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Research Article

Study of a novel crystalline form of ibuprofen

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ABSTRACT

In this study, a novel crystalline form of ibuprofen (IBF) was prepared using glycerol as a medium and PEGylated rosin derivative as a crystal-habit modifier. The crystals were characterized for morphology, particle size and melting point. FT-IR spectroscopy was performed to examine the difference in peak characteristics of IBF and its novel crystalline form (IBF-glycerol). Tablets were prepared by the wet granulation method and characterized for pharmacotechnical properties. Dissolution study of IBF, IBF-glycerol and their tablets was performed in distilled water. IBF and IBF-glycerol exhibited rod and rhombic shape crystals, respectively. FT-IR spectra revealed slight differences in absorption peaks of IBF and IBF-glycerol. The colour and IR spectra of IBF and IBF-glycerol did not differ significantly. The particle size of IBF-glycerol was smaller (5-10 µm) compared to IBF (15-35 µm). Melting point of IBF and IBF-glycerol was in the range of 74-76°C and 65-68°C, respectively. The drug release from IBF and IBF-glycerol powders at the end of 600 min was 52.13% and 69.22%, respectively. Tablets could release 47.72% IBF and 58.21% IBF-glycerol at the end of 600 min. Drug release from all the tablets followed first order kinetics. Results revealed that glycerol and PRD could produce the novel rhombic crystals of IBF having lower particle size, melting temperature and markedly faster dissolution than native IBF.

INTRODUCTION

PEGylated rosin derivatives (PRDs) are improved in series ester adduct derivatives of rosin. A series of papers has been published from our laboratory describing the synthesis, characterization and evaluation of PRDs for drug delivery applications [1-4]. A novel crystalline form of IBF was coincidentally discovered during investigation of PRD as a microencapsulating material. The primary aim of study was to design PRD microparticles containing IBF by the solvent evaporation technique. PRD contains rosin, polyethylene glycol 400 and maleic anhydride. The detail synthesis and characterization of PRDs is described in prior arts [1-2]. PRD could produce discrete, spherical and free flowing microparticles with IBF in acetone (internal phase) / liquid paraffin (external phase) system by solvent evaporation technique. However, the microparticles adhered to filter paper after treating with petroleum ether (60-80), which is required to remove the residual paraffin from microparticles. Presuming this may be due to high relative humidity (RH above 65%) or temperature in laboratory, an attempt was made to control these parameters, but the problem could not be eliminated. In addition, even the replacement of petroleum ether with different washing solvents like n-hexane, cyclohexane and n-heptane could not resolve the concern. Therefore, it was decided to replace liquid paraffin with the aqueous medium for preparation of microparticles. Since IBF has higher solubility at alkaline pH, 0.1 N HCL (pH 1.2) was evaluated as an external phase. However, when the solution of PRD and ibuprofen in methylene chloride was poured in the 0.1 N HCL, it settled to the bottom of beaker as large droplets. So, the stirring was increased to re-disperse them, but it resulted in a huge variation in microparticle size. Different stabilizers like PVP and tween 80 were also

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added in external phase but the problem could not be eliminated. Therefore, it was decided to use the viscous water-miscible medium having a solvent-extracting propensity similar or comparable to that of liquid paraffin for the efficient processing. In this context, acetone/glycerol system was evaluated. The PRD and IBF solution in acetone was poured in glycerol rotating at a speed of 1000 rpm in a glass beaker. Initially the droplets of internal phase were uniformly distributed, however, after 280 min, numerous IBF crystals dispersed in the external medium and changed the appearance of medium from translucent to milky. The polymeric material was lying at the bottom of the beaker. These crystals of IBF when observed under light microscope showed a unique rhombic shape structure. It is worth mentioning that their morphology varied with the type of PRD used; PRD with high and low amounts of hydrophilic components (polyethylene glycol 400 and maleic anhydride) produced needle and rhombic shape crystals, respectively.

