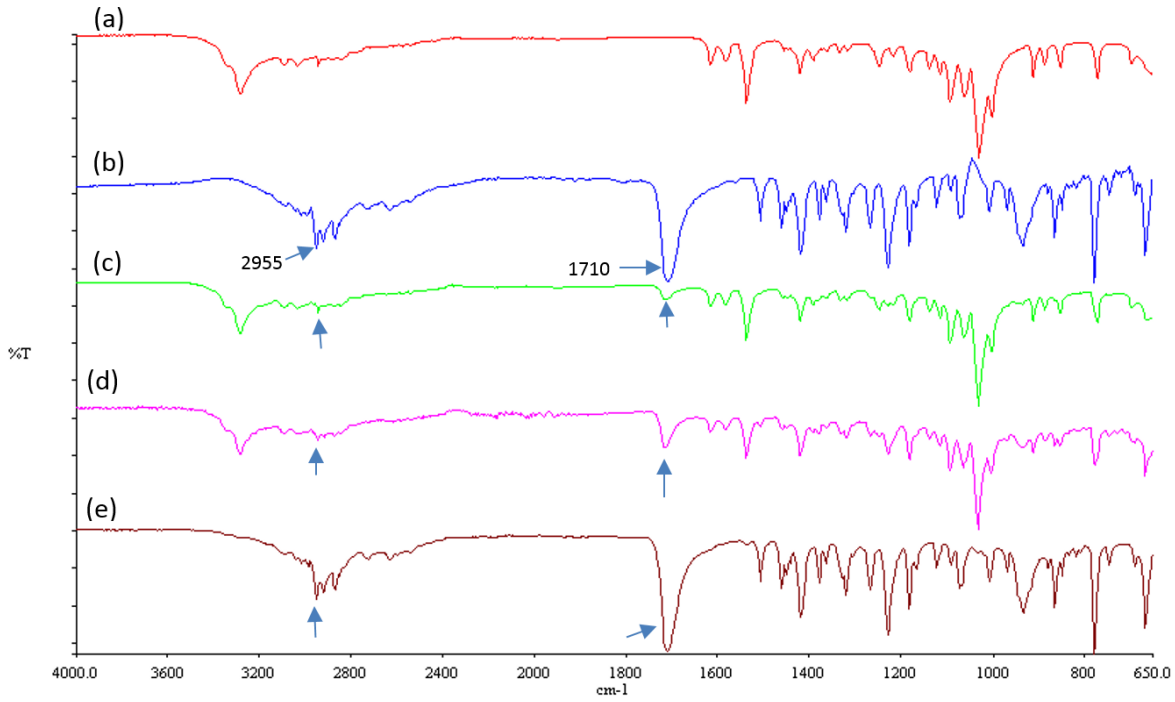

Fig. 8 XRPD spectra of ibuprofen, glucosamine and different solid dispersion of Ibuprofen: glucosamine (1:10) using acetone, ethanol, acetone/water and ethanol water as a solvent

