Research Article

Improvement of Physicomechanical and Pharmacotechnical Parameters of Ibuprofen by Crystal Engineering

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ABSTRACT

The aim of present work was to improve the physicochemical and processing parameters of the drug having poor aqueous solubility and poor flowability of the drug Ibuprofen (IBU) by its crystallization in presence of different excipient/s for direct compression. Crystals could be successfully prepared by solvent evaporation method of crystallization technique in presence of Saccharin sodium. Treated crystals were resulted with unique melting behavior, enhanced aqueous solubility (22.02 folds) and dissolution (3.29 folds) having a stoichiometric molar ratio of 1.58 : 0.014. Control batch crystals showed improvement in different properties by crystal engineering approach. SEM images of treated crystals revealed bigger and platy shaped crystals with aspect ratio near to unity. Treated crystals showed improvement in flowability and packability with higher drug content (99.83 %). Heckel plot analysis depicted the greater plastic deformation (K= 0.222) and tensile strength with negligible elastic recovery compared to pure drug (K=0.833). FT-IR spectra concluded formation of hydrogen bond between drug and excipient. Treated crystals were also characterized by DSC study revealed the formation of a crystal form and compatibility of drug with the excipient under study. The improvement in physicochemical, pharmacotechnical and mechanical parameters of Ibuprofen by the crystal engineering approach could be highlighted.

Keywords: Crystallization; Kawakita; Bioavailability; Pharmacotechnical; Heckel plot.

INTRODUCTION

In the pharmaceutical industry, poor biopharmaceutical properties rather than lethal effect or non-efficacy that are the key reasons to bring less than 1% of active medicaments i.e., Active Pharmaceutical Ingredients (API) into the market place[1].

Among these biopharmaceutical properties, solubility remains a key issue[2]. Drugs often are discarded during commercial production due to their low solubility. Improvement in the aqueous solubility of drugs is presently one of the major challenge for the pharmaceutical industry.

There are various approaches can be used for the improvement in aqueous solubility of drugs including salt formation, emulsification[3], solubilisation using cosolvents, micronisation, complexation of poorly soluble drugs with β-cyclodextrin[4], jet milling to create microparticles, high-pressure homogenization to form nanoparticles, co-precipitation, crystal engineering[5] and the use of polymers for the delivery of poorly soluble drugs[6].

Oral bioavailability of these approaches has been successful but is highly dependent on the specific physicochemical nature of the drugs under investigation[2]. In crystal engineering approach, there has been a growing interest in the design of pharmaceutical treated crystals, which acts as a potential method for enhancing the oral bioavailability of the drugs under investigation having low aqueous solubility.

It has been predicted that only less than 20% of the API can be processed into tablets via direct compression since the majority of API lack the flow, cohesion, packability, compactibility, compressibility or lubricating properties required for direct compression[7]. Therefore, formulator has the alternative to wet granulation techniques to obtain API/excipient with suitable compression properties. Wet granulation involves several processing steps (dry mixing, granulation, drying), different equipments, and extensive downstream testing for powder homogeneity/segregation[8]. Therefore, a more feasible attractive interest and option for manufacturing of tablets by direct compression in the pharmaceutical industry is due to its cost effectiveness as it needs very few processing steps, stability towards moisture and heat, faster dissolution, less wear and tear of punches and simplified validation[9]. The simple unit operation i.e., direct compression process is highly influenced by powder properties like flow property, compressibility, packability, compactibility, dilution potential and plastic behavior.

Not a single drug substance or excipient possesses all the desired physicomechanical properties required for the direct-compression processing, which can be scaled easily

from laboratory to production scale. Majority of the pharmaceutical preparations contain about 70–80% of excipients at a higher concentration than the API[10]. But this concept could be erroneous for drugs with high dose and poor compactibility, as it might increase the final weight of tablet above the standard limits[11]. Ibuprofen (IBU) is a typical example of this type of drugs[12,13].

Ibuprofen is a potent non-steroidal anti-inflammatory drug (NSAID), is a proprionic acid derivative which is used for symptomatic treatment of osteoarthritis, anti-inflammatory, spondylitis, rheumatoid arthritis, antipyretic properties and is widely used clinically. Ibuprofen is of BCS Class II drug which is having poor aqueous solubility and higher permeability with analgesic activity[14-16]. On the basis of powder rheology, it is also classified as a powder with poor flow property and compressibility[15-17] which is not processed by directly compressible technique.

Therefore, Ibuprofen API is selected for the preparation of its treated crystals to improve its physical and mechanical properties as well as its pharamcotechnical parameters which were the key issues while processing and formulation of the directly compressible tablets of the selected API. The excipient selected for the processing of treated crystals is Saccharin sodium which helps in the formation of hydrogen bonding with Ibuprofen which is the prime requirement for the preparation of treated crystals. The solid state of the prepared treated crystals was also investigated to identify any changes in Ibuprofen during the selected crystallization process.

MATERIALS AND METHODS

Materials

Ibuprofen (IBU) was gifted by Marksans Pharma Limited, Goa. Lactose, Benzoic acid (BA), Oxalic acid (OA) and Maleic acid (MA) were purchased from Sisco Research Lab., Mumbai, India.

