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RESEARCH

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Nicotinamide-based agglomerates of ibuprofen: formulation, solid state characterization and evaluation of tableting performance with in-silico investigation

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Abstract

Background The objective of the present investigation was to obtain directly compressible agglomerates of ibuprofen with nicotinamide by a quasi-emulsification solvent diffusion technique. Ibuprofen-nicotinamide agglomerates were prepared by quasi-emulsification solvent diffusion technique using ethanol (good solvent), water (poor solvent), and chloroform (bridging liquid). The prepared agglomerates were characterized by ATR-FTIR, powder X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy and were evaluated for tableting performance and in vitro drug release. To appropriately identify the hydrogen bonding sites, a thorough understanding of the structures of API and coformer is necessary, hence molecular docking approach was implemented to depict the interaction between the proposed coformer and COX-2 protein (PDB Id:4PH9).

Results The percent yield of agglomerates was in the range of 85–98 w/w%, and drug content for all batches was in the range of 96–99%. The microphotographs showed irregular circularly shaped agglomerates. ATR-FTIR study showed a strong possibility of hydrogen bonding between ibuprofen and nicotinamide. The crystallinity of ibuprofen was slightly reduced and confirmed by P-XRD and DSC. Crushing strength and friability studies showed good handling qualities of ibuprofen agglomerates. Heckel plot studies showed low mean yield pressure and high tensile strength, indicating excellent compressibility and compactibility of ibuprofen agglomerates. More than 90% drug release was obtained within 60 min in PBS (pH 7.4). The docking studies revealed that nicotinamide individually has –CDOCKER energy 16.8109 where coformer showed 29.0584, which indicates coformer has a better binding affinity to target as compared to nicotinamide individual.

Conclusions It can be concluded that the agglomerates improved the dissolution, tableting performance, and solid-state properties of ibuprofen and hence can be useful to improve the therapeutic performance of ibuprofen.

Keywords Ibuprofen, Nicotinamide, Agglomerates, Dissolution rate, Quasi-emulsification method, Molecular docking

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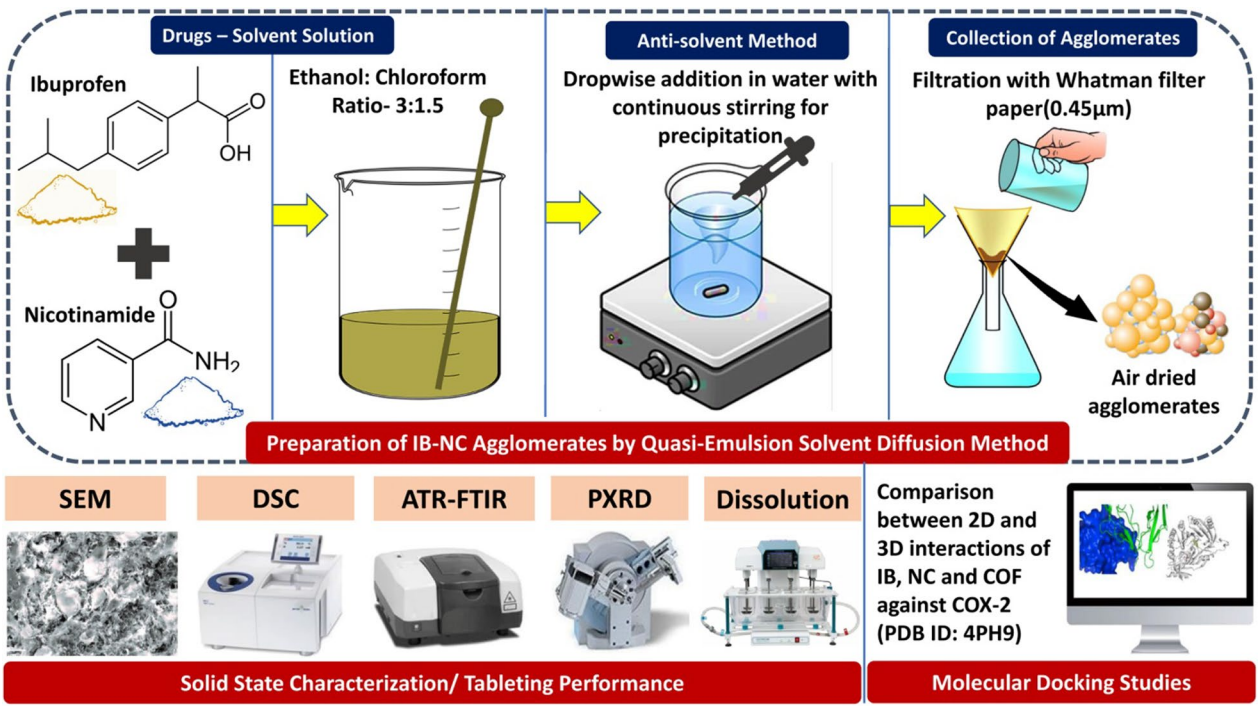
Graphic Abstract



Background

The solid-state properties of pharmaceutical compounds have a decisive impact on dosage form development, stability, and in vivo performance of the drug. Approximately, 60% of the drugs possess poor solubility and dissolution properties, which are a decisive determinant of its oral bioavailability. Most of the drugs belong to the biopharmaceutical classification system, BCS class II or IV [1–3]. Many pharmaceutical drugs are problematic due to their inappropriate physical and mechanical properties and poor aqueous solubility. The dissolution rate of drugs can be improved by micronization methods but due to high-energy input during the micronization process gives rise to increased free surface energy, electrostatic tendencies, and thus poor flowability and/or compressibility. Which makes them difficult to use in downstream processing in the pharmaceutical industry such as the direct tablet-making process or filling of the capsule [4]. The direct tableting technique is generally preferred to save the time and cost of the process in comparison with wet granulation technique. This technique has been successfully applied to various drugs on the industrial scale. The success of any direct- tableting procedure and resulting mechanical properties of tablets are strongly affected by the quality of the crystals used in this process. Thus, compressibility, flowability, and micrometric properties of drug particles are of essential importance for the formulation of solid high-dose units. When the mechanical properties of the drug particles are inadequate and preliminary granulation is necessary, spherical crystallization technique appears to be an efficient alternative [5].

