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Research Article

Solid state and dissolution behaviour of ibuprofen in co-milled mixtures of *Sesamum radiatum* gum.

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ABSTRACT

The search for non-toxic and cost effective carriers for solid dispersion formulations has increased the focus of researchers on renewable resources. In this study, gum was extracted from the leaves of *Sesamum radiatum* (SRG) and its role in solid dispersion formulations of Ibuprofen (IBU) investigated. Physical mixing and co-milling using different ratios of IBU to SRG (4:1, 1:1, 1:4) and milling times of 1 min, 5 min, and 10 min was employed. Solid state of these formulations was characterized using DSC, FT-IR and XRPD. The effect of the co-milling ratio and time on drug dissolution was also studied. Solid state characterization showed that SRG does not interact with IBU in the solid dispersion formulations. However, SRG retarded the release of IBU from all the formulations. Although the co-milled solid dispersions gave a higher dissolution than the physical mixes (PM), with the dissolution rate increasing as the ratio of SRG decreases, the technique did not result in appreciable improvement in the dissolution of IBU. The gel layer that surrounded the formulations suggest SRG may prove useful as a hydrophilic carrier in matrices for extended release and perhaps a modified form of the gum could be used in solid dispersions.

INTRODUCTION

Poor bioavailability of drugs as a result of poor aqueous solubility leads to high doses, reduced efficacy and longer development times, which increases the cost of medicines and decreases patient compliance (Patil et al., 2013). One of the major challenges facing drug development and manufacture is ways to improve the aqueous solubility of these drugs. Oral bioavailability depends on the release of these drugs from their dosage forms, therefore the absorption of Biopharmaceutical Classification System (BCS) class II drugs which have poor aqueous solubility and high membrane permeability is limited by their dissolution and solubility. Thus, when the dissolution profile of these drugs is improved, the bioavailability is increased and the side effects decreased (Vasconcelos et al., 2007). Solid dispersion (SD) is one of the most effective and useful techniques to improve the water solubility of several poorly soluble drugs, and it is a promising technique for enhancing the aqueous solubility, bioavailability, and absorption of class II drugs for oral administration (Adebisi et al., 2016a, 2016b, Al-Hamidi et al., 2015, 2014, 2013, 2010; Asare-Addo et al., 2015; Nokhodchi et al., 2017; Patil et al., 2013). SD are solid state

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mixtures of hydrophobic drugs with inert hydrophillic carriers in which the dissolution profile of the finely dispersed drug in the SD is controlled by the inert carrier (Islam et al., 2010, Reddy et al., 2011). SD preparation has been achieved by several methods including spray drying, freeze-drying, hot-melt extrusion, and co-milling. In the pharmaceutical industry, there is increasing interest and research into cost effective and non-toxic carriers. Even though there are concerns regarding batch-to-batch variability, naturally sourced excipients are easily available and cheap in comparison with synthetic excipients. In addition, they exhibit excellent modified drug release results in pharmaceutical applications (Bhardwaj et al., 2000; Jayasree et al., 2014; Li et al., 2015). In the last few years, large numbers of natural polymers such as carbohydrates, cyclodextrins and gums have been investigated for use as carriers in SD formulations (Kaialy et al., 2014; Nep et al., 2016a, 2015, Nep and Conway, 2011, 2010; Nep and Okafor, 2006; Siahi-Shadbad et al., 2011). Natural polymeric materials and their modified forms have become good alternative carriers in SD formulations in a bid to improve the water solubility of these poorly soluble drugs (Patel et al., 2008; Rodde et al., 2014; Sapkal et al., 2013).

Natural materials however do have some drawbacks. *Sesamum radiatum* (Fam. Pedalaceae) (SR) plants grow in several regions of tropical Africa. In the wild, these plants grow as weeds, but they are cultivated in some societies for their clinical and culinary uses. The gum used in this study is mucilage obtained from the hydration of SR leaves. Although the binding properties of *Sesamum radiatum* gum (SRG) has been reported (Allagh et al., 2005), there is very little information on the application of this gum in drug delivery. This study was conducted to characterise SRG in the solid state and thereafter to determine the effect of using it as a carrier in SD formulations of Ibuprofen (IBU) prepared by physical mixing or co-milling, and to demonstrate the effect of increasing the co-milling time on the release of IBU from these formulations.

MATERIALS AND METHODS

Materials

IBU was obtained from BASF (Germany); sodium hydroxide and potassium monobasic phosphate were obtained from Fisher (UK). *Sesamum radiatum* gum (SRG) was extracted in our laboratory.

