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Improved dissolution of ibuprofen after crystallization from polymeric solution: Correlation with crystal parameter

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Abstract: The objective of the present work was to investigate the effect of various hydrophilic polymers, such as hydroxypropylmethyl cellulose, methyl cellulose, carboxymethyl cellulose and poly vinyl alcohol, on the *in vitro* dissolution property of ibuprofen (IBU) crystallized from aqueous polymeric solutions. By using the solvent-change technique, IBU crystal products were produced in the presence of the selected polymers. The results showed that in the presence of polymers, the crystallization yield of IBU was higher than that of pure drug crystals (absence of polymer). SEM photographs revealed visible changes in the crystal morphology in the presence of polymers. The FTIR spectra of the crystallized IBU (polymer-treated) showed a shift of the acid--dimer peak from 1718 to 1721 cm^{-1} but the absence of specific peaks for polymers. An XRD study further confirmed the absence of polymers in the crystallized IBU as no specific peaks were observed for the polymers. A higher percentage of cumulative drug release was reported for the polymeric-treated IBU crystals than that of plain IBU. Further *in vivo* studies are warranted to establish the *in vitro–in vivo* correlation for future technology transfer of the formulation.

Keywords: steroidal anti inflammatory drug; *in vitro* solubility; lattice strain; dislocation density.

INTRODUCTION

Enhancement of the dissolution rate for poorly water soluble drugs is the need of the time in formulation design of orally administered dosage forms to obtain improved bioavailability and rapid onset of action. Controlled crystallization of poorly soluble drug from an aqueous polymeric solution is an emerging strategy to increase their solubility and dissolution rate.[1] The crystallization method was evolved as a simple, effective and industrially viable technique,

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although several drug delivery techniques, such as solid dispersion, salt forms, multiple emulsion, complexation *etc.*, have been reported to improve the solubility and dissolution rate of poorly soluble drugs.[2] Manipulation of the crystallization process from an aqueous polymeric solution is comparatively less explored and could be a promising area of research in drug delivery. Crystalline products could be produced by using several conventional techniques, including solvent evaporation, pH change, thermal treatment, vapor diffusion, growth in the presence of additives (surfactants/polymers), *etc.*[3] The crystallization approach of poorly soluble drug from an aqueous polymeric solution to improve the aqueous solubility and dissolution rate of the drug has not been explored properly. The presence of a soluble polymer at a low concentration may assist in maintaining super saturation level of the drug after dispersion into the vehicle.[4,5] Side by side, polymers have the ability to alter the viscosity of the medium *via* manipulation of the nucleation phase during crystal development, which ultimately leads to alternation in crystal habits or generation of crystal defects. Changes in nanostuctural parameters of the crystallized products from a polymeric solution can be estimated quantitatively. Modification of crystal forms by defect crystallization may in turn lead to increase in solubility and oral bioavailability.[5]

Ibuprofen (IBU) is a non-steroidal anti inflammatory drug that has been commonly recommended in the treatment of arthritis (rheumatoid/osteoarthritis/ /gout), spondylitis, inflammation, fever, *etc*.[6] Chemically, IBU is a propanoic acid derivative (*i.e.*, 2-(4-isobutylphenyl)propanoic acid) with an *n*-octanol/water partition coefficient of 11.7. Its profound analgesic effect is mostly related to the inhibition of the enzyme cyclooxygenase-2. However, being a class II type drug (under the Biopharmaceutical Classification System), the main problem associated with oral administration is its extremely low solubility in aqueous media.[7,8] Thus, its dissolution rate is the major limiting step for the successful absorption of the drug to achieve the desired onset of action. Several advanced formulation techniques have been reported over the past years to improve the solubility and bioavailability of IBU.[9–13] In a recent study, Yuliandra *et al.* reported the co-crystal formulation of IBU with nicotinamide (as conformer) for improved solubility and *in vivo* analgesic activity. The co-crystal form of IBU showed significant increase in solubility as compared to a physical mixture of drug/coformer and pure IBU.[14] Similarly, in another study, dissolution of IBU was found to be increased by co-milling with different polymeric excipients.[15] As per a report, co-milling of IBU with hydroxymethylpropyl cellulose polymer improved the solubility and dissolution rate of IBU up to 4-fold compared to pure IBU. Crystallization of ibuprofen from aqueous polymeric solution for improved dissolution has rarely been reported to date. Further, establishing the correlation of dissolution with crystal grain size and crystal lattice strain is really novel.