Potassium dihydrogen phosphate (KH_2PO_4) and Disodium hydrogen orthophsophate dihydrate (Na_2HPO_4) were purchased from SDFCL, Mumbai. Sodium Hydroxide (NaOH) and Sodium acetate trihydrate were procured from Rankem, New Delhi, India. Saccharin sodium dihydrate (SAC-Na) was gifted by Pure Chem. Pvt. Ltd., Ankleshwar, Gujarat. All other solvents, excipients and chemicals used were of analytical and HPLC grade (Merck Pvt. Ltd., Mumbai, India).

Crystal Preparation by Conventional Solvent Evaporation Technique[18]

Molar proportion (1:2) of Ibuprofen (2.063 g, 0.01 mol) was mixed with Saccharin sodium dihydrate (2.412 g, 0.01 mol) and were dissolved in sufficient volume of ethanol (95%) to get saturated solution and stirred the content at Room temperature. The stirring was continued until all the solvent evaporated and left with the solid residue of treated crystals. Solvent residue, if any, was then removed by vacuum oven at 30 °C for 48 h. The obtained crystals were gently triturated in a mortar and pestle and were then passed through a sieve 60 ASTM before characterization.

A batch of control crystals was also formulated without adding excipient (Saccharin sodium dihydrate) by keeping same other experimental parameters.

Saturation Solubility Study[19]

An excess quantity of Ibuprofen, its control batch and treated crystals were added separately into 10 mL of Distilled water, Acidic buffer pH 1.2, Acetate buffer pH 4.5, Phosphate buffer pH 6.8 and dissolution media of Ibuprofen (Phosphate buffer pH 7.2). The samples were placed in Cryostatic constant temperature reciprocating shaker bath at the temperature 37 ± 1 °C with constant shaking at 120 RPM for 48 hours to allow saturation. The solutions were then centrifuged and if necessary, the supernatant was filtered through whatman filter paper No. 41 and the filtrate was analyzed spectrophotometrically (UV-1800, Shimadzu) at 222 nm.

% Yield and Drug Loading Efficiency

The practical % yield of API loaded crystals was calculated by weighing the prepared API loaded crystals after drying stage [Eq. (I)].

$$\% \text{ Yield} = \frac{\text{Total weight of treated crystals}}{\text{Total weight of drug and excipient}} \times 100 \quad \text{--- Eq. (I)}$$

For determining the drug loading efficiency [Eq. (II)], treated crystals (10 mg) were dissolved and diluted the content up to 100 mL with Phosphate buffer pH 7.2 solution and mixed well. If necessary, the solution was filtered through whatman filter paper No. 41 and the filtrate was suitably diluted with the same buffer solution and analyzed spectrophotometrically (UV-1800, Shimadzu) at 222 nm against blank solution (IP X). Concentration of Ibuprofen in the treated crystal was calculated from the absorbance obtained using regression line equation of calibration curve. The procedure was repeated for three times.

$$\% \text{ Drug loading efficiency} = \frac{\text{Drug entrapped in treated crystals}}{\text{Theoretical drug content}} \times 100 \quad \textbf{Eq. (II)}$$

Melting Point Determination

The melting point was determined by using a Melting point apparatus (Veego®, Model: VMP-DS) in order to find the melting point of pure drug, control batch and treated crystals.

Micromeretic Properties[20]

Optical Microscopy

Particle size of randomly selected 300 particles of respective samples was measured by optical microscopy using pre calibrated eye piece. Sample was placed on the slide and particle size was determined by taking longest dimension of the particle for minimum of 100 particles. Mean aspect ratio (AR), defined as the ratio of the

horizontal maximum (longest length of the particle oriented parallel to the ocular scale) to the vertical maximum (longest dimension of the particle measured at right angles of the length) of the particle, was determined[21].

Angle of Repose[22]

Angle of repose was determined using fixed height method. The powder was poured through a funnel till the maximum cone height (h) was achieved. Radius of the pile (r) was measured and angle of repose was calculated using equation [Eq. (III)].

$$\theta = \tan^{-1}\left(\frac{h}{r}\right) \quad \text{--- Eq. (III)}$$

Where, θ = angle of repose

h = height of the pile

r = radius of the base pile

% Carr's Compressibility Index

Flowability of pure drug, control batch and treated crystals was also evaluated by Carr's Index (CI)[23,24].

The CI was calculated from the poured (bulk) and tapped densities. Tapped density was estimated by tapping the accurately weighed samples (5 gms) into a 10 mL measuring cylinder using a Tap density apparatus. The CI was calculated according to the equation [Eq. (IV)].

$$\%\ \text{Carr's Compressibility Index} = \left[\frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}}\right] \times 100 \quad \textbf{Eq. (IV)}$$

Hausner's Ratio[22]

Hausner's ratio is an indirect indication of ease of powder flow. It was calculated by the equation [Eq. (V)].

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}} \quad \text{--- Eq. (V)}$$

Measurement of Packability, Compactibility and Compressibility Properties[20]

Kawakita Constants[25]

The packability of the samples was estimated by tapping them into a 10 mL graduated cylinder using the Tap density tester USP (Elactrolab, ETD-1020). Accurately weighed powder (5 gms) was gently filled into a graduated cylinder. The volume occupied by the powder was noted. The poured density (minimum density) was found from the powder mass (5 gms) and the occupied volume. Then the cylinder was tapped and the reduced volume was noted after every 100 taps until the volume remains constant. The packability was determined by measuring the tapped density according to the modified Kawakita Eq. (VI) and Eq. (VII).

$$\frac{n}{C} = \frac{n}{a} + \frac{1}{ab} \quad \text{--- Eq. (VI)}$$

Where, a and b are the constants

n = tap number

C = volume reduction

$$C = \frac{V_0 - V_n}{V_0} \quad \text{--- Eq. (VII)}$$

Where, V_0 and V_n are the powder bed volumes at initial and n^{th} tapped state, respectively

The packability and compactibility parameters are ---

a = Packability of the powder or extent of densification due to tapping

$\frac{1}{b}$ = Apparent packing velocity obtained by tapping i.e., how fast the final packing state was achieved.

