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Preparation and evaluation of solid dispersions of Ibuprofen using Glucosamine HCl as a carrier

[1,2]Abdul Wahab, [1,3]Gul Majid Khan*

1Drug Delivery Research Group, Faculty of Pharmacy, Gomal University, D. I. Khan, KPK, Pakistan.
2Department of Pharmacy, Kohat University of Science and Technology, Kohat, KPK, Pakistan.
3Department of Pharmacy, Quaid-e-Azam University, Islamabad, Pakistan.

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ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Aims: The aim of this study was to enhance the solubility and dissolution rate of sparingly soluble drug ibuprofen using glucosamine HCL as a carrier by solid dispersion technique.
Methodology: As Ibuprofen is sparingly water-soluble drug and has low bioavailability, so to enhance its solubility and improve bioavailability solid dispersions with different drug to carrier ratios (1:1, 1:2 and 1:3) were prepared, as solid dispersion is the most effective method for enhancing the solubility and improving the bioavailability of poorly or sparingly water- soluble drugs. In this study Glucosamine HCl was used as a potential hydrophilic carrier to improve the solubility, dissolution rate and bioavailability of poorly water-soluble drug, Ibuprofen from physical mixtures and solid dispersions. Solid dispersions with different drug to carrier ratios were prepared, using solvent evaporation method. Physical mixtures of Ibuprofen and Glucosamine HCl were also prepared for comparison
Results: All solid dispersions of Ibuprofen and Glucosamine showed considerably higher dissolution rate than corresponding physical mixtures and pure Ibuprofen. Different techniques such DSC, FT-IR, XRD and SEM were used to study the properties of pure Ibuprofen, solid dispersions and physical mixtures. These results confirmed that Glucosamine HCl can increase the solubility and dissolution rate of poorly water-soluble drug, Ibuprofen.

Conclusion: The study shows that the dissolution rate and solubility of sparingly soluble drug Ibuprofen can be improved and enhanced to great extent by solid dispersion technique, using Glucosamine HCl as a carreir. The current study also showed that amino sugar could be used as new carrier for solid dispersion formulations of non-steroidal anti-inflammatory drugs.

Keywords: Solid dispersions, Ibuprofen, Glucosamine HCl, Solvent Evaporation, Solubility, Dissolution rate.

1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Nearly one third of drugs in development are water insoluble which are mostly failed during trail phase of development because of underprivileged pharmacokinetics [1]. Poorly water-

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

soluble drugs belong to class II and Class IV of Biopharmaceutical Classification System (BCS). Poor water solubility of a drug leads to low dissolution, slow absorption, variable bioavailability and gastrointestinal toxicity [1]. Formulation of poorly soluble drugs for orally drug delivery now represent one of the most interesting challenges to formulation scientist in the pharmaceutical industries and for formulation containing poorly soluble drugs, dissolutions is the rate limiting step in the process of drug absorption [2].

Ibuprofen [(±)-2-(4'-isobutylphenyl) propionic acid] a phenyl propionic acid derivative, is widely accepted as one of the best tolerated non-steroidal anti-inflammatory and common analgesic drugs available for the treatment of rheumatoid arthritis, osteoarthritis, and mild to moderate pain [3]. The drug has been classified as class II drug as per the Biopharmaceutical Classification System (BCS) having low solubility and high permeability through stomach as it remains 99.9% unionized in stomach, so because of its solubility limitation and fast emptying time from stomach to intestine (30min to 2 hrs) cannot enter into systemic circulation. After this time it goes to small intestine where it is solubilized but cannot permeate through its membrane because of its pH dependent solubility and permeability [2]. Thus solubility and dissolution become the rate limiting steps for absorption. Drugs with low dissolution rates generally show erratic and incomplete absorption leading to low bioavailability when administered orally. To enhance solubility and improve dissolution rate of Ibuprofen is challenging and rational because its serum concentration and therapeutic effects are correlated, rapid Ibuprofen absorption is prerequisite for the quick onset of action. Several techniques have been reported to improve the solubility and dissolution rates of poorly water soluble drugs which include solid dispersions, micronizton, lipid based formulations, melt granulation, direct compaction, solvent evaporation, adsorption, coprecipitation, ordered mixing, inclusion complexation, liquisolid compacts, steam aided granulation, solubilization in surfactant systems, formation of water soluble complex and use of prodrugs [1][4]. Among all these methods and techniques micronizton and liquidsolid are most commonly used for class II drugs but these techniques are having some disadvantages as the micronized particles are stick together and make larger agglomerates, consequently leads to a reduction in effective surface area for dissolution [4]. The most effective method for improving dissolution rate is the use of solid dispersion technique. This technique has been widely used for poorly soluble drugs such as nimsulid, ketoprofen, tenoxicam, nifidipine and nimodipine [5-9].Solid dispersion is defined the dispersion of one or more active ingredients in an inert carrier or matrix in a solid state prepared by melting, dissolution in solvent or melting solvent method [10][11].