Techniques utilized to improve flow properties of the drug and/or compression blend comprise of extrusion-spheronization [6], melt solidification [7], melt granulation [8], melt extrusion [9]. Tablets containing poorly aqueous soluble drugs, the start of dissolution is often delayed by the poor wettability of the tablet surface and/or slow liquid penetration in to the tablet matrix. This property causes increased disintegration time and retarded drug release that can be overcome by agglomeration technique. Spherical agglomeration is a novel technique to improve dissolution properties and thereby ameliorate bioavailability by reducing particle size. This method is also used for high-dose drugs having poor micromeritic properties. Various investigators have reported the utilization of the spherical agglomeration technique for amending the rate of drug dissolution [10–13] and micromeritic properties of the drug [14–19].

Ibuprofen (IB) is a drug widely used for its analgesic and anti-inflammatory properties and is available in oral dosage forms either tablets or hard gelatin capsules. IB powder possesses poor compressibility, compactibility, flowability, and dissolution properties. The therapeutic dose of the drug is relatively high and this is the main reason why dosage forms frequently contain several excipients and why the tablets are mostly prepared using a granulation technique. Hence this attempt has been made to improve flow properties, compression ability, and the dissolution rate of IB. In this study, nicotinamide (NC) is used as a co-former and it is hydrophilic. The interaction will take place at O–H, C=O group of IB and NH, C=O, and CN group of NC respectively. NC molecule has three proton donor/acceptor sites, pyridine ring nitrogen, amino nitrogen, and carbonyl oxygen. So, these interactions are responsible to improve the compressibility, compactibility, flowability, and dissolution properties of IB co-crystal agglomerates. Hence this attempt has been made to improve flow properties, compression ability, and the dissolution rate of drug [2, 20].

The present work reports IB agglomerates prepared by Quasi emulsification solvent diffusion method (QESD) using nicotinamide. The agglomerates were evaluated using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and tableting and drug-release properties. Along with, docking.

Methods

IB was purchased from Alembic Pharma Pvt. Ltd. Vadodara. NC was purchased from Loba chemicals, Mumbai. Ethanol, Chloroform, Magnesium stearate, Microcrystalline cellulose, and Talc were procured commercially from Loba chemicals, Mumbai. All other chemicals were of analytical grade.

Quasi-emulsion solvent diffusion method

The co-crystal agglomerates were prepared by QESD method. The weighted quantity of IB (206.28 mg) and NC (122.13 mg) were dissolved in a 3:1.5 ratio of ethanol and chloroform and then this solution was added dropwise into the 100 ml of water under continuous stirring at various speeds 600, 800 and 1000 rpm for the 30 min (Table 1). Then the precipitated agglomerate co-crystals were filtered through Whatman filter paper (0.45 µ) and dried at room temperature [21–23]. Overall, a schematic representation of the QESD is shown in Fig. 1. The proportions of solvents, Ethanol (good solvent), Water (poor solvent), and Chloroform (bridging liquid) were optimized by ternary phase solubility diagram in preformulation study.

Saturation solubility of a drug in volatile solvents

An excess amount of the drug was dissolved in 20 ml of different volatile solvents i.e., chloroform, ethanol, methanol, and acetone, respectively. The samples were sonicated for 30 min at room temperature and then shaken in an orbital shaker at 37.5 °C for 48 h. The suspensions were subsequently filtered, and absorbance was measured at 221 nm.

Percentage yield

The percentage yields of all formulations were calculated by determining the weight of recovered co-crystal powder divided by the total original weight of the powder mixture.

$$\text{Percentage yeild} = \frac{\text{weight of Cocrystal powder}}{\text{Total weight of powder mixture}} \times 100$$

Percent drug content

Co-crystals equivalent to 10 mg of the drug was weighed accurately and dissolved in phosphate buffer having, pH 7.2 (PBS), and the final volume was made up to 100 ml

Table 1 Composition of co-crystal agglomerates

Contents	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen (mg)	206.28	206.28	206.28	206.28	206.28	206.28	206.28	206.28	206.28
Nicotinamide (mg)	122.13	122.13	122.13	122.13	122.13	122.13	122.13	122.13	122.13
Ethanol (ml)	3	3	3	3	3	3	3	3	3
Chloroform (ml)	0.5	1	1.5	0.5	1	1.5	0.5	1	1.5
Water (ml)	100	100	100	100	100	100	100	100	100
Stirring speed(rpm)	600	600	600	800	800	800	1000	1000	1000

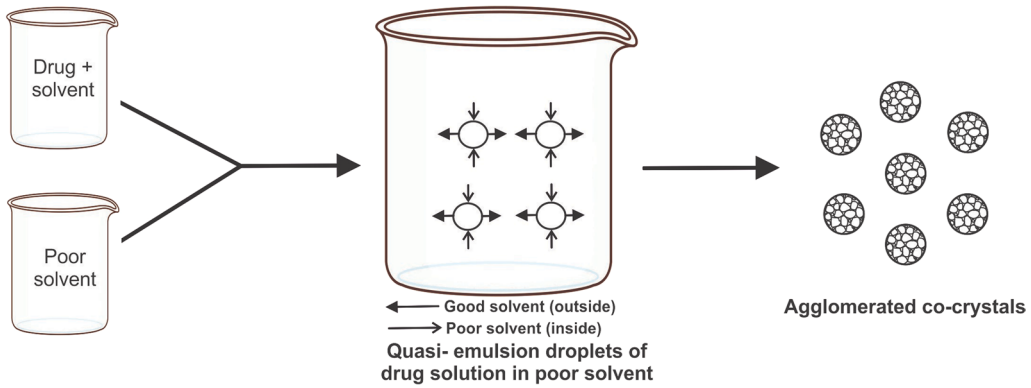


Fig. 1 A schematic representation of the agglomerated co-crystal process by QESD method

with PBS. The solutions were sonicated for 30 min until the complete removal of the drug. The solutions were filtered and diluted suitably and drug content was analyzed by UV spectrophotometer at 221 nm.

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)

Infrared spectroscopy of pure drugs, physical mixtures, and their optimized co-crystals was recorded using an ATR-FTIR spectrophotometer (MIRACLE 10 Shimadzu IR Affinity-1 FTIR) in the region of 4000–400 cm^{-1}.