In the present study, IBU crystals were produced by the simple controlled crystallization method using the anti-solvent technique in presence of an aqueous polymeric solution. Ethanol was used as the main solvent to solubilize IBU; whereas aqueous solution of polymer was used as the anti-solvent. Polymers, as discussed previously, tend to prolong the super saturation process, offer steric hindrance with simultaneous increase in the viscosity of the dispersed system to induce controlled crystallization. Four different hydrophilic polymers, *i.e*., hydroxypropyl methylcellulose (HPMC), methyl cellulose (MC), carboxymethyl cellulose (CMC) and poly(vinyl alcohol) (PVA) were used for crystallization of IBU and the correlation of dissolution with crystal imperfection parameters such as grain size, full width at half maximum (FWHM), lattices strain and dislocation density were investigated.

EXPERIMENTAL

Materials

IBU was a free sample from Tejani Life Care, Cuttack, India. HPMC, CMC, MC and PVA were purchased from Merck Private Ltd. Mumbai, India. All other chemicals/solvents used during the experiments were of analytical grade.

Method of preparation

An ethanolic solution of IBU (2 g in 50 ml) was prepared in a 1 L crystallization vessel and maintained at 50 °C under continuous agitation at a speed of 100 rpm. Then, in another container, a polymer solution (0.5 mass %) was prepared in 600 ml of water and added slowly to the above drug solution (3.0 ml min^{-1}).[16] Simultaneous cooling was also applied to the above crystallization vessel (50 down to 10 °C) at a rate of 0.22 °C min^{-1} using an external probe. Four such batches were prepared separately with each of the above four polymers (*viz*. HPMC, MC, CMC and PVA) at a constant drug–polymer concentration. The crystals were separated by filtration (Whatman®, Grade 40 circle) and dried in an incubator at 40 °C until constant weight was attained.

Yield percentage

The crystallized yield was evaluated from the weight expressed as the % of IBU dissolved initially in 50 ml of ethanol during first step of the preparation to the weight of final amount of crystal products recovered and the mean value was recorded (mean ± *SD*; $n = 4$).

Scanning electron microscopy (SEM)

Scanning electron microscopy (Carl ZEISS Sigma 300, India) was used for visualizing the surface morphology of the experimental crystal products by introducing a high beam of electrons through 0.5–1.5 kV acceleration voltage.[17]

FTIR spectroscopy study

FTIR spectroscopy is the commonly used technique to analyze the presence of the types of functional groups in drugs, drug crystals as well as to detect any interaction between them. For the study, the experimental samples were placed over zinc selenide crystal and pressed on to the attenuated total reflectance crystal by using an integrated pressure application device.[15] The experimental samples were observed using a FTIR spectrometer (FT/IR-4600, JASCO)

over the wave number range 4000 to 400 cm^{-1} and the data were interpretated by Spectra Manager Software (version 2.0).

Powder X-ray diffraction (PXRD)

For the study, about 1 mg of dry powdered sample was taken on the glass slide and analyzed using an X-ray diffractometer (RIGAKU ultimate PXDL software, Japan). Anode Material Cu, K-Alpha (1.5406 Å) was used as the source of X-rays.[18] The voltage and current were set at 40 kV and 15 mA, respectively. Measurements were undertaken at a scan speed of 1° min^{-1} over the scanning angle 2θ range from 5 to 50°.