In solid dispersion carrier plays an important role in improving solubility and dissolution rate. Different polymers, superdisintegrants, surfactants are extensively studied in recent years for improving dissolution rate and enhancing solubility but in this study Glucosamine HCl was used as a hydrophilic carrier to increase the solubility and dissolution of poorly soluble drug Ibuprofen because glucosamine HCl is more stable as compared to other salts of glucosamine. The same study was conducted by Al-Hamidi [4], using glucosamine HCl as a carrier for improving dissolution rate and enhancing solubility of poorly water-soluble drug Carbamazepine.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

2.1. Materials

Model drug Ibuprofen (Gratis sample by drug testing laboratory, Peshawar, Pakistan), Glucosamine HCl (Sigma, UK), Distilled water, ethanol (Fisher Scientific, UK), KH_2PO_4 (Sigma, UK), NaOH (Sigma, UK). All chemicals and solvent used in this study were of analytical grade and used as obtained.

2.2. Methods

2.2.1. Preparation of solid dispersions

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

Solid dispersions of Ibuprofen were prepared with drug and carrier (Glucosamine HCL) ratio 1:1, 1:2 and 1:3 by weight, using solvent evaporation technique [12][13]. The drug was dissolved in ethanol followed by the addition of carrier dispersion in ethanol. The solvent was then removed by evaporation keeping at 40^{o} C under stirring condition (100rpm) for 24 hours. The solid dispersions prepared were then collected and kept at room temperature for 48 hours. Then the mass was pulverized in porcelain mortar and pestle and passed through sieve no 100, and stored at room temperature in a desiccator until further use.

2.2.1. Preparation of physical mixtures

For comparative studies of solid dispersions, physical mixtures were also prepared. The physical mixtures prepared were having the same composition of the solid dispersions; however, they were prepared by simple trituration of drugs and carrier in porcelain mortar followed by thorough blending in poly bags. The mixtures were then sieved and stored in desiccator at room temperature until further evaluation.

The composition of physical mixtures and solid dispersions of the model drugs is shown in tables [1].

Table 1 Composition of solid dispersions and physical mixtures of Ibuprofen

Formulation Code	Carrier	Drug : Carrier	Method
F1IBF	Glucosamine HCL	1:1	Physical mixture (trituration)
F2 IBF	Glucosamine HCL	1:2	Physical mixture (trituration)
F3 IBF	Glucosamine HCL	1:3	Physical mixture (trituration)
F4 IBF	Glucosamine HCL	1:1	Solid dispersion (solvent evaporation)
F5 IBF	Glucosamine HCL	1:2	Solid dispersion (solvent evaporation)
F6 IBF	Glucosamine HCL	1:3	Solid dispersion (solvent evaporation)

2.2.3. Evaluation of solid dispersions and physical mixtures

The evaluation of solid dispersion and physical mixture was performed using the following different techniques:

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

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98 ***2.2.3.1. Determination of drug content***

99 The drug content in each formulation was determined by taking the solid dispersions or
100 physical mixtures equivalent to 50mg of the respective model drug (Ibuprofen) and
101 transferring it to volumetric flask of 100ml and then small volume of phosphate buffer (pH
102 7.4) was added to hydrate the samples. Finaly the volume was made upto the mark. The
103 samples were shaked for some time to dissolve the drugs completely and were filtered
104 carefully. The absorbance values of standard (Ibuprofen, supplied by Abott Labortory,
105 Karachi, Pakistan) and the samples were determined at λmax 223 nm, using double beam
106 spectrophotometer (UV-1601, Shimadzu, Japan). Three reading were taken and then mean
107 and standard deviation were calculated.

108

109 ***2.2.3.2. Differential scanning calorimetry (DSC) studies***

110 The differential scanning calorimetry (DSC) study of carier Glucosamine, pure Ibuprofen, the
111 solid dispersions and physical mixtures of the model drug was performed using DSC
112 instrument (Mettler Toledo DSC 822e, Greifensee, Switzerland) equipped with Star^{e}
113 computer program. Approximately 3-6mg of sample was weighed in aluminum pan and then
114 sealed with punched lid. The temperature ranged between 20-300^{o}C with heating rate of
115 10^{o}C/min under nitrogen gas flow.