Powder X-ray diffractometer (PXRD)

Powder X-ray diffraction pattern of the pure drugs, physical mixture, and optimized Co-crystals were obtained by using a Philips PW1700 X-ray diffractometer with Cu k-a ($\lambda = 1.540$ Å) radiation and a crystal monochromator, with a voltage of 40 mV and a current of 30 A. The diffraction patterns run at 5–10 °C min^{-1} terms of 2θ angles.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was conducted using a Mettler-Toledo DSC 821e instrument equipped with an intracooler (Mettler- Toledo, Greifensee, Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples of the drug, physical mixture, and optimized co-crystals were hermetically sealed into pierced aluminum pans and heated at a constant rate of 10 °C/min over a temperature range of 30 to 400 °C. The inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min.

Scanning electron microscopy (SEM)

The shape and surface topography of the optimized IB agglomerated co-crystals were examined using Scanning Electron Microscopy (SEM) (JSM–6360; JEOL Ltd., Tokyo, Japan) at magnifications of 2000× and 5000×.

Micromeritics and tabletability evaluation

The optimized batch of IB-co-crystal agglomerates was evaluated for various micromeritic and compressibility properties, such as angle of repose[24], Compressibility index, and Hausner's ratio, Heckel's plot [25, 26]. Initially, co-crystal agglomerates were gently passed through a sieve with an aperture of 1.0 mm (#16 sieve number) to break up any lumps before carrying out any micromeritics and compressibility evaluation studies[27]. The tablets containing optimized agglomerates were prepared by direct compression method using a hydraulic press having 10 mm flat-faced punch and dies at 1 ton pressure for 1 min of dwell time (Table 2). The tablets were subject to dissolution studies similar to IB-co-crystal agglomerates in triplicate. Disintegration testing of tablets containing agglomerated co-crystals (six tablets) was performed at 37 °C in phosphate buffer (pH 7.4) using the disintegration test apparatus (Bio Technics India Pvt Ltd) without disk.

In vitro drug dissolution study

The dissolution studies of pure drug, agglomerated co-crystals, and tablet containing agglomerated co-crystals were performed using a US Pharmacopeia type II

Table 2 Formulation of conventional tablet

Ingredients	Quantity (mg)
Co-crystals equivalent to 200 mg of IB	300
Magnesium state	5
Microcrystalline cellulose	87
Talc	8
Total weight of a tablet	400

dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The agglomerated co-crystals equivalent to 200 mg of the drug was dispersed in a dissolution vessel containing 900 ml phosphate buffer (pH 7.4) maintained at a temperature 37 ± 0.5 °C and stirred at 50 rpm. During the dissolution study, 5 ml aliquot was withdrawn at different time intervals from 5 to 60 min and replaced with an equal volume of fresh medium. The withdrawn samples were filtered, and absorbance was measured at 271 nm. The experiments were performed in triplicate.

Molecular docking studies and proposed structure of cocrystal

Coformer selection is influenced by the supramolecular synthon approach that depicts the possibility of hydrogen bond formation with IB. To appropriately identify the hydrogen bonding sites, a thorough understanding of the structures of API and coformer is necessary, hence molecular docking approach was implemented to depict the interaction between the proposed coformer and COX-2 protein (PDB Id:4PH9). We down loaded IB (PubChem CID: 3672), NC (PubChem CID: 936) in.sdf format and coformer (drawn with ChemDraw 20.1.1) in.cdx format then converted to.sdf format with Open Babel 2.4.1. The respective.sdf format file for IB, NC, and coformer as ligands were docked with BIOVIA Discovery Studio 2019(v.19.1.0) with the target as COX-2 protein (PDB Id:4PH9) using CDOCKER function. The protein preparation was done by removing unwanted water molecules and a side chain devoid of co-crystals and then the binding side was defined which was specific to ligands. The ligands IB, NC and coformer were individually docked, and results were compared in terms of bonding interactions, –CDOCKER energy, and amino acids involved for the outcome-based conclusion. Among the top 10 best-fitted poses the comparison was done for one selected pose with the highest interaction in terms of –CDOCKER energy[28–30].

Results

Nine batches of IB-co-crystal agglomerates were prepared successfully by QESD method to improve flow properties, compression ability, and the dissolution rate of IB. Different proportion of chloroform (bridging liquid) was used such as 0.5, 1, and 1.5 ml under continuous stirring at 600, 800, and 1000 rpm for 30 min. It has been observed that batches F1, F4, and F7 showed no agglomeration or incomplete agglomerates, whereas F2 and F3 showed higher size or coarser agglomerates. The irregularly shaped agglomerated co-crystals with small sizes were observed in batches F8 and F9 and batch F6 showed higher-size agglomerates or higher coalescence may be due to a higher proportion of bridging liquid. The batch F5 showed the optimum size of agglomeration. This may be due to a sufficient amount of bridging liquid with medium agitator speed. The formulation batch was optimized on the basis of drug content, solubility and size of agglomerates. The batch F5 showed optimum size of agglomerates, higher drug content (96%) and higher solubility (Table 3) and hence F5 batch was optimized.

At a lower proportion of chloroform, no agglomeration or incomplete agglomerates were observed due to the unavailability of bridging liquid for efficient agglomeration. On the other side, the proportion of the chloroform increases with the enhancement of agglomeration of co-crystals was found. It means that size of the agglomeration of co-crystals was increased with an increasing amount of chloroform. It might be due to enhanced agglomeration of co-crystals or coalescence of co-crystals. The agglomeration of co-crystals or coalescence is carried out by the deposition of an excess amount of chloroform on the surface of co-crystals. The movement of the droplets in the medium induces circulation inside the droplets. The internal circulation depends on the speed of the agitator. At the lower stirring speed (600 rpm) larger or coarser agglomerates were found with clumps, whereas the higher stirring speed (1000 rpm) irregularly shaped and small or very fine agglomerates were observed. The size of the agglomerated co-crystals depends on the speed of the agitator.