Extraction of *Sesamum radiatum* gum

The process for the extraction and characterisation of SRG has been reported in Nep et al., (2016) (Nep et al., 2016b). In brief, fresh leaves of SR (800g) were macerated in 5 L of distilled water (30 min, ~25 °C) containing sodium metabisulphite (0.1%w/v). The produced mucilage was obtained from filtration from the leaves using a muslin cloth and then precipitated with 2 volumes of 96 % v/v ethanol. The obtained precipitate was then filtered using a 200 µm sieve and oven dried (50 °C for 24 h).

Preparation of Physical mixtures (PM)

Physical mixtures of IBU in three different IBU to SRG ratios (4:1, 1:1, and 1:4) were prepared. The two materials were mixed in a Turbula mixer (Turbula® T2F, GlenMills® USA) for 10 min at 34 rpm.

Preparation of co-milled solid dispersion (CMSD)

The IBU co-milled formulations were prepared at the same ratio as the PM for co-milling times of 1 min, 5 min, and 10 min using a bench top ball mill (MM 400, Retsch® Germany) with two 10 mm grinding balls at 18 Hz vibrational frequency at room temperature. Not more than 10% of the total grinding jar (500ml) was filled with the sample.

Differential scanning colorimetry (DSC)

Thermal analysis -DSC of IBU, SRG, the PM and CMSD samples were carried out using a Mettler-Toledo DSC 1 calorimeter (Mettler-Toledo Ltd, UK), under nitrogen atmosphere flow rate of 50 cm^3 min^{-1}, and scanning from 25 to 250 °C at 10 °C min^{-1} using 40 µl aluminium pans without pins. Approximately 4 – 8 mg of sample was weighed and used in the experimentation.

Fourier transform-infrared (FT-IR)

FT-IR spectroscopy on all the samples was performed on a Nicolet 380 FT-IR Spectrometer (ThermoElectron

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Corporation, USA) in the range between 4000 and 400 cm^{-1} by placing a few milligrams of the sample at the centre of the sample stage and pressure applied to compress the sample using the arm of the sample stage. The background was collected and the spectrums obtained under 2 cm^{-1} resolution averaging 100 scans per sample.

X-ray powder diffraction (XRPD)

X-ray diffractogram scans of IBU, SRG, the PM and CMSD samples were obtained using a Bruker D2 Phaser (Bruker, UK) scanning for 4 min using coupled 2θ/θ as scan type. A stainless steel holder was used to place the samples in the machine and the powder surfaces were subjected to the X-ray beam from an X-ray generator running continuously at 30 kV and 10 mA and scanning regions of the diffraction angle, 2θ was between 5 - 50°.

***In-vitro* dissolution studies**

Drug release on the powder formulations (PM and CMSD) containing an equivalent of 200 mg of IBU were carried out using the basket method (USP apparatus I) in an automated dissolution system (Pharmatest PT-DT70, UK) at 37 ± 0.5 ˚C. The dissolution media was 900 mL of phosphate buffer (pH 7.2) and the speed was 75 rpm. The dissolution media was automatically sampled using a peristaltic pump at regular intervals between 5 to 120 min. The concentrations of the samples were measured by UV spectrophotometry at 221 nm (Al-Hamidi et al., 2014). The mean of the percentage of IBU released and dissolved in dissolution media at 10 min and at 30 min (Q10, Q30 parameters respectively as shown in Table 2) was used as an independent metric to help compare the effect of using different ratios of SRG and using different co-milling times on the drug release from all the formulations (Al-Hamidi et al., 2010).

RESULTS AND DISCUSSION

Differential scanning colorimetric (DSC) studies

The DSC thermograms of the PM and the CMSD are presented in Figure 1 and in Figure 2A-C, respectively. The shifts in the melting point of IBU in the PM and the CMSD samples are shown in Table 1. IBU which is a crystalline material showed a very sharp melting endothermic peak of high intensity at 77.39 ± 0.14 ˚C. This was in agreement with the results reported by Wahab and co-workers (Wahab et al., 2013). Conversely, SRG showed no peaks and this is characteristic of amorphous materials (Ke et al., 2012). The thermograms of PM in the 4:1, 1:1 and 1:4 **(**drug to carrier ratio respectively) (Figure 1) showed a decrease in the peak intensity of the melting endotherm of IBU with increases in the amount of SRG. This is attributed to the predominance of the amorphous material, SRG over the crystalline IBU in the PM.