In vitro *dissolution study*

The *in vitro* dissolution study was performed using a USP paddle type II dissolution apparatus (dissolution tester (USP) TDT06L, Electrolab). For the study, double distilled water (900 ml maintained at 37 °C) was used as the dissolution medium in each vessel and the test was conducted for 2 h. Briefly, 10 mg of IBU and experimental crystal products (equivalent to IBU 10 mg) were placed in the dissolution vessel.[19] The powder sample was allowed to settle at the bottom of the vessel before starting rotation of the paddle (50 rpm). About 10 ml of samples were withdrawn from the dissolution vessel at regular time intervals (10, 20, 30, 45, 60, 75, 90 and 120 min) through a syringe fitted with a membrane filter (0.45 μm) with simultaneous replenishment of fresh release medium. The collected samples were analyzed at 222 nm using a UV-Vis spectrophotometer (JASCO V-630, Japan) against water as the blank.[19] The studies were performed in triplicate (n=3), and the mean values of cumulative drug release (%) were obtained.

RESULTS AND DISCUSSION

The study was undertaken to understand the crystallization behavior of poorly soluble drug IBU from selected aqueous polymeric solutions of CMC, PVA, MC and HPMC and the correlation of the drug dissolution profile with the critical nanostructural parameters of the crystallized IBU. Super saturation was maintained after employing low concentration of polymeric additive that interfered with the regular crystal growth. The crystal arrangement pattern or packing of molecules of IBU crystal structure viewing randomly is depicted in Fig. 1. Centro-symmetric hydrogen bonded dimers are exhibited in the crystal packing of IBU. Four sets of product crystallized from aqueous polymeric solution and one in absence of polymer (as the control) are reported in Table I. The amount of polymer and drug were kept constant for each batch to compare the effect of selected polymers on the crystal property and the dissolution behavior of IBU.

Yield

The results showed that the crystallization yield of IBU was influenced by the presence of polymer (Table I). Among various polymers, HPMC resulted in the highest crystal yield (95.51 %) in contrast to IBU crystallized without polymer with the yield of 80.52 %. The presence of polymer clearly induced the crystallization process and the yield increased in presence of polymer in the order as: None < PVA < MC < CMC < HPMC.

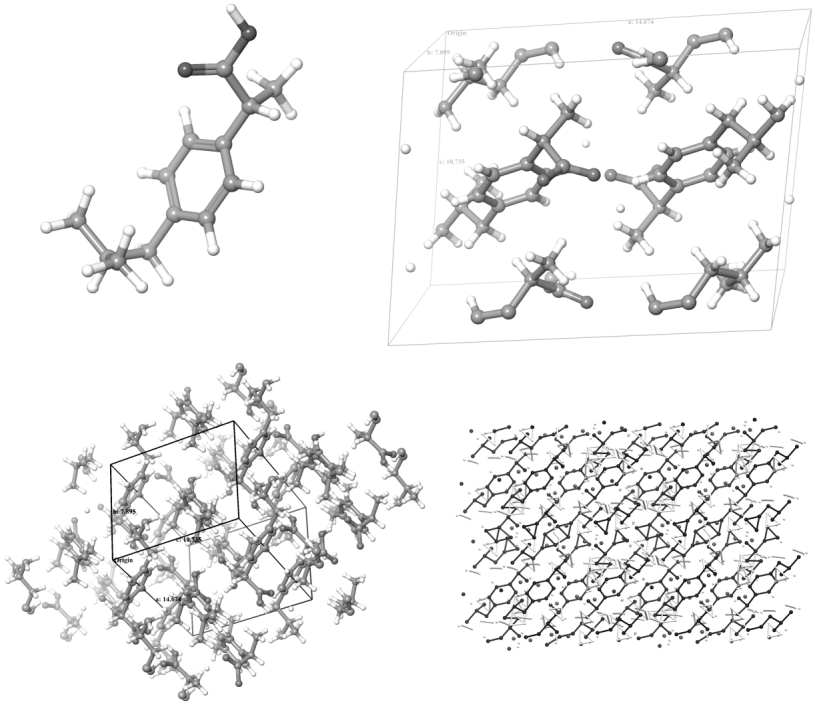

Fig. 1. Molecular packing arrangement of ibuprofen crystals viewed randomly (source: *Pubchem*).