Saturation solubility of a drug in volatile solvents

The saturation solubility of IB and their formulations in distilled water (DW), and PBS (pH 7.4) are shown in Table 3. From the results, it can be concluded that the batches F1, F4, and F7 showed less solubility, whereas

Table 3 Percent yield and drug content of IB co-crystal agglomerates

Bach code	Yield* (%)	Drug content* (%)	Saturation solubility* (mg/ml)	
			DW	PBS (pH 7.4)
IB	–	–	0.085 ± 2.32	0.435 ± 2.64
F1	85 ± 2.21	98 ± 2.25	1.1 ± 2.21	2.8 ± 2.31
F2	86 ± 2.91	96 ± 3.16	2.8 ± 3.33	4.5 ± 1.22
F3	96 ± 1.39	97 ± 3.05	3.1 ± 2.56	3.6 ± 2.36
F4	95 ± 1.91	98 ± 2.14	1.6 ± 2.47	2.7 ± 3.34
F5	96 ± 2.32	96 ± 2.16	2.9 ± 1.78	5.3 ± 2.37
F6	97 ± 1.56	99 ± 1.81	2.8 ± 2.89	4.9 ± 1.35
F7	92 ± 1.89	98 ± 2.17	2.0 ± 2.96	2.9 ± 3.37
F8	97 ± 1.78	99 ± 1.08	3.4 ± 1.36	4.8 ± 2.26
F9	98 ± 1.68	96 ± 1.45	3.8 ± 3.41	5.8 ± 1.36

*Values are expressed as the mean ± SD ($n = 3$)

other batches showed greater solubility. It might be due to incomplete agglomeration.

Percentage yield

The percentage yields of all batches of co-crystal agglomerates were found to be between 85 ± 2.2 and 98 ± 1.9% (Table 3).

Percent drug content

The percentage drug content in various batches of co-crystal agglomerates ranged from 96 ± 2.11 to 99 ± 1.89%, as reported in Table 3.

ATR-FTIR spectroscopy

ATR-FTIR analysis was carried out for evaluating molecular interactions and the ATR-FTIR Spectra of IB, NC (co-former), and their physical mixtures have been depicted in Fig. 2. The spectra of pure IB showed an intense, well-defined infrared band at 1228.66 cm^{-1} (O–H bending), 1708 cm^{-1} (C=O stretching) and 2949.16 (C–H stretching), respectively. Significant absorption bands were observed due to the amido group in NC at 3118 cm^{-1} (NH stretching), 1685 cm^{-1} (C=O stretching), and 1388 cm^{-1}C–N bending, respectively. NC molecule has three proton donor/acceptor sites, pyridine ring nitrogen, amino nitrogen, and carbonyl oxygen [31].

Powder X-ray diffractometer (PXRD)

The powder X-Ray diffraction patterns of pure IB, NC, and IB-agglomerates are presented in Fig. 3. Pure IB and NC showed numerous characteristic sharp and intense peaks, suggesting that the drug and co-former were present in a crystalline state. In the PXRD pattern of IB-agglomerates, diffraction peaks were observed clearly and a few peaks appeared very small reduction in intensity than that of pure IB.

Differential scanning calorimetry (DSC)

The DSC thermograms of IB and IB-Cocrystal agglomerates have been demonstrated in Fig. 4. Pure IB showed a sharp endothermic peak at 79.54 °C with the heat of fusion/enthalpy (ΔH) of 136.4 J/g, corresponding to its melting point. This sharp peak confirmed the purity of the drug substance, with no noticeable impurities present, corresponding to the literature value of 81.20 °C [32, 33]. In DSC thermogram of crystal agglomerates, a peak corresponding to melting point of IB was observed at 78.11 °C and it was negligibly broadened.

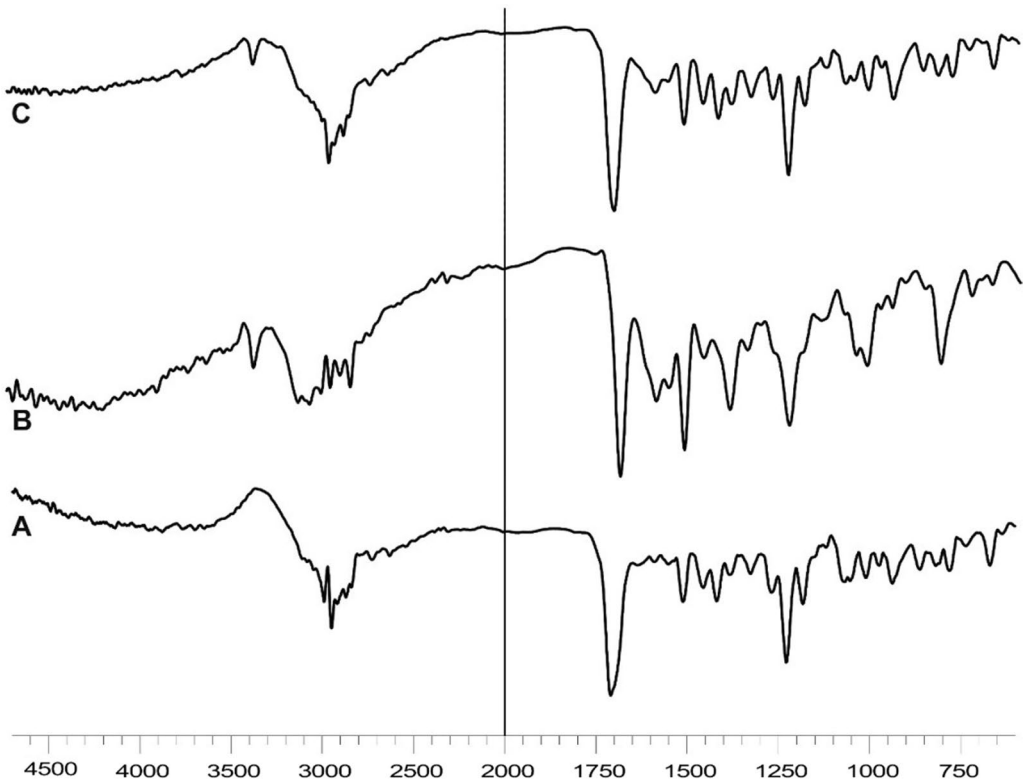


Fig. 2 Infrared spectra of IB (**A**), NC (**B**), and agglomerates (**C**)