116

117 ***2.2.3.3. Fourier transform Infrared (FT-IR) studies***

118 The FT-IR spectra of carrier Glucosamine, pure Ibuprofen, the solid dispersions and
119 physical mixtures were taken to observe the drugs-carrier interaction, using FT-IR
120 SpectrumOne spectrophotometer (Perkin Elimer, UK) in the range of 650 to 4000 cm^{-1}. The
121 sample of several milligrams was placed on the stage of machine and then handle of the
122 machine was placed on the sample for generation of enough pressure. Then sharp peaks
123 with reasonable intensities were obtained. The spectra obtained were the result of 4 scans at
124 1 cm^{-1} resolution.

125

126 ***2.2.3.4. X-ray powder diffractometory studies***

127 X-ray patterns of pure Ibuprofen, pure, physical mixtures and solid dispersions were taken
128 using a Philips PW 1830 powder diffractometor (Philips, Eindhoven, Netherlands). The
129 prepared samples were exposed to Cu Kα radiation (λ= 1.5418 Å) in the range of $0^{0} \leq 2\theta \leq$
130 50^{0}. The step size was 0.05^{0} and the time for each step was kept two seconds.

131

132 ***2.2.3.5. Scanning electron microscope (SEM) analysis***

133 Electron micrographs of carrier Glucosamine, pure Ibuprofen, pure, physical mixtures and
134 solid dispersions were obtained using scanning electron microscope (SEM; Joel JSM-5910,
135 Japan) operating at 10 kV. The samples were mounted on a metal stub using adhesive tape

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

with double sided and coated with gold for conductivity in an organ atmosphere before observation. To study the morphology of active drugs, physical mixture and solid dispersions, micrographs with different magnification were obtained.

2.2.4. Solubility measurement

The solubility measurements of pure Ibuprofen, physical mixtures and solid dispersions in distilled water were performed according to the well published method by Higuchi and Connors (1965), accordingly, surplus amount (100mg) of Ibuprofen, physical mixtures and solid dispersions were placed in 100ml volumetric flasks and then made the final volume with the distilled water up to 100ml. The flasks were sealed with aluminum foils using rubber bands to avoid solvent loss. Then these flasks were kept on shaking using thermostatically controlled shaking water bath (Shel Lab, 1217-2E, USA) for 24 hours at room temperature (25^{o}C). The oscillation speed was kept at 100 oscillations per minute. After 24 hours all flasks were kept undisturbed on flat surface for three hours. A few ml supernatant from each flask was taken and filtered through membrane filter (0.45µm). One ml each filtrate was diluted with the same distilled water up to 25ml to achieve suitable dilutions. The diluted samples were analyzed to determine the Ibuprofen solubility, using a UV/Visible double beam spectrophotometer (Shimadzu, 1601, Japan) at λ max 223nm. The calibration curve was used for the determination of the quantity of soluble drug per ml.

2.2.5. In –vitro dissolution studies

The *in-vitro* dissolution studies were performed by USP method II (Paddle method) using eight stations dissolution apparatus Pharma Test (PTWS-11/P, TPT, Hunburg, Germany) and the rotation speed of paddles was set at 100 r. p.m. Each station or flask of the dissolution apparatus was filled with 900ml of distilled water used as dissolution medium to study percentage dissolution of model drugs (Ibuprofen), physical mixtures and solid dispersions. The temperature of dissolution medium was kept 37^{o}C ± 0.5^{o}C. Samples of five ml were withdrawn at selected time intervals (5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 min) with the help of syringes consisting of 0.45um filters. After each sampling equal volume of fresh dissolution medium was replaced to maintain the dissolution medium constant. Then after appropriate dilution the samples were analyzed for Ibuprofen, using double beam spectrophotometer (UV-1601, Shimadzu, Japan) at λmax 223nm. Percent drug dissolution of Ibuprofen was calculated by using calibration standard curves of the drug. The study was conducted in triplicate.

3. RESULTS AND DISCUSSION

3.1. Preparation of solid dispersions

Different methods such as salt formation, solubilization, particle size reduction, complex formation, solvent evaporation, etc. are used to prepare solid dispersions to enhance the dissolution rate and thereby improve the bioavailability of poorly water soluble drugs [14], however, in this study solvent evaporation method was used due to its inherent ease of handling and no more steps were required. The solid dispersions of model drug (Ibuprofen) with different drug and carrier ratios were prepared. The respective physical mixtures with

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

the same drug and carrier ratios were prepared by simple trituration method for comparative evaluation.