TABLE I. Formulation of experimental ibuprofen crystallized from aqueous polymeric solutions

Formulation code	Polymer	Polymer concentration, wt. %	Yield ± *SD*, % (*n* = 4)
IBU^0	None	–	80.52±0.64
IBU^1	CMC	0.5	91.95±0.82
IBU^2	PVA	0.5	86.45±0.71
IBU^3	MC	0.5	88.38±1.31
IBU^4	HPMC	0.5	95.51±2.05

SEM study

The surface morphology of the pure drug and the crystallized products are depicted in Fig. 2. For pure IBU drug powder, polyhedral type of crystals were seen in the SEM image (Fig. 2A), very similar to pure crystallized IBU from aqueous medium (Fig. 2B). The size of the crystals was smaller when crystallized in presence of polymer as seen clearly in the photomicrograph. However, such a definite crystal geometry started to disappear in subsequent SEM images of crystal products; those were produced in presence of polymer. The rod shaped morphology of pure IBU gradually changed to a distorted plate and needle type (Fig. 2C–F) in case of polymer treated IBU crystals. Although, certain geometrical

forms still existed in IBU[1], IBU[2], IBU[3] and IBU[4] crystals, the overall morphology was somehow distorted. Clearly, some irregularities in the crystal geometry were noticed due to the influence of polymer presence relative to its absence. Irregularities in the crystal geometry could be the reflection of surface dislocation and defects in the crystal sample.

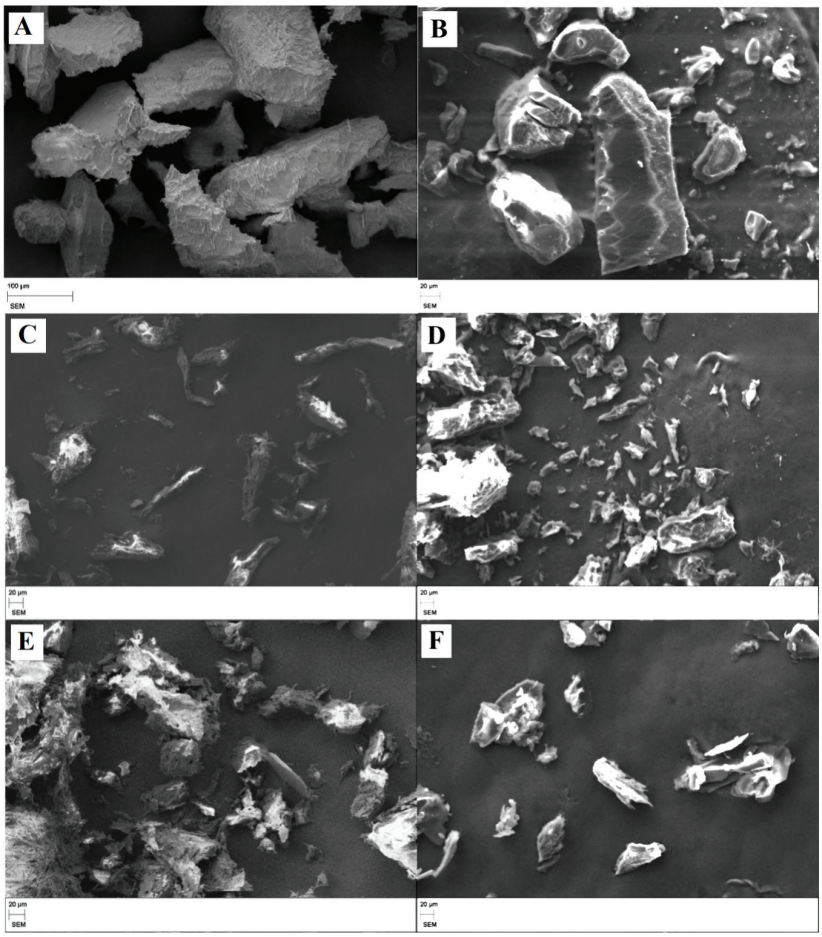

Fig. 2. Examination of photomicrograph of pure drug and the crystallized products: A) pure IBU, B) IBU[0], C) IBU[1], D) IBU[2], E) IBU[3] and F) IBU[4].