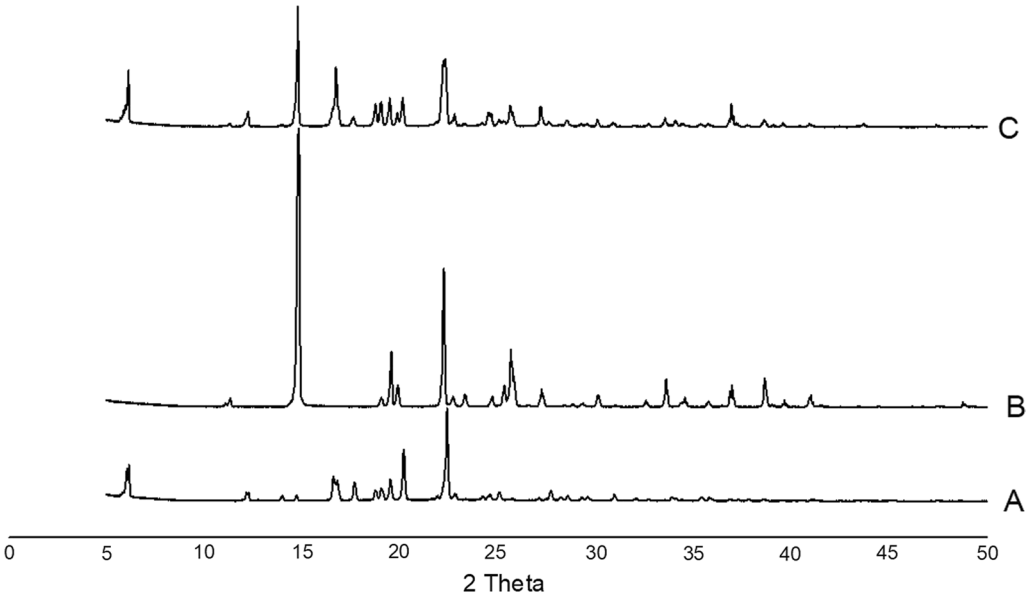


Fig. 3 PXRD patterns of IB (**A**) **B** (NC)and co-crystal agglomerates (**C**)

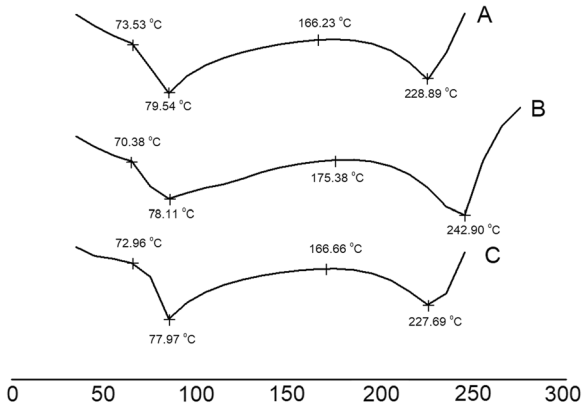


Fig. 4 DSC thermogram of IB (**A**) Physical mixture (**B**) and IB co-crystal agglomerates (**C**)

Scanning electron microscopy

Photomicrographs of IB and agglomerates depicted in Fig. 5. IB (Fig. 5A) showed needle-shaped or plate-shaped elongated crystals which hindered the flowability and compressibility. Agglomerates (Fig. 5 B) showed irregular circular-shaped crystals with porous structures.

Micromeritics and tabletability evaluation

The values of angle of repose, Carr's compressibility index, Hausner's ratio, and tabletability of all batches of cocrystal agglomerates are shown in Table 4. The results state that F5, F6, F8, and F9 batches of agglomerated cocrystals had better flowability, whereas F1, F2, F3, F4 and F7 showed satisfactorily. This might be

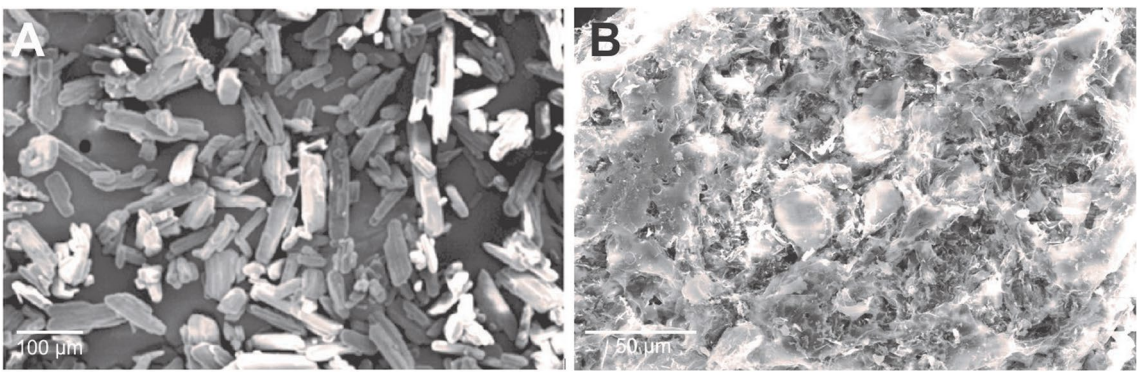


Fig. 5 Photomicrographs of pure IB (**A**) and agglomerates (**B**)

Table 4 Micromeritics and tabletability parameters for solid dispersions

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	33.01	33.11	32.22	34.35	30.14	28.23	32.45	28.23	30.75
Carr's Index	22.18	23.65	23.23	21.58	18.78	17.68	22.24	20.41	20.12
Hausner's ratio	1.22	1.21	1.19	1.18	1.17	1.16	1.18	1.20	1.23
a'	0.20	0.19	0.17	0.18	0.21	0.22	0.24	0.23	0.24
B	0.41	0.39	0.36	0.48	0.47	0.42	0.39	0.49	0.51
Mean yield pressure	0.86	0.74	0.82	0.68	0.87	0.66	0.74	0.82	0.79

due to poor or incomplete agglomeration and coarser size. The disintegration time of tablets is below 10 min. The results showed that the reduction in disintegration time of tablets resulted in an increase in rate of dissolution of IB.