From the Kawakita plot of $\frac{n}{C}$ Vs n of Kawakita's equation [Eq. (VI)][26], (a) value obtained from the slope and $\left(\frac{1}{b}\right)$ value from the intercept of the plot.

Kuno's Constant

The of Kawakita analysis was also evaluated by the Kuno's equation [Eq. (VIII)]. Packability was assessed by comparing the constants a, $\frac{1}{b}$ of Eq. (VI) and constant K of Eq. (VIII) respectively.

$$\ln(\rho_t - \rho_n) = -K_n + \ln(\rho_t - \rho_0) \quad \text{--- Eq. (VIII)}$$

Where, ρ_t, ρ_n and ρ_0 are the apparent densities at equilibrium, n^{th} tapped and initial state, respectively.

'K' is the Kuno's constant represents rate of packing process.

Heckel Plot Analysis

The Heckel equation [Eq. (IX)] provides a method of compression pressure and displacement signals to a linear relationship for materials undergoing compaction. The equation assumes that at applied pressure the densification of powder bed follows first order, with inter particulate pores as the reactant and the densification of the powder bed as the product. Pure drug, Control batch and treated crystals were compressed using 8mm flat-faced punch at various applied pressures (1, 3, 5, 7 and 9 tons) using KBr press[27]. The punch and die were lubricated using 1% w/v dispersion of Magnesium stearate in acetone.

$$\ln\left(\frac{1}{1-D}\right) = KP + A \quad \text{--- Eq. (IX)}$$

Where, 'D' is the solid fraction (the ratio of tablet density to true density of powder) at applied pressure 'P' in tons

(1-D) denotes the % porosity (Є) of the powder material

'K' is the material-dependent constant (the slope of the straight line portion of the Heckel plot)

The reciprocal of 'K' is the mean yield pressure (P_y)

Intercept 'A' gives the densification of the powder bed as a result of initial particle rearrangement

'D' value was calculated by determining the diameter and thickness of the compacts after each applied pressure in tons. Compression behavior of the respective powders was expressed as parameters of Heckel equation [Eq.

(IX)][28]. Heckel analysis was carried out by plotting the $\ln\left(\frac{1}{1-D}\right)$ Vs P.

Elastic Recovery

The compacts used in the Heckel plot analysis were subjected to relaxation period of 24 hours to judge the elastic behavior of the powder bed under investigation. The thickness of compacts was recorded immediately after ejection (H_c) from the KBr press and after 24 hours relaxation period (H_e). Elastic recovery was calculated using the equation [Eq. (X)][29].

$$\%ER = \left[\frac{(H_e - H_c)}{H_c}\right] \times 100 \quad \text{--- Eq. (X)}$$

Pressure-Tensile Strength Relationship

The compacts prepared for the Heckel plot analysis were subjected to the determination of pressure tensile strength relationship in which the force required to break the compacts (F) was recorded[30]. The tensile strength of the compacts was calculated using the equation [Eq. (XI)][31].

$$T = \frac{2F}{\pi D t} \quad \text{--- Eq. (XI)}$$

Where, D and t are diameter and thickness of the compacts respectively.

***In-vitro* drug release study of API loaded crystals, control batch and pure drug**

In-vitro drug release study was carried out by using USP dissolution test apparatus (Electrolab Dissolution Tester TDT-06P, USP). The dissolution profile of pure drug, Control batch and API loaded crystals were studied in 900mL of Phosphate buffer pH 7.2. Each of 100 mg pure drug and control batch were filled in capsule separately while in case of drug-loaded crystals, 100 mg equivalent to API was filled and placed in a dissolution flask containing 900 mL of the dissolution medium, thermostated at 37 ± 0.5 °C, with basket (USP Type I) with rotation speed of 50 RPM for one hour.

At scheduled time intervals, the samples (5 mL) were withdrawn and replaced immediately with fresh dissolution medium. The samples were filtered and one milliliter of the filtrate was diluted with the buffer solution till the absorbance was measured in the range of 0.2-0.8. All the samples were assayed similarly by measuring the absorbance spectrophotometrically at the wave length of 222 nm (IP X). The dissolution experiments were conducted in triplicate and the mean of the absorbance were calculated. After one hour of dissolution, the amount (%) of the drug dissolved were calculated graphically and used as comparison parameter in dissolution studies.

Solid State Properties of Treated Crystals

Scanning Electron Microscopy (SEM) Study

Morphology and surface topography of Ibuprofen drug, control batch and final formulation (treated crystals) were visualized by SEM instrument of Zeiss Evo® 18 special edition, Germany. Dried each sample under analysis were placed on the aluminum stubs previously stick with double-sided sticky carbon tape separately and placed each stubs in their appropriate position denoted on the stage of the instrument. The analysis was done under vacuum and photographs were taken at various magnifications to observe the surface morphology, shape and size of each sample.