FTIR study

The FTIR spectra of the pure IBU, IBU pure crystal as well as the polymeric treated IBU crystal products were recorded to obtain information about the possible interaction between IBU and the selected polymers during controlled crystallization (Fig. 3). The FTIR spectrum of IBU showed medium to very strong bands at 3094, 2958 and 2901 cm^{-1}, which could be assigned to CH_2 asymmetric

stretching, CH_3 asymmetric stretching and C–H symmetric stretching, respectively. Strong bands in the region of 2800 to 3000 cm^{-1} of IBU were due to symmetric and asymmetric stretching vibrations of alkyl chains. The high intensity carbonyl peak of IBU at 1722 cm^{-1} became slightly weaker in the polymeric-treated crystal products, which indicates the effect of polymers in modulating crystal habits. However, there was absence of specific peaks for polymers in the polymer treated crystal products. In the case of polymers such HPMC, a common peak appears in the FTIR spectrum at 2825–2845 cm^{-1} (assigned to OCH_3 stretching), which was clearly absent in the HPMC treated IBU crystal (IBU^4). Similarly, in the FTIR spectrum of PVA, the main peaks appearing at 3280, 1324 and 839 cm^{-1}, *etc.* (assigned to O–H stretching, CH_2 symmetric stretching, CH_2 bending respectively), were clearly absent in the PVA treated IBU crystal product. The peak around 2800 to 3000 cm^{-1} that often appears as a shoulder type peak (H–C=O stretching) was present in the IBU and polymer treated IBU crystal products, which overall indicate the absence of polymers in the final crystal products. Polymers in low concentration (0.5 mass %) were used to induce supersaturation (anti-solvent system) and slight modification in crystal habits; however, these were not present in the final recovered IBU crystals as evidenced by the FTIR study. The results further confirmed the absence of any incompatibility or interaction between the drug and the selected polymer during the crystallization process. Neither new peaks of polymer nor major shifting of any characteristics peaks of the drug were observed.

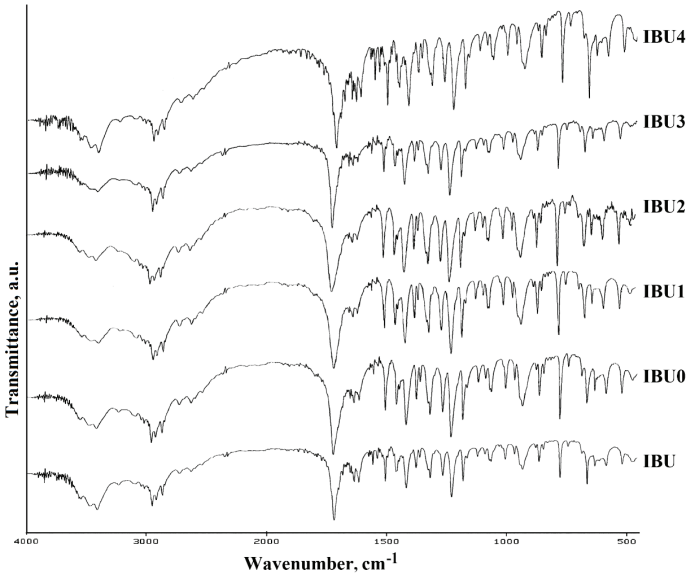

Fig. 3. FTIR spectra of pure ibuprofen, ibuprofen crystals and polymer treated ibuprofen crystal products.

PXRD study

PXRD has proved itself to be an essentional tool in the study crystalline structures at the supramolecular level. In XRD, the interaction of the incident X-ray with the experimental sample leads to the generation of constructive interference along with a diffracted ray, according to Bragg's Law ($n\lambda = 2d \sin \theta$).[20] The wave length of the incident X-ray is related to the angle of diffraction in a crystal lattice. In the present study, XRD measurements were performed to determine the possible changes in the crystallinity of the components during the crystallization process. Diffractograms of the pure IBU, IBU crystal and polymeric treated IBU crystals (IBU^1, IBU^2, IBU^3 and IBU^4) are depicted in Fig. 4. The XRD pattern of pure IBU exhibited characteristic diffraction peaks at various diffraction angles, *viz.* 6, 12.3, 16, 20.4 and 22.3° indicating the presence of crystallinity. These peaks although detected in the diffractogram of the polymer treated IBU crystal products were of much lower intensity compared to those of those of the pure drug and IBU^0 (without polymer treatment). The decrease in peak intensity in the polymer treated crystal products indicated a loss of crystallinity and generation of amorphization of the crystal samples. The X-ray diffraction peaks of the crystallized samples were slightly broader suggesting more nanosized particles compared to pure IBU. However, it should be further noted that no new peaks were identified for the polymers in the XRD data, which again indicated the absence of polymers in the final recovered IBU crystal products. However, the presence of polymer-induced slight amorphization in the crystal property could not fully alter the molecular arrangement of the crystals. Such limited amorphization would thus help to increase in solubility and dissolution profile of the drug compared to that of its pure form.