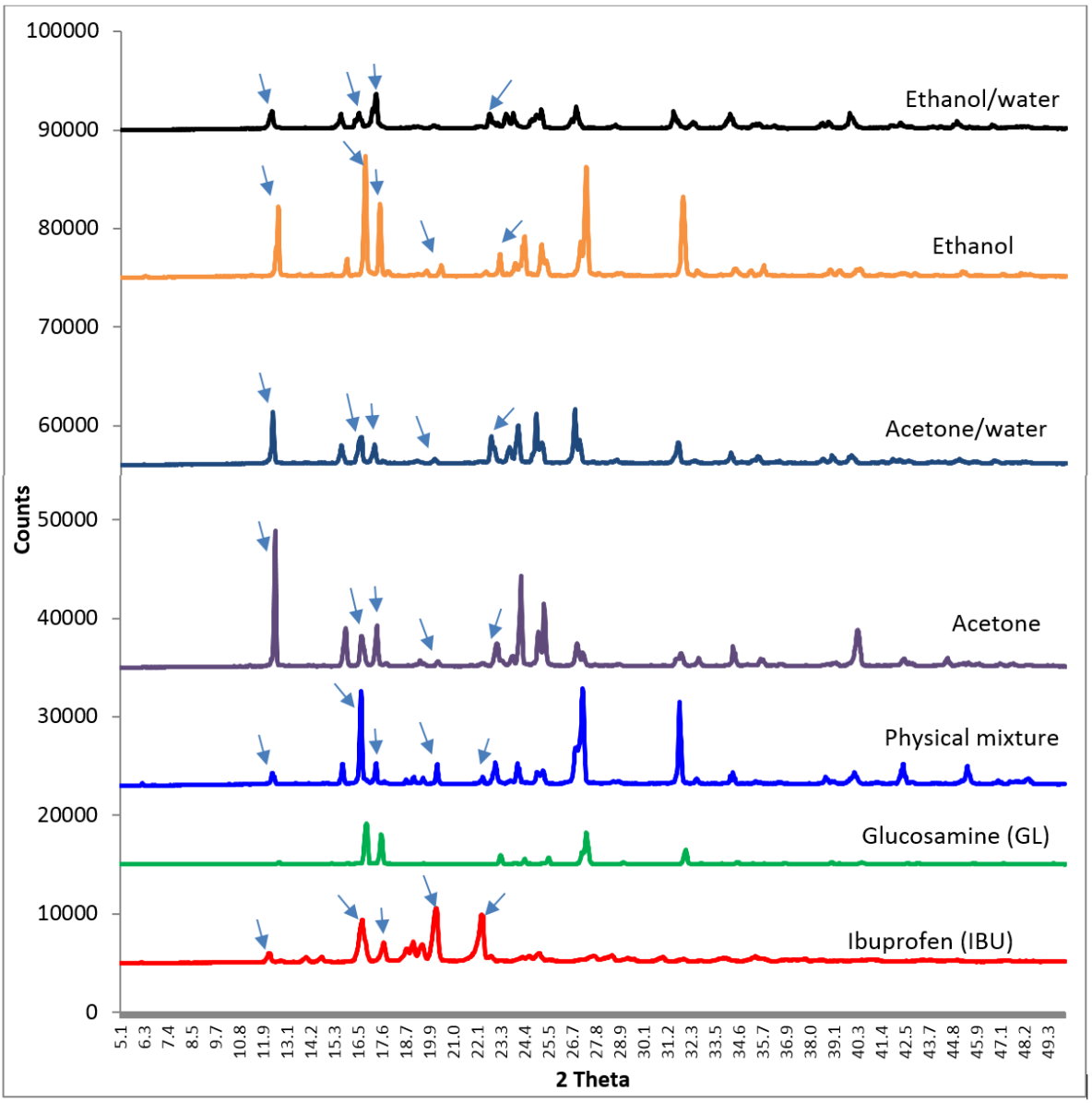

Table 1. Effect of solvents on dissolution parameters of solid dispersions

Drug: carrier ratio	Solvent	DE_{120min} (%)	MDT (min)	MDR (%.min^{-1})
Ibuprofen	---	45.4 ± 5.7	45.8 ± 1.4	0.79 ± 0.10
4:1	PM[a]	31.5 ± 7.8	45.5 ± 5.7	0.50 ± 0.14
1:4	PM	37.3 ± 8.4	52.1 ± 2.4	0.65 ± 0.16
1:10	PM	49.6 ± 1.0	40.9 ± 5.1	0.87 ± 0.04
4:1	Acetone	55.9 ± 1.1	36.3 ± 2.1	0.90 ± 0.01
1:4	Acetone	65.3 ± 6.2	22.9 ± 7.7	1.20 ± 0.10
1:10	Acetone	49.7 ± 0.5	32.7 ± 0.6	0.88 ± 0.04
4:1	Ethanol	44.8 ± 7.0	47.7 ± 5.5	0.77 ± 0.07
1:4	Ethanol	36.7 ± 9.2	46.4 ± 6.3	0.60 ± 0.17
1:10	Ethanol	43.9 ± 0.7	46.0 ± 3.0	0.75 ± 0.01
4:1	Methanol	46.7 ± 7.9	43.2 ± 9.5	0.76 ± 0.14
1:4	Methanol	21.5 ± 7.4	70.1 ± 2.9	0.50 ± 0.14
1:10	Methanol	19.7 ± 2.5	74.4 ± 1.2	0.58 ± 0.06
4:1	Dichloromethane	28.9 ± 4.8	53.5 ± 7.8	0.50 ± 0.10
1:4	Dichloromethane	37.6 ± 4.3	32.2 ± 8.2	0.70 ± 0.02
1:10	Dichloromethane	26.3 ± 4.8	50.0 ± 0.8	0.54 ± 0.11
4:1	Acetonitrile	40.3 ± 2.3	11.9 ± 6.4	0.70 ± 0.05
1:4	Acetonitrile	24.0 ± 3.5	55.7 ± 9.4	0.50± 0.06
1:10	Acetonitrile	40.5 ± 6.2	27.1 ± 5.9	0.80± 0.10
4:1	Acetone/Water	31.4 ± 4.8	61.8 ± 7.9	0.50 ± 0.02
1:4	Acetone/Water	31.1 ± 4.5	38.0 ± 12.2	0.45 ± 0.01
1:10	Acetone/Water	60.6 ± 2.5	35.1 ± 1.4	1.05 ± 0.01
4:1	Ethanol/Water	33.2 ± 3.2	55.5 ± 3.4	0.61 ± 0.07