For conformation of uniform dispersion of drug in solid dispersions and physical mixtures drug content analysis was performed and it was found between 99.57±0.7 % and 101.3 ±0.32 %. All the solid dispersions and physical mixtures indicated the high content and uniformly dispersion of drugs. These findings conformed that the solvent evaporation method appears to be reproducible for development and preparation of solid dispersions. Similar studies were conducted by Prasad [12][15], who prepared solid dispersions of Tebinanfine hydrochloride and NSAIDs by the same method obtaining good results in terms of content analysis and uinform distribution of the drugs used.

3.2. Solubility study

As shown in table 2, the aqueous solubility study of pure Ibuprofen, their physical mixtures and solid dispersions was performed in distilled water. The study showed that solubility of Ibuprofen was enhanced in presence of carrier (Glucosamine HCL). This effect of solubility enhancement was more prominent in case of solid dispersions as compared to that of their respective physical mixtures. The enhancement of drugs solubility in presence of solid dispersions may be due to conversion of drugs to amorphous form as amorphic forms of drug are more soluble than their crystalline form [12][16]. The increase in solubility of drugs in solid dispersions might also be due to good wettability and dispesrability [16].

Table 2 Solubility data of different Ibuprofen formulations.

Formulations	**Solubility (mg/ml)**
Ibuprofen	
IBF Pure	0.285
F1 IBF	0.297
F2 IBF	0.313
F3 IBF	0.333
F4 IBF	0.320
F5 IBF	0.357
F6 IBF	0.398

3.3. Differential scanning calorimetry (DSC) studies

Differential scanning calorimetric (DSC) studies of pure ibuprofen, their physical mixtures and solid dispersions were conducted to investigate the crystillinity and drugs carrier

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

interaction. The DSC run of the pure Ibuprofen and carrier (glucosamine HCL) show sharp endothermic peaks around 76.94^{o}C and 210^{o}C, corresponding to the melting point of Ibuprofen and Glucosamine HCL, respectively [Fig. 1a-d].

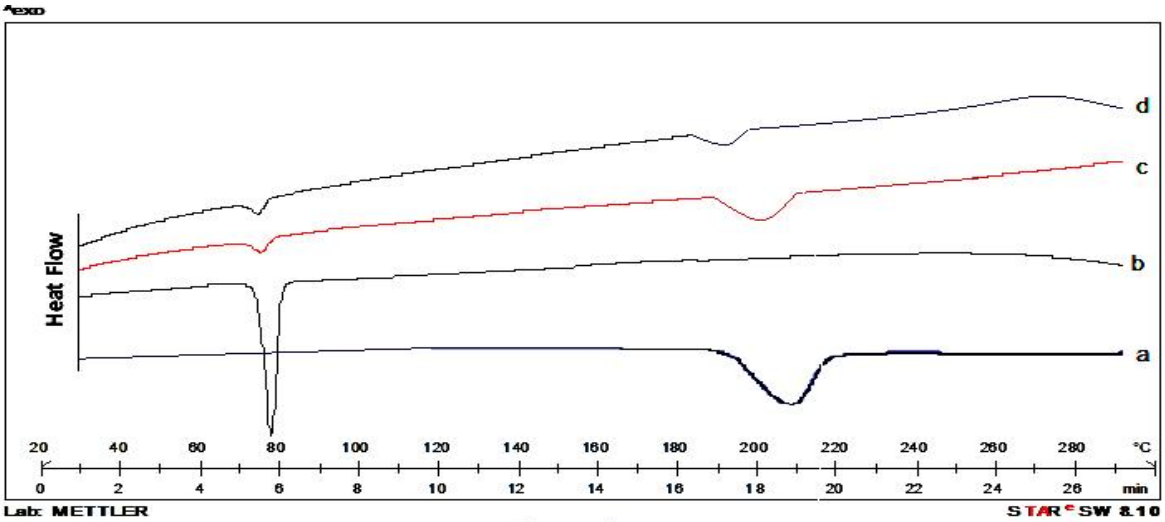

Figure 1 DSC Thermograms of (a) Glucosamine; (b) Pure ibuprofen; (c) Physical mixture; and (d) Solid dispersions of ibuprofen with glucosamine.