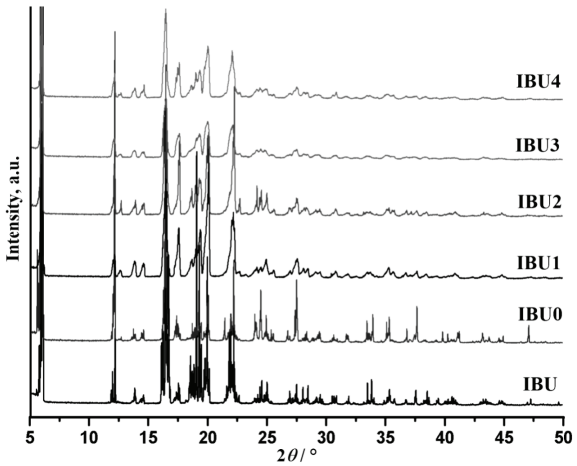

Fig. 4. PXRD data of pure drug, pure crystal (without polymer) and polymer treated crystal products.

TABLE II. Crystal grain size and lattice strain arising from crystal imperfection and their correlation with dissolution

Drug sample	Grain size±*SD*, nm	FWHM	(Strain±*SD*)×10^{-3}	(Dislocation density±*SD*)×10^{-4}, nm^{-2}
IBU	26.96±1.42	0.314	7.53±1.32	13.83±1.41
IBU^0	23.35±0.47	0.365	9.27±1.53	18.35±0.73
IBU^1	22.19±0.94	0.380	9.73±1.11	20.38±1.70
IBU^2	20.26±0.27	0.416	10.63±1.57	24.36±0.65
IBU^3	19.99±1.73	0.424	10.80±2.45	25.40±4.38
IBU^4	18.87±0.88	0.447	12.07±1.70	28.20±2.55
Correlation	T_{60} *vs.* grain size	T_{60} *vs.* FWHM	T_{60} *vs.* strain	T_{60} *vs.* dislocation
Equation	$y = -8.1877x +$ + 237.94	$y = 510.19x -$ –141.15	$y = 15.574x -$ –97.488	$y = 4.7402x - 44.782$
R^2	0.908	0.947	0.912	0.969

Using the XRD data, the Debye–Scherer formula was employed to determine other characteristic properties, such as particle size, strain, dislocation density, *etc.*, of the formed crystal products (Table II).

Thus, the Debye–Scherrer Equation was used to estimate the strain in the lattice, Eq. (1):

$$\varepsilon = \beta/4\tan\theta \quad (1)$$

The crystallite size was determined using Eq. (2):

$$D = 0.9\lambda/\beta\cos\theta \quad (2)$$

where ε = strain, β = FWHM (full width half maxima), D = crystallite size, λ = wavelength.

The dislocation density (δ) describes the extent of defects in the crystal sample. It is a measure as the length of dislocation lines per unit volume of the crystal and calculated by Eq. (3):

$$\delta = 1/D^2 \quad (3)$$

The particle size, strain, dislocation density showed small variations between pure drug, drug crystal and polymer treated drug crystal products. These variations could be due to the effect of polymers during the crystallization process, which generated to some extent amorphous properties of the experimental crystal products.