1:4	Ethanol/Water	45.0 ± 2.2	41.0 ± 3.8	0.75 ± 0.04
1:10	Ethanol/Water	49.5 ± 3.3	35.2 ± 1.9	0.86 ± 0.08

[a]PM is physical mixture

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

Formulation	$D_{10\%}$ (µm)	$D_{50\%}$ (µm)	$D_{90\%}$ (µm)
Ibuprofen (IBU)	5.9 ± 0.3	29.1 ± 0.6	83.9 ± 1.5
Glucosamine	30.3 ± 0.2	108.8 ± 0.2	156.0 ± 0.2
P.M IBU:GL[a]			
(4:1)	5.5 ± 1.1	30.0 ± 1.8	103.6 ± 2.6
(1:4)	5.7 ± 0.5	47.6 ± 1.9	145.2 ± 0.3
(1:10)	8.4 ± 0.7	88.9 ± 2.6	152.3 ± 0.7
SD IBU:GL (acetone)			
(4:1)	2.5 ± 0.1	14.9 ± 0.2	131.7 ± 1.3
(1:4)	4.3 ± 0.1	67.1 ± 0.1	149.3 ± 1.2
(1:10)	3.5 ± 0.1	71.7 ± 0.1	148.1 ± 0.4
SD IBU: GL (acetone/water)			
(4:1)	2.8 ± 0.1	21.6 ± 0.4	129.2 ± 0.3
(1:4)	6.5 ± 0.5	58.3 ± 5.1	146.7 ± 0.2
(1:10)	7.3 ± 0.1	85.3 ± 0.6	149.8 ± 0.3
SD IBU:GL (Ethanol)			
(4:1)	9.7 ± 0.1	84.6 ± 1.0	150.7 ± 0.19
(1:4)	8.7 ± 0.4	108.3 ± 1.2	157.5 ± 0.4
(1:10)	8.9 ± 1.0	109.2 ± 1.3	157.7 ± 0.6
SD IBU:GL (Ethanol/water)			
(4:1)	6.1 ± 0.2	33.8 ± 0.5	136.5 ± 0.1
(1:4)	4.4 ± 0.1	48.9 ± 0.5	143.0 ± 0.3
(1:10)	16.3 ± 0.3	109.4 ± 0.3	156.9 ± 0.1
SD IBU:GL (Methanol)			
(4:1)	12.0 ± 0.9	74.3 ± 3.3	146.1 ± 0.5
(1:4)	7.9 ± 0.2	95.1 ± 1.5	154.0 ± 0.4
(1:10)	5.0 ± 0.5	77.2 ± 2.7	150.6 ± 0.2
SD IBU:GL (Dichloromethane)			
(4:1)	3.2 ± 0.2	31.3 ± 1.6	138.8 ± 0.3
(1:4)	4.4 ± 0.1	86.3 ± 0.2	151.9 ± 0.2
(1:10)	2.9 ± 0.1	79.3 ± 1.4	149.9 ± 0.1