Fourier Transform Infra Red Spectroscopy (FT-IR) Study

FT-IR study was performed to determine the compatibility of Ibuprofen with the Saccharin sodium excipient by interpreting and comparing the IR spectra of Ibuprofen drug, Saccharin sodium excipient, physical mixture of Ibuprofen drug and Saccharin sodium excipient, control batch and the final formulation (treated crystals) by using Nicolet IS 10, FT-IR spectrometer (Thermo scientific, Japan). Each sample were triturated separately with KBr to form a very fine powder. The thin KBr pellets of each powder sample were prepared by compressing them in KBr press separately for analysis and their respective IR spectra were taken in the fingerprint region of 400-4000 cm^{-1}.

Differential Scanning Calorimetry (DSC) Study

Interpretation of DSC spectra of different samples analyzed by DSC-60, Shimadzu, Japan for the compatibility study as well as characterization of respective samples under analysis. DSC spectra of Ibuprofen pure drug, Saccharin sodium excipient, physical mixture of drug and excipient, control batch and the final formulation (treated crystals) were compared and analyzed for the compatibility study. The calibration was done by using Indium as standard. Analysis was performed under a nitrogen purging rate of 100 ml/min. Accurately weighed each sample under analysis (about 3 mg) were placed in aluminum crucibles separately and sealed with a pinhole-pierced cover. Thermal curves were recorded at heating rate of 10 °C/min from 30 °C to 300 °C against a sealed aluminum empty crucible as reference.

RESULTS AND DISCUSSION

Preliminary Trials for the Preparation of Ibuprofen Treated Crystals

Preliminary trial batches of Ibuprofen treated crystals were prepared using different excipients like Lactose, Oxalic acid, Maleic acid, Benzoic acid and Saccharin sodium dihydrate (SAC-Na) by changing various experimental conditions and techniques like antisolvent addition technique, fusion technique, solvent evaporation technique and deep freezing at 4 to 5 °C. All the techniques were processed with various molar ratios of drug and excipients (1:1, 1:2, 1:3, 2:1 and 3:1). Among various organic solvents used to obtain Ibuprofen crystals, one solvent i.e., Ethanol (95%) gave predictable results. Because of the very poor solubility of either drug

or excipient or both, solvents like methanol, hexane, chloroform and other low polarity organic solvent could not formulate the preferred crystals.

In each trials, treated crystals were obtained either with poor yield, poor drug loading, low aqueous solubility and dissolution rate or poor flow property.

Hence, those batches were screened from the present work. One excipient i.e., SAC-Na dihydrate gave encouraged result with solvent evaporation process to develop treated crystals of Ibuprofen where Ethanol (95%) was used as a solvent. Among different molar ratios of IBU : SAC-Na, only 1:1 and 1:2 molar ratios found to generate treated crystals with improved flow property compared to pure Ibuprofen. *In-vitro* dissolution rate of molar ratio 1:2 found much better than 1:1 molar ratio. Hence, this batch was subjected for further evaluations. A control batch of recrystallized Ibuprofen was also prepared to compare the effect of excipient/s and its concentrations on the crystal morphology and other properties of treated crystals.

Saturation Solubility Study

Saturation solubility (mg/mL) study was performed for pure drug, its control batch and Ibuprofen loaded crystals in buffer solutions of pH 1.2, pH 4.5, pH 6.8 and dissolution media of Ibuprofen (Phosphate buffer pH 7.2) under study at 37°C ± 0.5°C.

From the results of Table 1, it was depicted that treated crystals of IBU:SAC-Na (Molar proportion of 1:2) showed 22.02 fold increment in aqueous solubility compared to Ibuprofen pure drug. Moreover, there was a remarkable increment of solubility in HCl buffer pH 1.2, Acetate buffer pH 4.5, Phosphate buffer pH 6.8 and dissolution media of Phosphate buffer pH 7.2 compared to Ibuprofen pure drug. Saturation solubility results of Table 5 and Table 6 clearly suggested that treated crystals of IBU:SAC-Na prepared with molar ratio of [1:2] was optimized ratio and subjected for further evaluation parameters.

Table 1: Comparison of Solubility (mg/mL) in pH 1.2, pH 4.5, pH 6.8 and pH 7.2

S. No.	Sample	Number of fold increase in solubility at 37 ± 0.5°C as compared to Pure IBUPROFEN				
		Distilled Water	HCl buffer pH 1.2	Acetate buffer pH 4.5	Phosphate buffer pH 6.8	Phosphate buffer pH 7.2
1	CONTROL [C]	5.77	2.15	0.32	1.02	2.51
2	IBU:SAC-Na (1:2) [B]	22.02	12.01	15.12	16.71	30.24

Table 2: Micromeretic properties of pure drug, its control batch and treated crystals

S. No.	Parameters	Pure Ibuprofen [IBU]	CONTROL [C]	IBU:SAC-Na (0.05M:0.1M) [B]
1	Mean Particle Size (μm) ± SD*	Agglomerated form	29.345 ± 1.406[a]	32.748 ± 0.974[a]
2	Angle of Repose (θ) ± SD*	42.570° ± 0.301	31.619° ± 0.247[a]	25.363° ± 0.312[a]
3	% Carr's Compressibility Index (CI) ± SD*	35.7504 ± 0.438	20.6140 ± 0.510[a]	14.7959 ± 0.572[a]
4	Hausner's Ratio ± SD*	1.5564 ± 0.074	1.2597 ± 0.063[a]	1.1737 ± 0.029[a]