In vitro drug dissolution study

The In vitro dissolution of pure IB, IB-co-crystal agglomerates, and a tablet containing IB-co-crystal agglomerates of an optimized batch in PBS (pH 7.4) for 60 min are presented in Fig. 6. The pure IB showed drug release around 25% within 60 min. The batches F5, F6, F8, F9, and tablet showed drug release of more than 90% within 60 min, whereas, F1, F2, F3, and F4 showed drug release of about 60%.

Molecular docking

The 2D and 3D interactions are shown in Fig. 7 and Fig. 8 respectively and the results of interactions in Tab. 5. The docking studies revealed that NC individually has –CDOCKER energy 16.8109 where coformer showed 29.0584.

Discussion

The saturation solubility of the batches F1, F4, and F7 showed poor solubility, whereas other batches showed greater solubility. It might be due to incomplete agglomeration. The saturation solubility of the IB-agglomerated co-crystals is high in PBS than in DW because of pH-dependent solubility of IB. The solubility enhancement of IB might be due to establishing interactions between

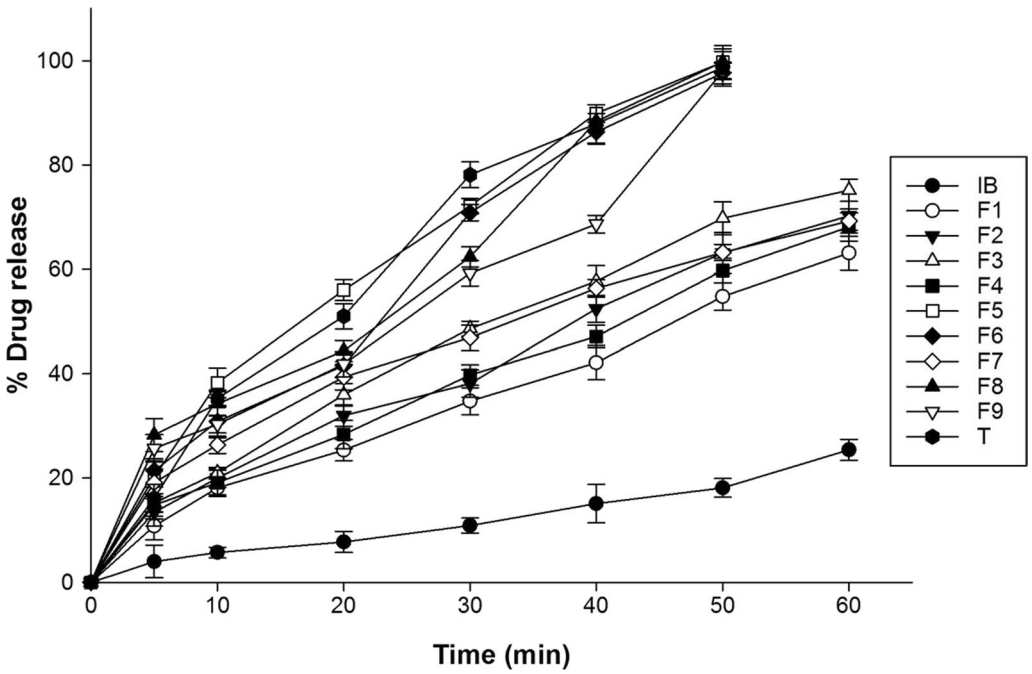


Fig. 6 In vitro dissolution profile of IB, agglomerates, and Tablet (T) containing optimized agglomerates