Dissolution of drug

Drug dissolution is the most important evaluation parameter of crystallized products. Dissolution data is inevitable to establish the *in vitro–in vivo* correlation, which is again essential for clinical translation of formulations from the laboratory to the bed side. A higher dissolution rate signifies higher rate of absorption, faster onset of action along with increased bioavailability.[21,22] In the

present work, *in vitro* dissolution studies of the pure drug, and drug crystallized from aqueous polymeric were performed in double distilled water at 37±0.5 °C in a USP type II dissolution apparatus (Fig. 5). In view of the very low solubility of IBU in aqueous medium, double distilled water was used as the release medium during the study. Similar reports for the use of water as release medium for poorly soluble drugs have already been reported previously including ibuprofen.[17,23–33] Hu *et al.* reported *in vitro* drug release of IBU from an experimental micro emulsion in distilled water.[26] It was found that the *in vitro* release profiles of IBU did not show much change in different drug release media, *i.e.*, the amount of drug release from the micronized formulation was very similar both in the case of double distilled water and simulated gastric fluid (pH 1.2). In addition, it has been reported that many non-steroidal anti-inflammatory drugs having low solubility (including IBU) tend to self-assemble themselves in aqueous medium by forming micelle-like structures, for which their solubility–pH profiles cannot be properly explained using the Henderson–Hasselbalch Equation.[34] Thus, in the present study, double distilled water was used as the drug release medium to obtain the overall idea about the possible improvement of dissolution of ibuprofen.

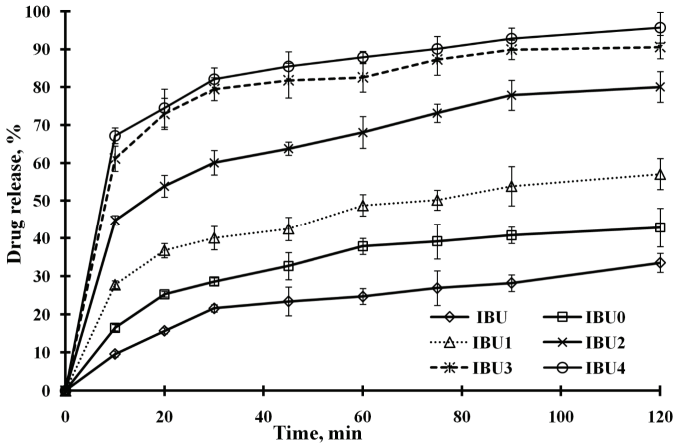

Fig. 5. Dissolution data of pure drug (IBU), pure drug crystal (IBU^0) and crystallized IBU from aqueous polymeric solution (IBU^1, IBU^2, IBU^3 and IBU^4) in double distilled water for 120 min. All sets of experiments were performed in triplicate. The data show mean ± *SD* (n = 3). Error bars indicate the standard deviation values.

From the data, it was observed that the dissolution rate of all experimental polymer treated crystal products was higher than that of plain IBU and IBU pure crystals during the period of the 120 min experimental study. Clearly, the presence of polymers during crystallization influenced the dissolution profile of IBU. Furthermore, among the four selected polymers, HPMC improved the drug

dissolution to an extent of 95 % as compared to the other polymers. The order of dissolution was observed as IBU < IBU^0 < IBU^1 < IBU^2 < IBU^3 < IBU^4. The reduced crystalline intensity of IBU to the maximum extent in the presence of HPMC could result in maximum dissolution of drug, which was supported by the XRD and SEM data. A significant improvement in dissolution of IBU^4 would be helpful for further *in vivo* studies to gather data for its future clinical translation. The dislocations due to linear defects on the atomic scale preferentially have been brought about improved dissolution. The highest dislocation density of IBU^4 exhibited a higher dissolution rate as compared to that of the other recrystallized product.

Correlation of *in vitro* dissolution with crystal imperfection parameters, such as grain size, dislocation density, lattice strain and FWHM, was attempted and the results are presented in Fig. 6. Dissolution at 60 min (T_{60}) is linearly correl-