* Results are mean of three observations ± SD; [a] Significantly different from the pure drug, P < 0.05

Table 3(a): Packability parameters of pure drug, its control batch and treated crystals

Samples	Kawakita's Constants		Kuno's constant
	$a = \frac{1}{m}$	$\frac{1}{b} = \frac{C}{m}$	K
Pure Ibuprofen [IBU]	0.482253086	59.36053241	0.000823987
CONTROL [C]	0.216085397	77.22027745	0.001035886
IBU:SAC-Na (1:2) [B]	0.142779634	115.9327793	0.00207308

Table 3(b): Compressibility parameters and Elastic recovery of pure drug, its control batch and treated crystals

Samples	Heckel Plot Constants		Mean yield pressure (P_y)	Yield Strength (σ_0 OR S)	% Elastic Recovery ± SD*
	K (Slop)	A (Intercept)	$Py = \frac{1}{K}$	$S = \frac{1}{3K}$	$\%\ ER = \left[\frac{(H_e - H_c)}{H_e}\right] \times 100$
Pure Ibuprofen [IBU]	**0.1242**	**1.0225**	**8.051529791**	**2.683843264**	**4.444444 ± 0.383**
CONTROL [C]	0.1747	1.0616	5.724098454	1.908032818	2.413793 ± 0.691
IBU:SAC-Na (1:2) [B]	0.2217	1.1630	4.51059991	1.503533303	0.833333 ± 0.763

% Yield and Drug Loading Efficiency

The % yield and % Drug loading efficiency of treated crystals of Ibuprofen:Sachharin Sodium (0.05M:0.1M) is 92.11 ± 0.54 and 97.67 ± 2.41 respectively. The results suggested that the % yield and % drug loading efficiency of both treated crystal batches were found to be good.

Melting Point Study

The melting point of Ibuprofen pure drug, Saccharin Sodium excipient, control batch and Treated crystal formulations was determined as 77.8°C ± 1.83, 126.8°C ± 1.63, 77.3°C ± 1.42 and 76.4°C ± 2.84 respectively.

As per the above results it was depicted that the slight depression in melting point of control batch compared to pure drug, there might be slight increase in solubility compared to pure drug. There was further reduction in melting point of treated crystals which clearly suggested that there was a drastic increase in solubility of drug. It was also found that the melting point of treated crystal was less than the melting point of pure drug (IBU) and excipient (SAC-Na) which again suggested that there might be a formation of a new treated crystal phase[32].

Micromeretic Properties

The AR for control batch was found as 1.65 ± 1.86 while in case of treated crystals of molar ration (1:2) was 1.72 ± 1.24. This modified habit of treated crystals with least AR was an indication of better flow property as compared to pure drug and its control batch[21].

As per the data shown in Table 2, it was found that the flow property of pure drug was very poor because of very small particle agglomerates with strong tendency to aggregate due to electrostatic charge generated on its surface with irregular shape[12,13].

Control batch crystals were improved in their flow property. A great improvement in flow property of treated crystals was observed which might be because of increment in the particle size of treated crystals[33,34].

Packability study by Kawakita and Kuno's Constants

It was depicted from the following Table 3(a), the packability parameters i.e., a & 1/b were suggested the decreased value of '**a**' (compressibility or extent of densification due to tapping) and increased value of '**1/b**' (how fast the final packing state was obtained) than pure drug was an indication of improvement in packability of treated crystals compared to pure drug.

Increased values of '**K**' (Kuno's constant) compared to pure drug showed marked improvement in the mechanical properties like compactibility, compressibility and packability of treated crystals compared to the pure drug[20,35].

Compressibility Study by Heckel Plot Analysis

From the Table 3(b) and Fig. 1, it was suggested that the slop of heckel plot 'K' is an indicative of plastic behavior of the material[36]. Larger the value of 'K', greater is the plasticity in material. The linearity in the graph (Fig. 1(a)) was an indication of plastic deformation. 'A' value of treated crystals was less than pure drug. This finding suggested that, low compression pressure was required to obtain closest packing, fracturing its texture and densifying the fractured particles in case of treated crystals[37].

(1-D) value in Heckel equation indicates porosity which was used to plot % porosity Vs Compression pressure (tons) as illustrated in Fig. 1(b). Yield strength (σ_0) is an indication of the nature of materials to deform either by plastic flow or fragmentation[38]. Low value of yield strength (σ_0) and yield pressure (P_y) was again an indication of low resistance to pressure, good densification and easy compaction[39]. Thus, heckel plot data suggested that treated crystals were fractured easily and new surface of crystals produced might contributed to promote plastic deformation under applied compression pressure[20,36].

The result of elastic recovery for treated crystals is given in the above Table 3(b). Elastic recovery of treated crystals was very small while the elastic recovery of pure drug and control batch was very high with a behavior of lamination. These results depicted that treated crystals were easily broken or fractured and the new surface of crystals produced might contributed to encourage plastic deformation under compression[36].