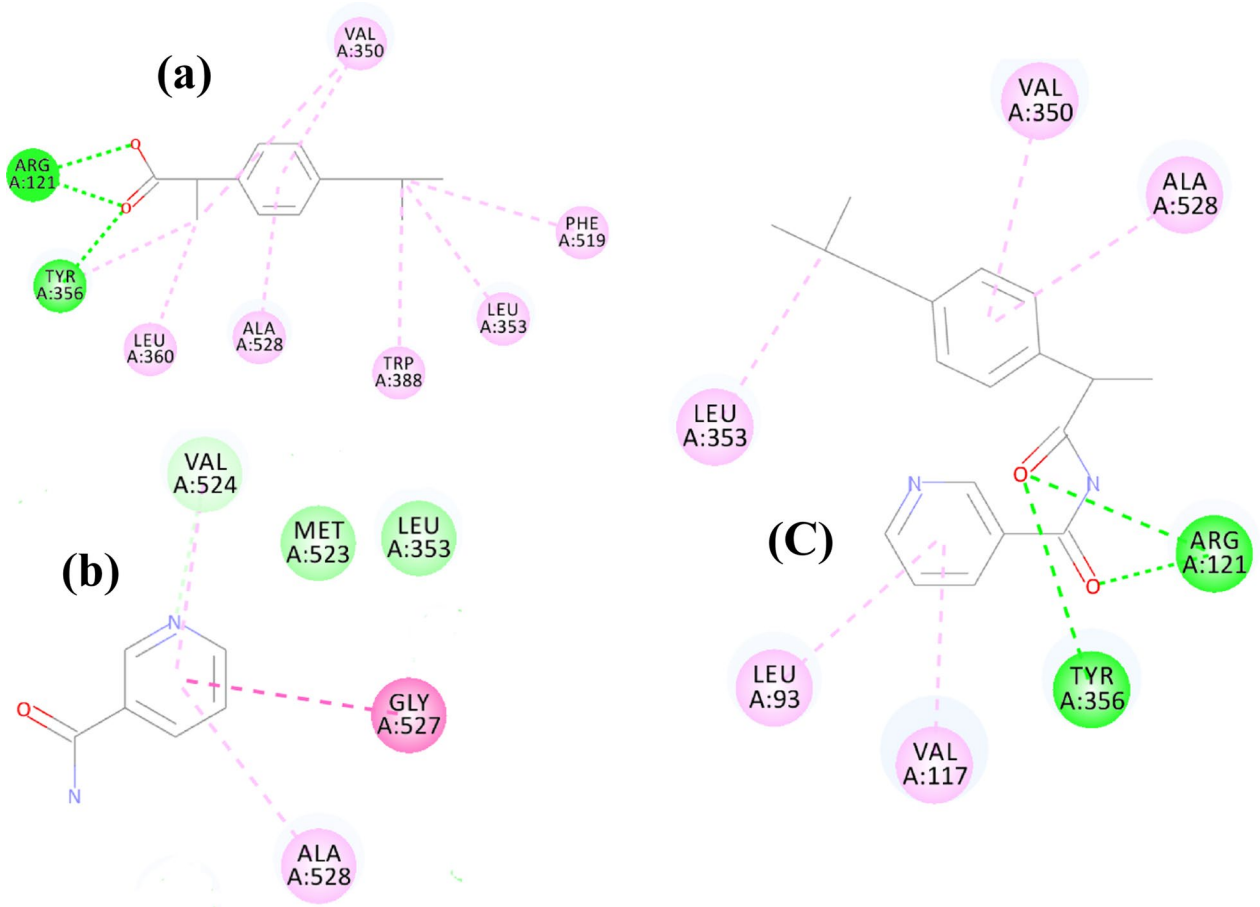


Fig. 7 2D interaction: **a** 2D interaction of IB with COX-2; **b** 2D interaction of NC with COX-2; **c** 2D interaction of COF with COX-2 IB- Ibuprofen; NC—Nicotinamide; COF—Coformer

Table 5 Comparison of interaction energies of Nicotinamide individual and Coformer

API	Pose No	−CDOCKER_Energy	−CDOCKER_Interaction_Energy
Nicotinamide	1	16.8109	20.0321
Coformer	1	29.0584	38.9046

IB and NC such as hydrogen bonds, hydrophobic bonds, and van der Waals dispersion forces [34]. The variation in percentage yield is might be due to loss in processing means sticking of particles to the wall of the container, equipment, beaker, etc. The % drug content indicated that IB was uniformly distributed in all these prepared co-crystal agglomerates. The high drug content indicates that the drug is uniformly dispersed within the polymer matrix. The high drug content is the function of the hydrophilic groups present in polymer and also it indicates that the drug is uniformly dispersed in the polymer matrix.

According to the ATR-FTIR spectrum, it revealed that no major changes in drugs, co-former, and IB-agglomerates spectra confirmed no polymorphic transformation or alteration in physical properties of a drug into agglomerates. Also, no new peaks were observed in IB-agglomerates spectra depicting no traces of degradation or residual solvents. Hence, IB stability without significant molecular interactions during the agglomeration process has been confirmed by the ATR-FTIR study. Also, it revealed that spectral changes such as slight shifting or broadening or disappearance of the characteristic peaks of the IB-agglomerates indicated a good degree of interaction between IB and NC. A shift in the peaks corresponding to O–H stretching, N–H stretching, C=O stretching of NC and IB, respectively, indicates a strong possibility of hydrogen bonding. Moreover, peaks corresponding to NC and IB in the low-frequency region of the spectra exhibited only a slight change concerning

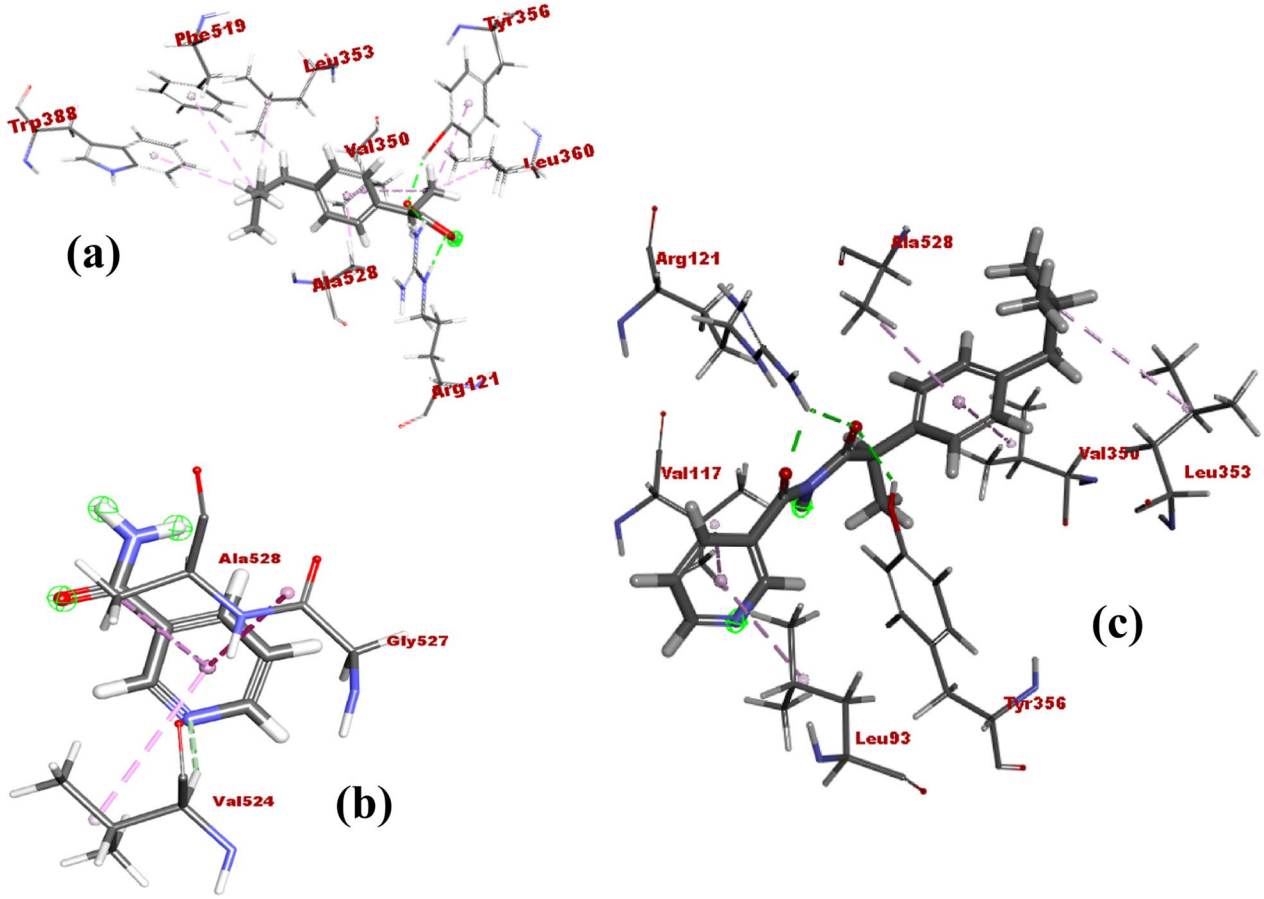


Fig. 8 3D Interactions: **a** 3D interaction of IB with COX-2; **b** 3D interaction of NC with COX-2; **c** 3D interaction of COF with COX-2 IB—Ibuprofen; NC—Nicotinamide; COF—Coformer

shifting and broadening which might be due to intermolecular hydrogen bonding. The broadening of peaks could also be attributed to the partial amorphous form of agglomeration [27].