The endothermic peak of Ibuprofen is of very high intensity, showing the crystalline form of ibuprofen. The DSC thermograms of Ibuprofen-carrier (Glucosamine HCL) physical mixture and solid dispersions showed both the endothermic peaks [Fig. 1c-d] with some changes in the characteristics of the peaks shown by individual components; for example the endothermic peaks of physical mixture and solid dispersions lost its sharpness and distinctive appearance. It showed that no possible interaction was found between drug and carrier but the loss of peaks sharpness may be due to conversion from crystalline form to amorphous form of the drug.

3.4. Fourier transform Infrared (FT-IR) studies

For the conformation of interaction between drugs and carrier in presence of physical mixtures and solid dispersions FT-IR studies were performed. The FT-IR spectrums of pure Ibuprofen, and Ibuprofen-Glucosamine physical mixtures and solid dispersions were obtained as shown in the Fig. 2a-d. Pure Ibuprofen showed sharp characteristic peaks at 1706 cm^{-1} which corresponds to the carboxyl acid (COOH) present in ibuprofen. Other smaller peaks in the region 1200-1000 cm^{-1} are the indication of benzene ring [17]. These peaks can also be seen in the ibuprofen-carrier physical mixture and solid dispersions, but in this case IR spectrum for Ibuprofen-carrier mixture and solid dispersion shows the overlapping of carboxyl acid group [Fig. 2c-d]. Therefore, it can be concluded that no chemical interaction occurred between Ibuprofen and glucosamine HCL.

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

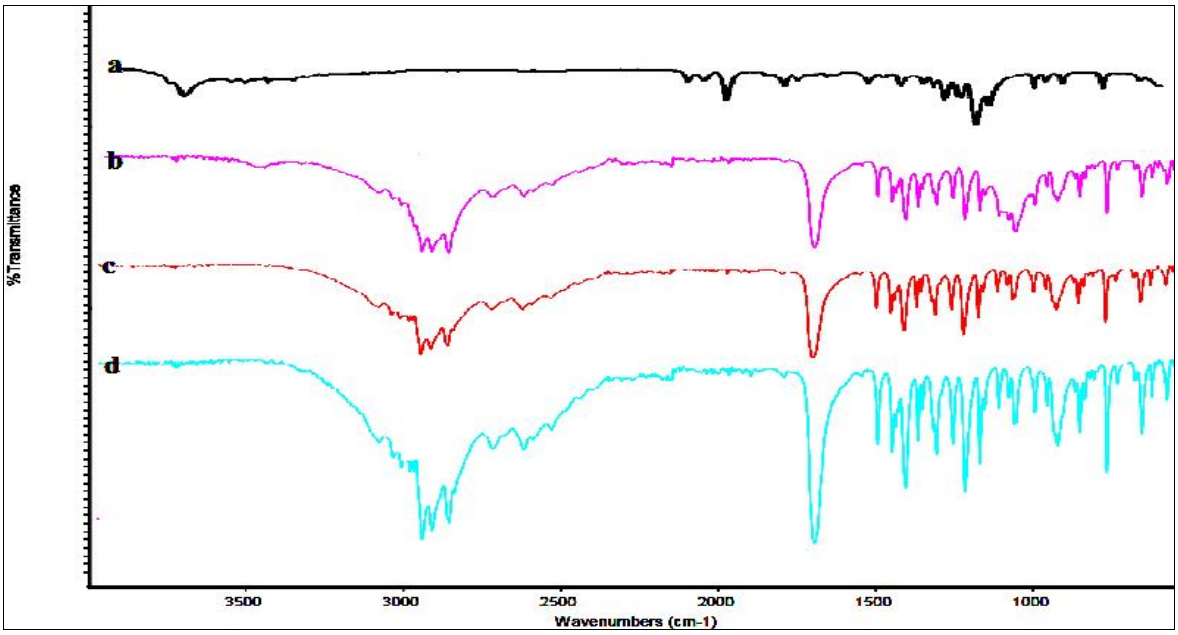

Figure 2 FT-IR spectra of (a) Glucosamine; (b) Pure ibuprofen; (c) Physical mixture; and (d) Solid dispersions of ibuprofen with glucosamine.

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

3.5. X-ray diffractometry studies

Figure (3a-c) shows the diffractograms of pure Ibuprofen, Ibuprofen-carrier physical mixture and solid dispersion.