Pressure-Tensile Strength Relationship

Compacts which were prepared for the Heckel plot analysis were subjected for the determination of the pressure-tensile strength relationship as plotted in the Fig. 1(c). It was found that as the compression pressure increased, there was an increase in the tensile strength for all samples under investigation but it was greater for the treated crystals with molar ratio 1:2 of IBU:SAC-Na because of its higher packability, compactibility and compressibility than pure drug. It was also suggested the plastic behavior of the prepared treated crystals[20,40].

***In-vitro* drug release study of powder samples and their directly compressible tablets**

In-vitro dissolution profile of powder samples (Fig. 2) depicted that treated crystals with 1:2 molar proportion of Drug:Excipient (IBU:SAC-Na) showed greater drug release (99.83%) compared to 1:1 molar ratio (58.30%), control batch (43.97%) and pure drug (30.35%) within one hour.

Results also revealed that the treated crystals of 1:2 molar ratio of IBU:SAC-Na showed drastic increase in drug release rate within one hour compared to powder samples of 1:1 molar ratio, control batch and pure drug.

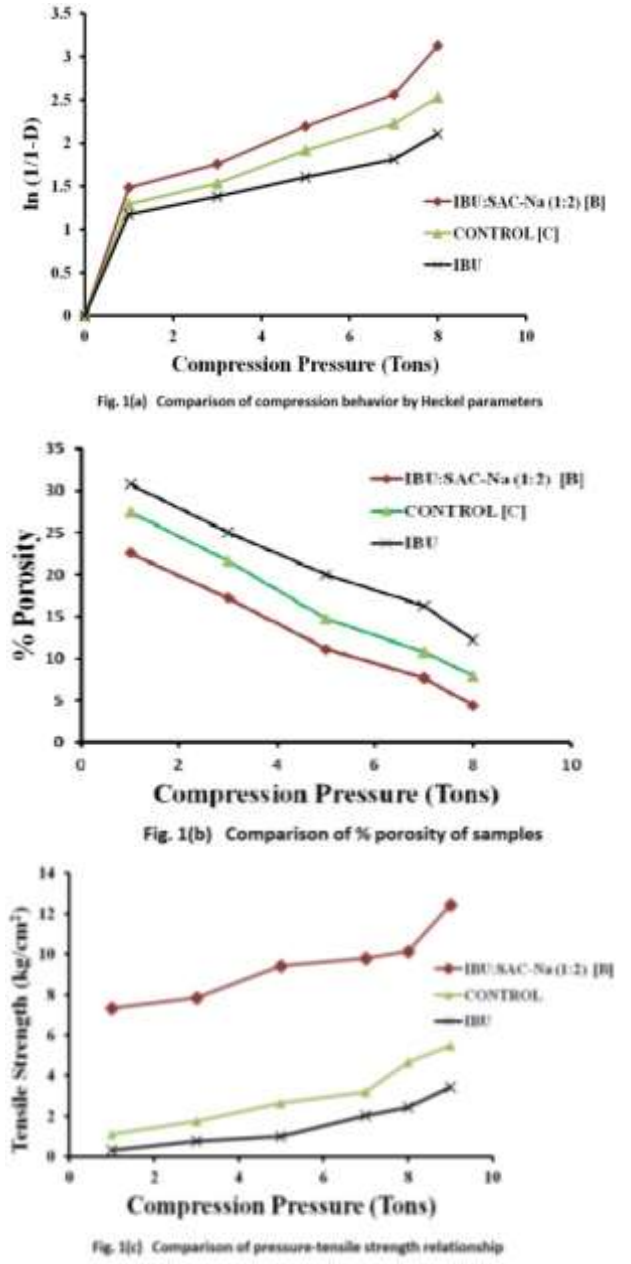

Figure 1: Comparison of (a) compression behavior, (b) % porosity and (c) pressure-tensile strength relationship

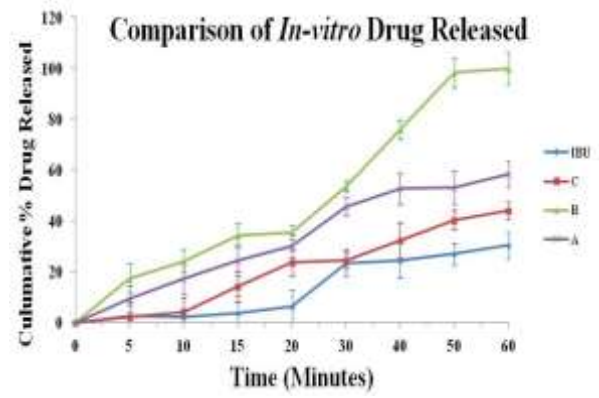

Figure 2: Comparison of *In-vitro* drug release profile in Phosphate buffer pH 7.2 at 37 °C ± 0.5 °C. Ibuprofen drug (IBU), Control batch (C), Treated crystals of IBU:SAC-Na 1M:1M (A) and Treated crystals of IBU:SAC-Na 1M:2M (B)

From the above results, it was concluded that the solubility, mechanical properties and dissolution rate of treated crystals with molar proportion 1:2 of IBU:SAC-Na [B] was better than the control batch [C], pure drug [IBU] and the other molar ratio 1:1 of IBU:SAC-Na [A], as well.

Therefore, molar ratio of 1:2 [B] was selected as optimized ratio for characterization study.

Solid State Properties of Treated Crystals

Scanning Electron Microscopy (SEM) Study

Scanning electron image of pure Ibuprofen drug (Fig. 3(a)) illustrated the smaller size with irregular shape of the drug.