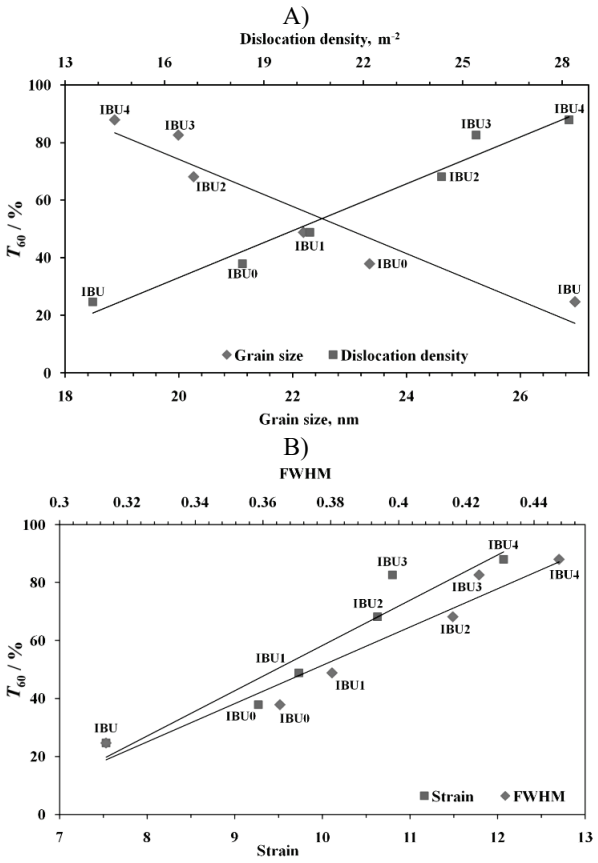

Fig. 6. Establishing linear correlation of: A) *in vitro* dissolution (T_{60}, %) *vs.* grain size and dislocation density and B) *in vitro* dissolution *vs*. strain and FWHM of the crystal data.

ated with grain size, dislocation density, lattice strain and FWHM. The respective regression equation and R^2 values (0.908 to 0.969) are presented in Table II. From the dissolution data, any of the crystal imperfection parameters could be predicted using the regression equation.

CONCLUSIONS

Ibuprofen was successfully crystallized from aqueous polymeric solutions in good yields, 86.45 to 95.51 %. The highest crystal yield was obtained from HPMC solution where crystallized IBU without polymer showed 80.52 %. Polymer presence in the supersaturation process induced the crystallization process and increased the crystal yield. Absence of any specific peaks in the FTIR spectra of the respective polymer in the experimental crystal product clearly indicated that the resultant IBU crystals were free from polymer in their crystal lattice. In XRD diffractogram, diminishing in intensity/broadening of certain peaks of IBU in polymer-treated crystal products indicated the extent of defects in the crystal sample, which might be responsible for their improved solubility and drug release property. Crystal grain size and lattice strain parameters arising from crystal imperfection were evaluated and their correlation with dissolution was established. The dissolution data any of the crystal imperfection parameters can be estimated using regression equation. Further *in vitro* and *in vivo* studies were hereby warranted to establish the optimized drug crystal for its future technology transfer to the industrial scale.

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ИЗВОД

ПОБОЉШАНА РАСТВОРЉИВОСТ ИБУПРОФЕНА НАКОН КРИСТАЛИЗАЦИЈЕ ИЗ РАСТВОРА ПОЛИМЕРА: КОРЕЛАЦИЈА СА ПАРАМЕТРИМА КРИСТАЛА

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Предмет рада је било испитивање утицаја различитих хидрофилних полимера као што су хидроксипропилметил целулоза, метил целулоза, карбоксиметил целулоза и поли винил алкохол на *in vitro* карактеристике растварања ибупрофена (IBU) кристалисаног из водених раствора полимера. Применом технике замене растварача, кристални производи IBU су добијени у присуству одабраних полимера. Резултати су показали да је у присуству полимера кристализациони принос IBU већи него у случају чистих кристала лека (без полимера). SEM фотографије су показале видљиве промене у морфологији кристала у присуству полимера. FTIR спектри кристалисаног IBU (третираног полимером) показују померај траке која потиче од димера киселине са 1718 на 1721 cm^{-1} и одсуство трака карактеристичних за полимере. XRD испитивања су потврдила одсуство полимера у случају кристалисаног IBU јер нису детектоване карактеристичне реф-

лексије полимера. Већи проценат кумулативног ослобађања лека је детектован у случају IBU кристала третираних полимерима у односу на чист IBU. Даље студије *in vivo* ће успоставити корелацију *in vitro–in vivo* за будући технолошки трансфер формулације.

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