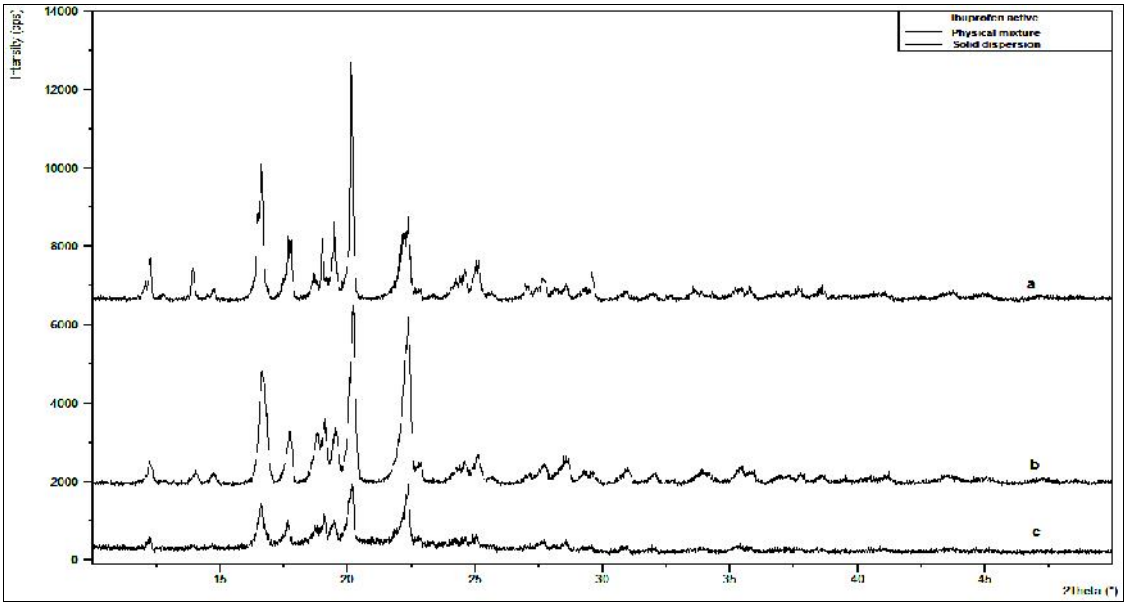

Figure 3 X-ray diffractograms of (a) Pure Ibuprofen; (b) Physical mixture; and (c) Solid dispersions of Ibuprofen and glucosamine.

The diffractograms of pure Ibuprofen with numerous distinctive peaks showed that the drug is highly crystalline in nature, conforms the DSC studies as shown in figure (3b). Four peaks with high intensity were present in the diffractogram of Ibuprofen around 17^{o}, 20^{o}, 23^{o} and 25^{o} along with some other peaks of lower intensity. The same peaks were present in the diffractogarm of Ibuprofen-carrier physical mixture and solid dispersions, but with lower intensity. This indicates that Ibuprofen crystallinity has been diminished. As compared to pure Ibuprofen and physical mixture of Ibuprofen-carrier, the peaks in the diffractogram of solid dispersions were of much reduced intensities, indicating the amorphous nature of the Ibuprofen in presence of solid dispersions.

3.6. Scanning electron microscope analysis

Figure 4a-d shows the scanning electron micrographs of Glucosamine HCL, pure Ibuprofen, Ibuprofen-carrier physical mixture and solid dispersions of Ibuprofen with glucosamine HCL. After analysis, the scanning electron microscopy (SEM) revealed that Glucosamine has prismatic shape (polygonal) and pure Ibuprofen has irregular crystalline shape. Both of these crystals can easily be identified in the physical mixture, as shown in the Figure 4c. In

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

physical mixture, there are numerous small crystals of Ibuprofen which are responsible for more solubility and enhanced dissolution rate as compared to pure compound, while in case of solid dispersions the crystals of Ibuprofen are in smallest size and they have irregular, circular and plate like shapes. The dissolution rate of Ibuprofen in solid dispersions was rapid and more as compared to pure Ibuprofen and physical mixture because the particle shape irregularity and small particle size increased the specific surface area and enhanced the dissolution rate [18].