Moreover, it was also found that the pure drug was appeared as agglomerated form because of charge distribution on its surface which lead to the greater cohesive force between the particles and resulted into very poor flow of the drug[12,13].

SEM images of control batch (Fig. 3(b)) suggested that, increase in the particle size might improve the flowability compared to pure drug[41].

SEM images of treated crystals (Fig. 3(c)) showed marked change in the appearance of the particles with platy shaped equidimentional crystals having larger size. It was also a sign of the improvement in the mechanical properties of the pure drug[33,34]. Moreover, the treated crystals were not cohesive in nature which revealed the flow property was improved[42].

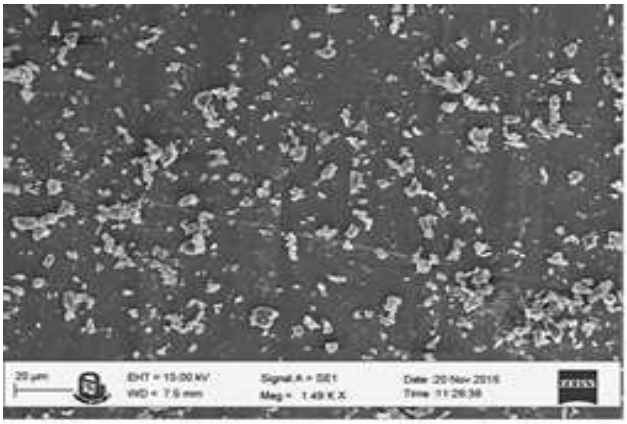

Fig. 3(a) Scanning Electron Microscopy of Pure drug Ibuprofen

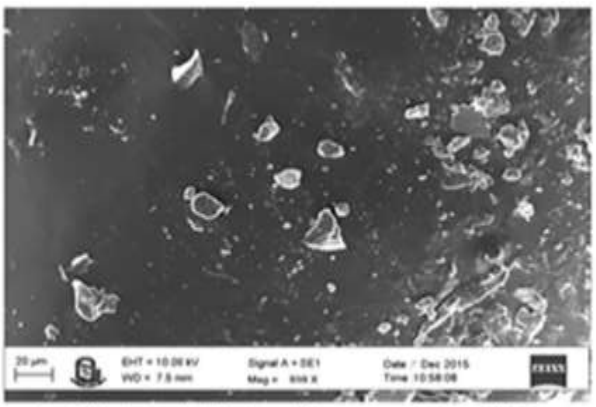

Fig. 3(b) Scanning Electron Microscopy of Control batch

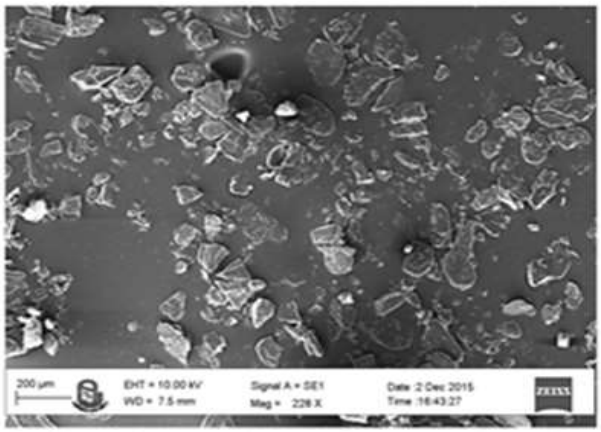

Figure 3: Scanning Electron Microscopy of (a) Pure drug Ibuprofen, (b) Control batch and (c) Treated crystal formulation

Fourier Transform Infra Red Spectroscopy (FT-IR) Study

FT-IR spectra shown in the following Fig. 4 suggested that there was no any possible intermolecular interactions found between the drug and excipient as there was no change in the characteristic peaks of the respective components.

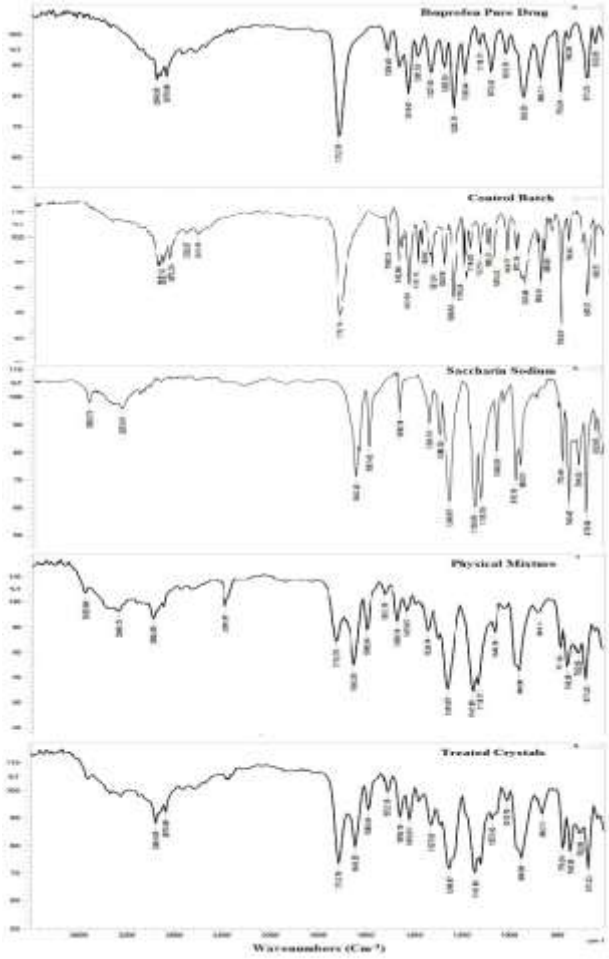

Figure 4: FT-IR spectra of Ibuprofen pure drug, Control batch, Saccharin Sodium, Physical Mixture and Treated Crystals