The powder X-Ray diffraction patterns showed decrease in intensities of IB in agglomerates. This reduction in the crystallinity of IB in agglomerates indicating a reduction in partial crystallinity or partial amorphization of the drug in its agglomerated form. Results also indicated that the particles crystallized in the presence of a co-former did not undergo structural modifications. Most of PXRD peaks of the agglomerates were consistent with the pattern of pure IB crystals, indicating that there was no structural change or drug-co-former incompatibility detected after re-crystallization [35].

From the DSC thermograms, it has been observed that a slight lower melting point and reduction in ΔH of IB (137.4 J/g) implies the presence of amorphousness in the sample which might be due to weakening as well as disrupting of crystal lattice and order [36, 37]. Also, these occurrences may be due to the dispersion of partial crystalline IB into amorphous and it was not a sign of pharmaceutical incompatibility. Partial amorphization of crystalline IB in crystal agglomerates may also be a reason for such phenomena.

The needle-shaped or plate-shaped elongated crystals were observed in photomicrographs of IB, which hindered the flowability and compressibility. Agglomerates showed irregular circular-shaped crystals with porous structures. Improved flowability of agglomerates was mainly because of the circular shape of modified crystals [38, 39].

The excess amount of deposition of bridging liquid on the surface of agglomerates could be responsible for coarse size. From Kawakita plot, obtained values, a' of agglomerates were less than values of b, respectively, indicating a reduction in the volume of agglomerates bed with an increase in number of tapings and hence good compressibility. The Heckel plot analysis showed lower mean yield pressure (Py) values for cocrystal agglomerates compared to IB, confirming the improved compressibility. Also, the crushing strength of the tablets

compressed containing pure IB was significantly lower (4.5 kg/cm^2) than the tablets compressed containing cocrystal agglomerates (8 kg/cm^2) indicating that the strength of cocrystal compact was much higher than IB compact [40, 41]. The improved compactability of the agglomerates was attributed to their structural characteristics and this structural characteristic was responsible for the large relative volume change which occurred during the early stage of the compression process, as a consequence of fragmentation. Improved fragmentation during compression resulting in increasing the contact point area to produce a strong bond between particles leading to strong tablets [42, 43]. The improved flow properties and compressibility of the agglomerated co-crystals would indicate that they might be directly compressible. The results showed that the reduction in disintegration time of tablets (< 10 min) resulted in an increase in rate of dissolution of IB. The reduction in disintegration time of tablets is a prerequisite for improving the rate of dissolution of drug. This could be attributed to an increase in the surface area of the poorly aqueous soluble drug exposed to the dissolution medium after disintegration of tablet. Therefore, it was expected that any changes in disintegration time of tablet would alter the dissolution profiles of IB [43].

All of the batches of the agglomerates and tablets containing agglomerate showed improved dissolution of IB over that of pure IB. The improved dissolution of IB is mainly attributed to increased wettability and therefore solubility due to the higher level of hydrophilicity by the use of a co-former. Again, batches F5, F6, F8, F9, and tablet revealed more improved dissolution than the batches F1, F2, F3, and F9. The improvement of the dissolution rate of agglomerates was also attributed to the smaller size of agglomerates and partial amorphous of IB in agglomerates [35, 44].

The docking studies revealed that NC individually has –CDOCKER energy 16.8109 where coformer showed 29.0584, which indicates coformer has a better binding affinity to target as compared to NC individual (Tab.5). It justifies the reason behind forming coformer out of IB and NC. A fusion at C=O stretching of IB and C-N bending of NC has hydrogen bonding with ARG and TYR which is also seen promptly in IB individually. Also, the interaction of the phenyl ring of IB with ALA, VAL and terminal carbon of 2-methylpropyl group with LEU remained undisturbed in conformer (Fig. 7). Pyridine ring interaction remained unchanged in the NC individual and coformer with VAL. The docking results conclude coformer has better target binding as compared to individual API [29, 30].

Conclusions

Quasi emulsification solvent diffusion method was successfully used to produce cocrystal agglomerates of IB using NC. The circular irregular agglomerates of IB were observed by SEM. According to the results, the particle size of the agglomerates could be well controlled by the speed of the agitator. Also, agglomerates showed satisfactory compressibility and compatibility properties. Moreover, an excellent improvement in tabletability performance of the IB cocrystal agglomerates was seen. More importantly, the rate of dissolution of the agglomerates obtained was markedly improved when compared to the pure drug. PXRD and DSC studies showed that obtained agglomerates did not undergo structural modifications. In conclusion, the agglomerates of IB prepared by QESD method showed appreciable improvement in tableting performance with an enhanced rate of dissolution.

Abbreviations

BCS	Biopharmaceutical classification system
IB	Ibuprofen
NC	Nicotinamide
QSED	Quasi emulsification solvent diffusion method
PXRD	Powder X-ray diffraction
DSC	Differential scanning calorimetry
SEM	Scanning electron microscopy
PBS	Phosphate buffer
ATR-FTIR	Attenuated total reflectance Fourier transform infrared spectroscopy
DW	Distilled water

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Author contributions

PS, NS, KM and VM contributed to the overall study design and supervised all research work. PS and NS carried out the experiments and analyzed the data. NS, KM and VM drafted and revised the first version of the manuscript. DB carried out molecular docking studies. All authors were also responsible for the final editing of the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable for this work.

Consent for publication

Not applicable

Competing Interests
The authors declare that they have no competing interests.

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