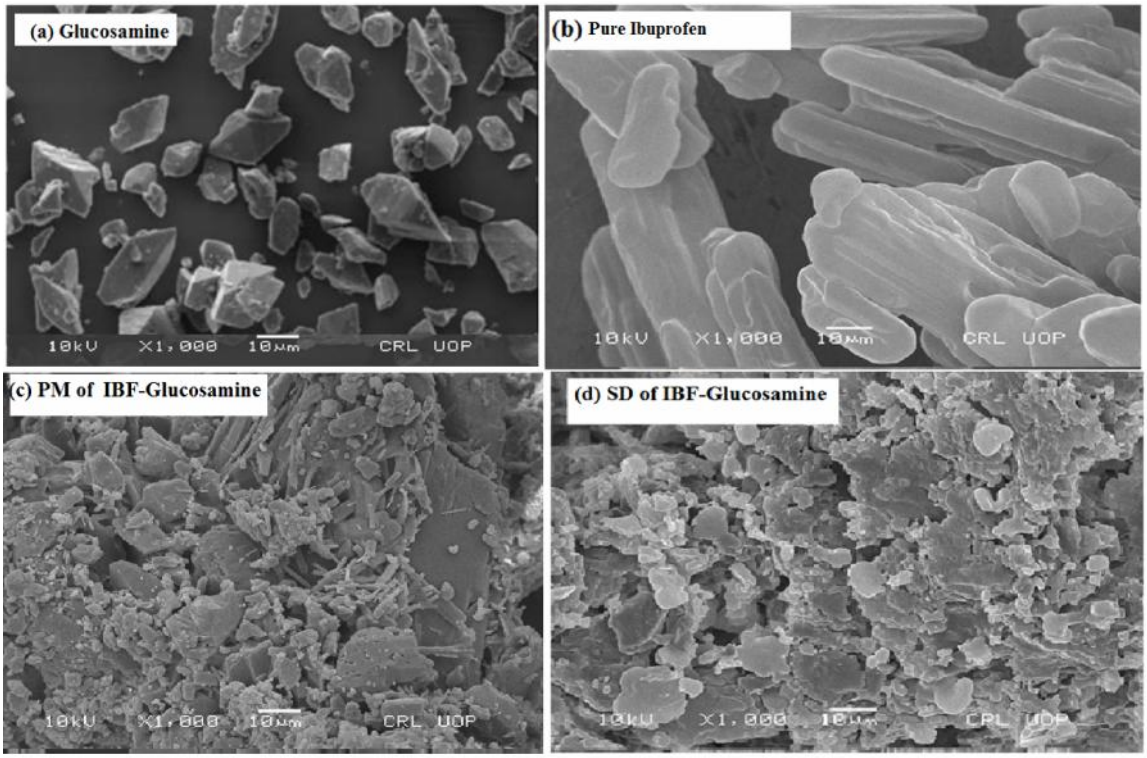

Figure 4 Scanning electron photomicrographs of (a) Carrier (Glucosamine HCL); (b) Pure Ibuprofen; (c) Physical mixture of Ibuprofen-Glucosamine HCL; (d) Solid dispersion of Ibuprofen-Glucosamine HCL.

3.7. In –vitro dissolution studies

The dissolution profiles of pure Ibuprofen, Ibuprofen physical mixtures and solid dispersions prepared with Glucosamine HCL are shown in Figs. 5 and 6. It is shown that pure Ibuprofen has the slowest dissolution rate and 22.3% of drug was dissolved after 120 minutes, while in case of physical mixtures and solid dispersions with different Drug: Carrier ratios (1:1, 1:2 and 1:3) the dissolution rate was linearly increased and 25%, 27.1%, 32.8% and 29.65% 40.75, 43.3% of drug was dissolved after 120 minutes from formulations F1 IBF, F2 IBF, F3 IBF and F4 IBF, F5 IBF, F6 IBF, respectively. The fastest dissolution rate was obtained for the formulation (F6 IBF) with the D: C ratio of 1:3 in carrer concentration dependent manners. The fast and rapid dissolution rate of Ibuprofen in solid dispersion may be due to the presence of Ibuprofen in amorphous form which is revealed by the results of different techniques as mentioned above. On the other hand it may be that if the percentage of carrier is too high, this may lead to increase in solubility and dissolution rate due to absence of

*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

299 crystallinity of drug [19] or It may be partially due to the formation of Ibuprofen-glucosamine
300 HCL complex [20].