By interpreting and comparing the absorption bands of treated crystal formulation with pure Ibuprofen (Fig. 4), it was clearly depicted that the excipient Saccharin sodium was capable to form hydrogen bond with the drug as there was a broad band formed between 3600 cm^{-1} to 2200 cm^{-1} in the treated crystal formulation.

Differential Scanning Calorimetry (DSC) Study

DSC spectra of pure Ibuprofen drug, Saccharin sodium, Control batch, Physical mixture of IBU and SAC-Na in 1:2 molar ratio and Treated crystal formulation are illustrated in the following Fig. 5.

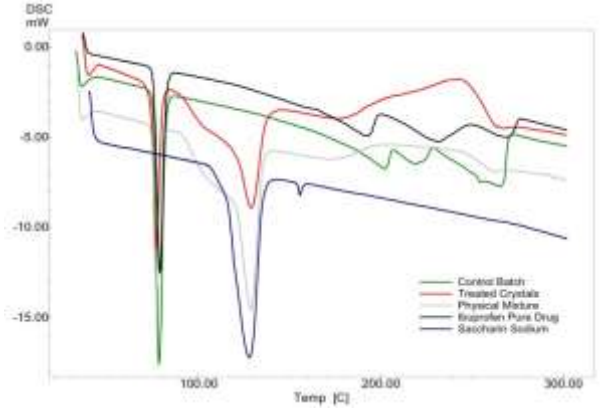

Figure 5: DSC spectra of Ibuprofen pure drug, Saccharin sodium excipient, Control batch of Ibuprofen, Physical mixture of Ibuprofen and Saccharin sodium and Treated crystal formulation of Ibuprofen

The DSC thermograms for Ibuprofen pure drug showed sharp melting endothermic peaks at 78.74 °C (ΔH_f = -273.60 mJ). The sharp peak suggest the crystalline nature of the sample.

Thermogram of Excipient Saccharin sodium demonstrated an endothermic melting peak at 127.85 °C (ΔH_f = -820.95 mJ) which is an agreement with the reported melting point of Saccharin sodium.

The thermogram of control batch showed an endothermic melting peak at 78.17 °C (ΔH_f = -350.48 mJ).

The compatibility of Ibuprofen pure drug and Saccharin sodium excipient were further confirmed by comparing their respective DSC spectra with their physical mixture. It was illustrated that physical mixture showing almost similar identical melting endotherm which indicates that there was no any interaction between the drug and excipient. The melting peak of the drug was quite shifted might be due to mixing with excipient.

The DSC thermogram for IBU:SAC-Na [1M:2M] treated crystals showed endothermic sharp melting behavior with sharp peak at 76.73 °C (ΔH_f = -214.83 mJ) and a broad peak at 128.70 °C (ΔH_f = -256.97 mJ) respectively. The downward shift in the endothermic peak of drug also indicated the interaction of drug with Saccharin sodium[43]. It might be possible that drug and Saccharin sodium physically behaved like two phase system[44].

The thermal behavior of treated crystal was distinct from the individual respective components, suggests the formation of a new Ibuprofen-Saccharin sodium treated crystal phase (Gao). Moreover, the melting endotherm of Ibuprofen in the treated crystal was sharp but the endothermic peak of Saccharin sodium was found shorten and more broader compared to its pure form, perhaps due to greater disorder in the crystal structure happened during solvent evaporation process with excipient[45].

CONCLUSION

The aim of present work was to prepare Ibuprofen treated crystals for the improvement in solubility, drug release rate and mechanical properties which lead to the improvement in phsicochemical, mechanical and pharmacotechnical parameters of Ibuprofen, BCS Class II drug having poor flow property. In the present study, crystal engineering approach with solvent evaporation technique at Room temperature has been carried out to enhance the physicochemical and pharmacotechnical parameters of drug along with its pharmacotechnical parameters. Out of various excipients, Saccharin sodium dihydrate gave encouraging results. Solubility and *In-vitro* dissolution of Ibuprofen was enhanced to a greater extent compared to pure drug. The mechanical and compressibility parameters suggested plastic nature of treated crystals, which might be enable treated crystals to formulate directly compressible tablets without using any directly compressible excipients. SEM, FT-IR and DSC studies suggested the treated crystals were stable in nature and there were no any incompatibility observed between the drug and excipient. Hence, treated crystals can become a wonderful option to improve the physicochemical and mechanical parameters of Ibuprofen.

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Abbreviations: DSC - Differential Scanning Calorimetry; HPLC - High Performance Liquid Chromatography; ICH - International Conference on Harmonization; pXRD - powder X-ray Diffraction; rpm - revolution per minute; FT-IR - Fourier Transform Infrared Spectroscopy; ppm - parts per million.

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