Scientists have prepared and characterized many different crystalline forms of IBF over past few years. However, these studies used either the conventional techniques like precipitation [5], solvent change, temperature change, solvent evaporation [6], or the solvents such as ethanol, methanol, isopropanol and hexane [7,8]. Few hydrophilic excipients namely PEG 6000, 8000, Brij 98P and polyvinyl alcohol 22000 have also been used to modify the IBF crystals [9]. Since, the new IBF crystals of this study were formed in the presence of specific excipients like PRD and glycerol, these were expected to be different substantially than the earlier reported forms of IBF. Thus, it was decided to compare them against the native IBF. Moreover, when the new IBF crystals of this study were washed with distilled water to remove glycerol, they became tacky and could not be retrieved from the filter; such behavior was different from that of native IBF and that encouraged us to briefly investigate this further. Therefore present study was undertaken with an objective to prepare and investigate a novel crystalline form of IBF.

MATERIALS AND METHODS

Materials,

PRD was synthesized in our laboratory and used. IBF was received as gift samples from Zydus-Cadila Healthcare Ltd., Ahmedabad, India. The acetone, chloroform, isopropyl alcohol, hydrochloric acid and methylene chloride were procured from Qualigenes Fine Chemicals, Mumbai, India. All other chemicals used were of pharmaceutical grade.

Preparation of ibuprofen crystals,

PRD (0.3 g) and IBF (2 g) were dissolved in 7 ml of acetone. This clear solution was poured gradually in 100 ml of glycerol rotating at a speed of 1000 rpm at 32±1°C. To this 4 ml of distilled was added drop-wise to increase the rate of solvent removal from the internal phase. This dispersion was maintained at the same stirring speed and temperature for 300 min. IBF crystals were vacuum filtered, rapidly washed with little cold water and dried to constant weight in desiccators maintained at 0% relative humidity (RH) at room temperature.

Color,

Color was observed visually and noted.

Scanning electron microscopy,

The particle shape and morphology was examined by scanning electron microscopy ((JEOL, JXA-840A, Japan)). The samples were mounted on stubs, vacuum coated with gold and photographed.

Bright field microscopy,

To determine the particle size, the samples were observed under Leica LaborLux Leitz S bright field microscope (Germany). The mean particle diameter was determined by measuring approximately 30 particles using 1-mm stage micrometer.

FT-IR spectroscopy,

FT-IR spectroscopy has been a method of choice to recognize the functional groups and various interactions between the therapeutic and polymeric materials. IR spectra were obtained by FT-IR spectrophotometer (FT-IR-8101 A, Shimadzu, Japan). Potassium bromide was chosen to prepare the pellets of the test-material. The spectra were obtained by averaging 40 scans at a resolution of 4.0 cm^{-1}.

Melting point determination,

Herculus drop technique was used to determine the melting point of samples [7]. For this purpose thistle tube, partially filled with liquid paraffin was used. A small amount of sample was filled in the capillary sealed at one end. It was then tied to precalibrated thermometer and the tube was heated gradually. The temperature at which the solid sample melts was recorded.

Dissolution rate study,

In vitro dissolution rate study was carried out in USP 25 dissolution apparatus type 2 (paddle method). The samples were secured in a muslin cloth (mesh 500), which was then tied to the paddle rotating at a speed of 75 rpm. 900 ml of distilled water was used as a dissolution medium, which was maintained at 37±0.5°C throughout the experiment. 5 ml of sample was withdrawn at predetermined time points and analyzed at 222 nm for drug content by UV-Spectrophotometer (UV 1601, Shimadzu, Japan).

Preparation and evaluation of tablets,

The drug (20%), microcrystalline cellulose (PH 101) (74%), povidone K-30 (3%), magnesium stearate (1%) and talc (2%) were used to prepare the tablets. Tablet weight (250 mg) and diameter (8 mm) was kept constant. Tablets were prepared by the wet granulation technique. The specified quantities of drug and diluents were mixed manually in polybag. The mixture of drug and diluent was granulated with 2% povidone (K-30) solution in isopropyl alcohol. Granulation end point was achieved with isopropyl alcohol. The wet cohesive mass was then sifted through 10-mesh screen and dried in oven at 40°C. The dried granules were then sifted through 22-mesh screen and lubricated with 2% talc and 1% magnesium stearate (60-mesh). The lubricated granules were compressed into tablets on a 10-station Pilot press tablet machine (Chamuna Pharma Machinery, Ahmedabad, India).

Tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche friabilator), drug content uniformity and drug release profile. The drug release profile of tablet was determined similarly as of the powder samples of IBF and IBF-glycerol; the method has been described earlier in the text. The drug release data was computed in the light of different kinetic equations [10] to study the exact mechanism of drug release from tablets.

RESULTS AND DISCUSSION

During initial trials, it was noticed that PRD has potential to improve the solubility of certain active pharmaceutical ingredients (APIs) like diclofenac sodium, diltiazem hydrochloride, propranolol hydrochloride and IBF in organic solvents like acetone, chloroform and methylene chloride. Depending on the composition of PRD, its solubilizing potential varies; higher amount of hydrophilic components in PRD increases the solubility of above mentioned APIs in organic solvents.

In this study, PRD comprised of rosin, PEG 400 (5% of rosin wt) and maleic anhydride (5% of rosin+PEG 400 wt) was used to prepare the novel crystalline form of IBF. PRD and IBF were dissolved in acetone and added to glycerol. At the end of 300 min, two distinct layers of PRD (at the bottom) and IBF (dispersed and floating) were observed. This novel form of IBF was collected by vacuum filtration, washed rapidly with a small amount cold water and was investigated in comparison with the native IBF.

SEM revealed that PRD was capable of producing a novel rhombic crystalline form of IBF (Figure 1). Although, it is mentioned elsewhere in the text that the needle shape crystals were obtained; it was true when the PRD of higher hydrophilic component was used. The PRD used in this study was synthesized with low amounts of hydrophilic components (PEG 400 and maleic anhydride) and it produced rhombic shape crystals of IBF.

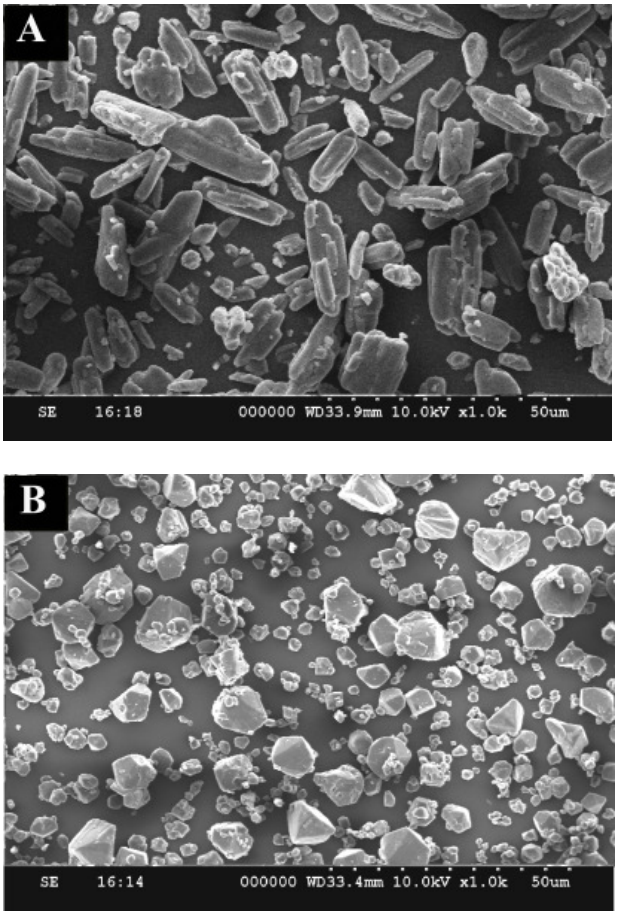

Figure 1: SEM of A) IBF and B) IBF-glycerol crystals

These crystals were morphologically different from the forms of IBF described earlier by the researchers [5-9]. Also, to know the impact of PRD, IBF crystals were produced without PRD using glycerol alone, but the crystals obtained did not differ significantly from the native IBF, which confirmed that PRD has potential to modify the crystal-habit of IBF.