[a]These formulations are subjected to 10 min simple physical mixture in turbula blender; GL is glucosamine HCl

Table 3. Effect of acetone or ethanol concentration on dissolution performance of IBU-GL solid dispersions

Formulation	DE_{120min} (%)	MDT (min)	MDR ($\%.min^{-1}$)
Acetone (%):			
100	49.7 ± 0.5	32.7 ± 0.6	0.88 ± 0.40
83	61.6 ± 5.2	21.2 ± 2.4	1.25 ± 0.14
75	71.2 ± 7.6	24.5 ± 3.3	1.32 ± 0.15
66.6	57.9± 5.8	26.0 ± 3.4	1.07 ± 0.10
50	60.6 ± 2.5	35.1 ± 1.4	1.05 ± 0.19
40	58.0 ± 11.6	27.3 ± 2.5	1.08 ± 0.22
Ethanol (%):			
100	43.9 ± 0.7	46.3 ± 3.0	0.75 ± 0.01
83	41.4 ± 2.1	50.2 ± 2.3	0.68 ± 0.01
75	47.2 ± 3.1	44.9 ±3.0	0.75 ± 0.03
66.6	46.8± 3.8	43.6 ± 3.1	0.75 ± 0.02
50	49.5 ± 3.3	35.2 ± 1.9	0.86 ± 0.08
40	52.3± 4.1	46.5 ± 3.8	0.85 ± 0.03

Table 4. DSC data obtained for various solid dispersion formulations

Drug: carrier ratio	Solvent	Melting point (C)	Enthalpy (J/g)
Ibuprofen	---	78.6 ± 0.1	127.8 ± 4.4
4:1	PM	78.9 ± 0.9	99.1 ± 2.2
1:4	PM	77.5 ± 0.2	22.3 ± 1.4
1:10	PM	77.1 ± 0.02	8.2 ± 1.9
4:1	Acetone	77.5 ± 0.1	88.2 ± 6.2
1:4	Acetone	76.8 ± 0.3	21.6 ± 3.0
1:10	Acetone	76.5 ± 0.1	10.5 ± 0.4
4:1	Ethanol	76.9 ± 0.2	91.5 ±1.2
1:4	Ethanol	74.9 ±0.3	20.0 ±1.5
1:10	Ethanol	74.7 ±1.0	3.9 ±1.4
4:1	Methanol	75.7 ± 0.5	91.5±2.3
1:4	Methanol	74.9 ± 0.4	21.0 ±1.1
1:10	Methanol	74.3 ±0.4	11.7 ± 0.9
4:1	Dichloromethane	75.6 ± 0.3	95.9 ±1.5
1:4	Dichloromethane	74.7 ± 0.5	23.4 ±0.6
1:10	Dichloromethane	74.3 ± 0.4	11.0 ±0.9
4:1	Acetonitrile	74.4± 0.6	94.8 ±2.4
1:4	Acetonitrile	75.1 ± 0.7	22.1±2.7
1:10	Acetonitrile	75.0 ± 0.6	10.8±3.4
4:1	Acetone/Water	77.0± 0.8	103.7 ± 2.1
1:4	Acetone/Water	74.8± 0.9	15.2 ± 1.3
1:10	Acetone/Water	74.4 ± 0.9	13.1 ± 1.2
4:1	Ethanol/Water	77.0 ± 0.3	94.5 ±2.5
1:4	Ethanol/Water	74.6 ± 0.5	47.6 ±1.3
1:10	Ethanol/Water	75.0 ± 0.6	23.8 ±1.1