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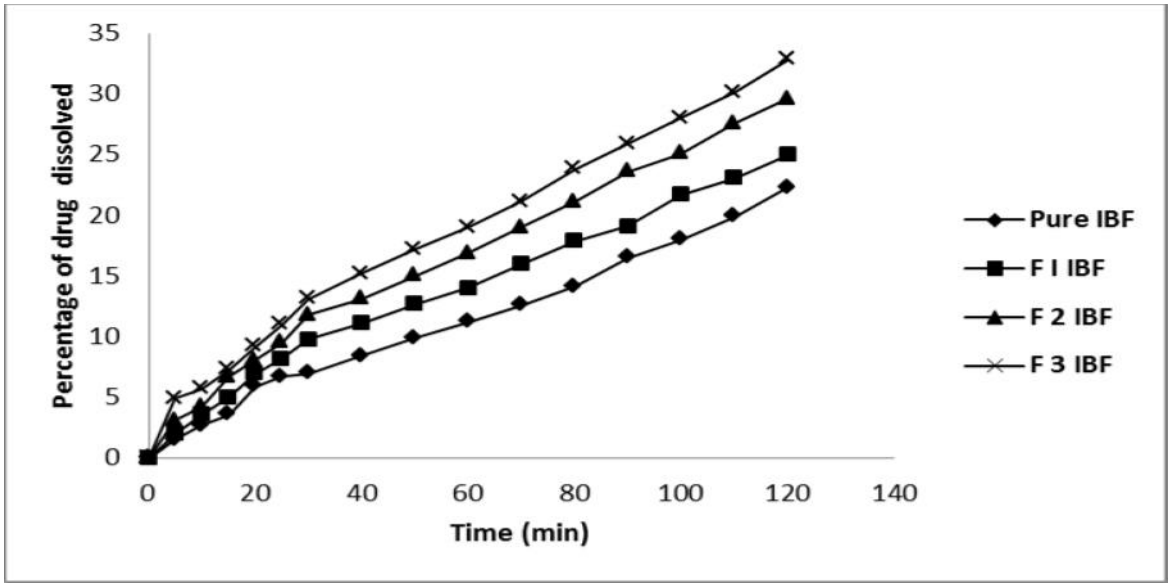

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304 **Figure 5** ***In-vitro*** **dissolution profiles of pure Ibuprofen and physical mixture with**
305 **different drug-carrier (Glucosamine HCL) ratio.**

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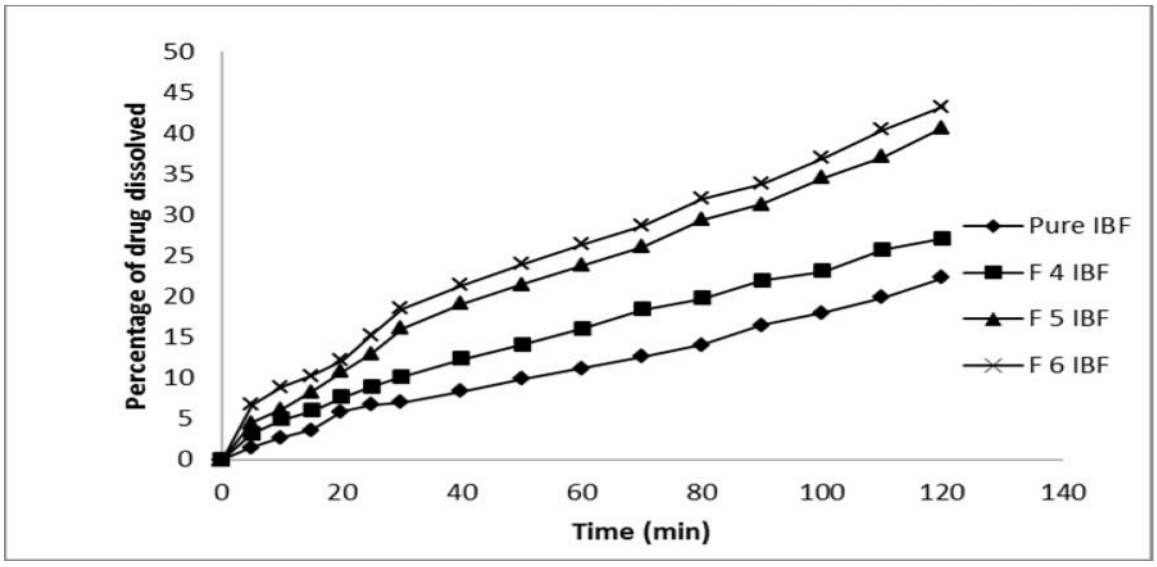

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*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

Figure 6 *In-vitro* dissolution profiles of pure Ibuprofen and solid dispersions with different drug-carrier (Glucosamine HCL) ratio

4. CONCLUSION

The study shows that the dissolution rate and solubility of sparingly soluble drug Ibuprofen can be improved and enhanced to great extent by solid dispersion technique, using Glucosamine HCl as a carreir. The current study also showed that amino sugar could be used as new carrier for solid dispersion formulations of non-steroidal anti-inflammatory drugs.

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*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.

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*Corresponding Author: Prof. Dr. Gul Majid Khan
E-mail address: drgulmajeed@yahoo.com.