The rhombic shape crystals obtained were clear white. The physicochemical properties of IBF and IBF-glycerol crystals are summarized in Table 1. The melting point range for IBF was 74-76°C and its particle size ranged in 15-35 µm. On the other hand, IBF-glycerol exhibited melting point in the range of 65-68°C and its particle size varied between 5-10 µm. The crystalline form of material changes because of alteration in the molecular arrangement, hydrogen bonding and other intermolecular interactions. Since, change in melting point is indicative of such type of alterations, the difference in melting points observed in this study provided supportive evidence that IBF-glycerol differ from IBF. The IR-Spectra showed slight changes in the absorption patterns of IBF and IBF-glycerol particularly in the region of 2800-3200 nm (Figure 2). The alteration could be due to the variations in the resonance structure, rotation of part of molecule or certain bonds and minor twist in bond angles.

Table 1: Physicochemical properties of IBF and IBF-glycerol

No	Form	Solvent used[a]	Crystal habit [b]	Particle size [b] (µm)	Melting point (°C)
1	IBF	None	Rod shape	15-35	74-76
2	I-Glycerol*	Glycerol	Rhombic shape	5-10	65-68

*IBF-glycerol, [a] solvent as external phase, [b] as observed under the light microscope (Germany).

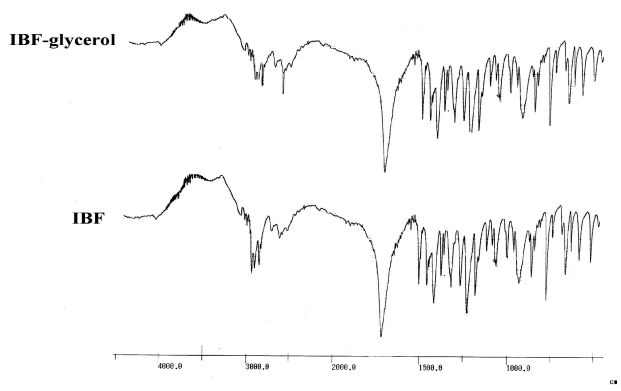

Figure 2: FT-IR spectra of IBF and IBF-glycerol

Figure 3 represents the drug release profile of IBF and IBF-glycerol from powder form. T_{50} for IBF and IBF-glycerol was 570 and 300 min, respectively. At the end of 600 min, 52.13% of IBF and 69.22% of IBF-glycerol was dissolved in distilled water. In one of the study, Labhshetwar et al. have reported that the T_{70} for the prism, needle and plate shape IBF crystals was in the range of 48 min to > 480 min [11]. As can be seen from Figure 3, T_{70} for both, the IBF and IBF-glycerol was much higher than 400 min, which suggests the substantial difference between the IBF-glycerol crystals of the study and previously reported forms. The dissolution of IBF-glycerol was faster than native IBF. This suggests that although the color, melting point and IR-spectra did not differ significantly, IBF-glycerol crystals, due to their smaller particle size, had substantially improved dissolution characteristics as compared to native IBF.

Table 2: Dissolution values of IBF and IBF-glycerol powder

No	Form	Dissolution time* (min)	
		T_{30}	T_{50}
1	IBF	230	570
2	IBF-glycerol	120	300

*Dissolution was carried out in distilled water by USP paddle method

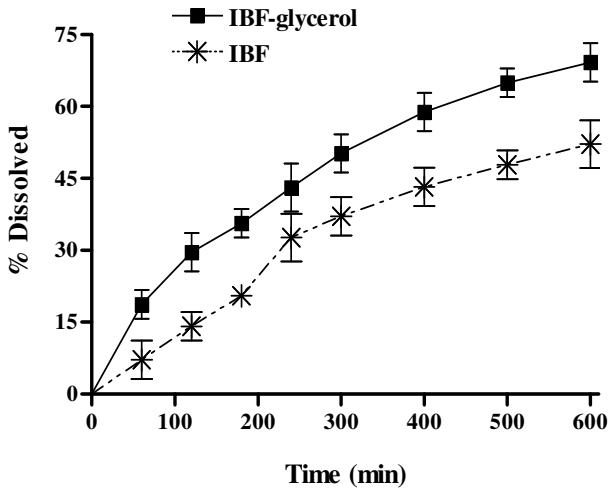

Figure 3: The drug release profile of IBF and IBF-glycerol in distilled water.

The tablets showed good strength for handling; hardness value ranged from 4-5 kg/cm^2 as determined by Monsanto hardness tester. IBF-glycerol tablets were slightly softer than native IBF tablets. This may be attributed to the lower melting temperature of IBF-glycerol (Table 1), which imparted softness to tablets. This observation was contrary to Nokhodchi et al., who reported that Ibuprofen samples crystallized in the presence of PEG 6000 and 8000 and PVA showed remarkable increase in the tensile strengths of the directly compressed tablets [9]. Also, they found that the dissolution was comparable between new IBF crystals and native IBF tablets. The friability values for all study formulations were less than 0.5%, which indicates a good strength for handling. All tablet formulations showed satisfactory drug content.

Table 3: Correlation coefficients for linearity according to different kinetic equations

No.	Kinetic model	Correlation coefficients of tablets containing	
		IBF	IBF-glycerol
1	First order	0.996	0.998
2	Baker-Lonsdale	0.979	0.972
3	Hixson-Crowell	0.944	0.995
4	Zero order	0.991	0.993
5	Higuchi	0.987	0.984

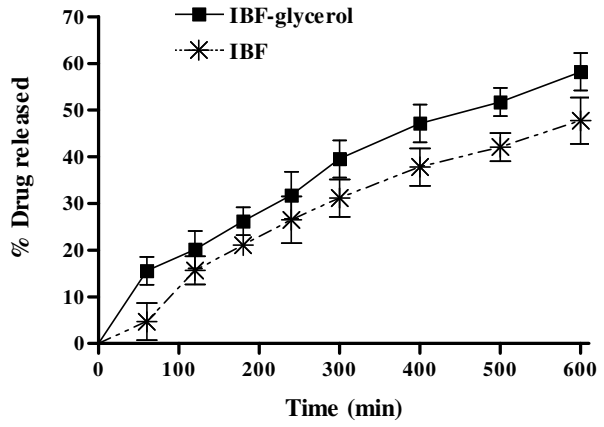

Figure 4: The drug release profile of IBF and IBF-glycerol tablets.

The drug release profiles of tablets are shown in Figure 4. As can be seen, IBF and IBF glycerol tablets released 47.72% and 58.21% drug at the end of 600 min, respectively. The drug release from tablets was slower compared to the drug-powder secured in muslin cloth. This was because of the lower surface are of tablets compared to free powder and the presence of povidone in tablets. Povidone binds the drug and diluent particles together to form the granule. It also forms a viscous gel layer around dug particles in dissolution slowing down their release in media. The values for correlation coefficient according to different kinetic equations used to describe the drug release profile of tablets are given in Table 3. The non-linearity of the % drug released versus time plots for tablets (Figure 4) suggests that these formulations do not release drug by the zero order kinetics [10]. This can be confirmed further by poor correlation coefficient values (Table 3). The drug release data from IBF and IBF-glycerol tablets followed first order kinetics indicating that the drug release rate was dependent on its concentration in tablet in both the formulations.

CONCLUSION

A novel crystalline form of IBF was prepared in glycerol using PRD. Initially, the solubility of IBF in organic solvent was modified by using PRD and then it was crystallize in glycerol solution to form the rhombic shape crystals. These crystals were slightly different in color, melting point and FT-IR spectra compared to native IBF. However, the dissolution of IBF-glycerol was substantially faster than the native IBF; the trend was similar in tablet dosage forms. In conclusion, novel from of IBF with small particle size and improved dissolution characteristics can be prepared using glycerol as a solvent and PRD as a crystal-habit modifier for IBF.

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