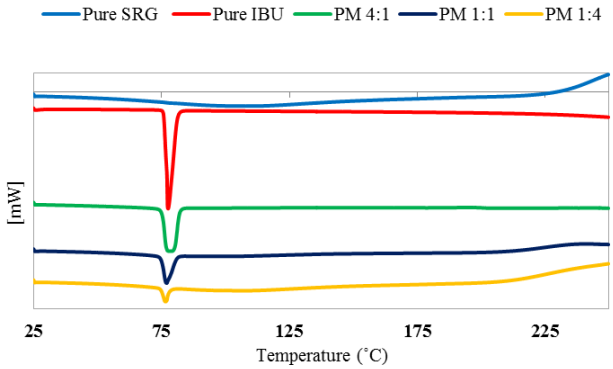

Fig. 1: *The thermograms of pure ibuprofen (IBU), pure Sesamum radiatum gum (SRG) and physical mixtures (PM 4:1, PM 1:1 and PM 1:4 of drug and carrier ratio respectively).*

There was a noticeable depression of the melting point from 77.39 ± 0.14°C to 76.86 ± 0.01 °C (Table 1) when the ratio of PM was 1:4, while an increase in the melting point was noticeable at a ratio of 4:1. The thermograms of the CMSD at a drug: polymer ratio of 4:1 and milling times of 1 min, 5 min and 10 min (Figure 2A) showed a lowering of the peak intensity of the melting endotherm of IBU at the different milling times which however increases with increasing co-milling time. There was significant depression of melting point at milling times of 5 min and 10 min, and the reverse at a milling time of 1 min. Similarly, thermograms of CMSD at a drug: polymer ratio of 1:1 and different milling times (Figure 2B) showed a lowering of peak intensity of the melting endotherm of IBU in the formulations at the different co-milling times with an attendant depression in the melting point at all co-milling times. Also, the lowering of peak intensity of the melting endotherm of IBU for CMSD (drug: polymer ratio of 1:4) at all co-milling times with an attendant depression of melting point at all co-milling times can be seen(Fig. 2C). The present result shows that the order of lowering of peak intensity of the melting endotherm of IBU for the

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CMSD was 4:1>1:1>1:4. The sequence was also the same for the depression of melting point. The thermograms showed no new peaks indicating no chemical interactions between IBU and SRG (Gowda et al., 2014). All CMSD formulations showed a general decrease in the melting point of the IBU with increasing co-milling time, suggesting a possible amorphization of the IBU with increasing co-milling time (Barzegar-Jalali et al., 2010; Lin et al., 2006).

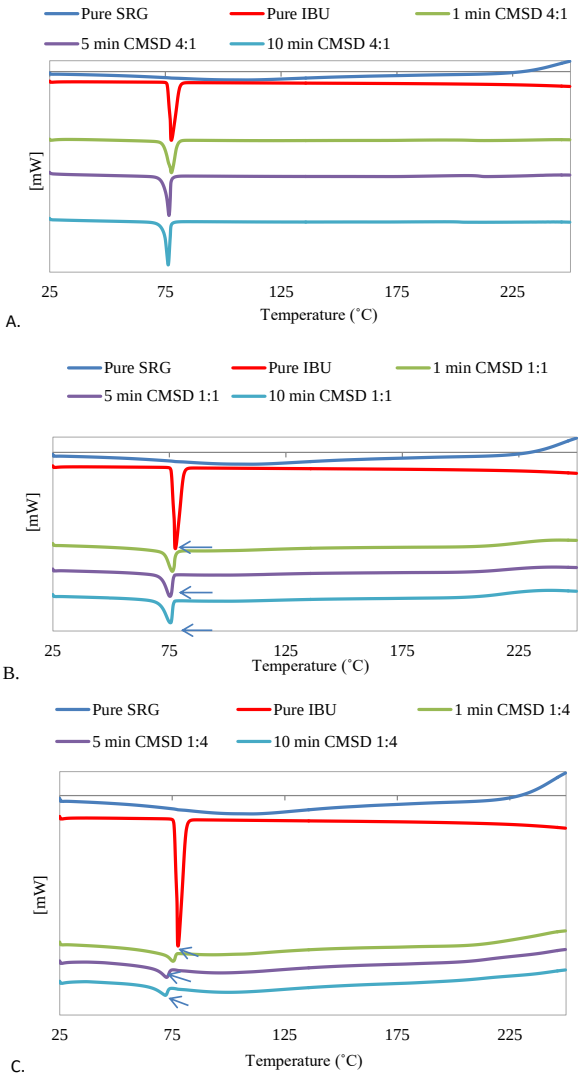

Fig.2: *DSC thermograms of CMSD (A) 4:1 (B) 1:1 and (C) 1:4 showing the thermograms of IBU, SRG, and the solid dispersions milled for 1 min, 5 min and 10 min.*

This amorphization did not occur to a large extent as the largest difference between the melting points was observed from pure IBU (77.39 ± 0.14 °C) to 10 min CMSD 1.4 (71.79 ± 0.23 °C), therefore, indicating that co-milling conditions up to 10 min do not affect the stability of IBU, as was also reported by Barzegar-Jalali and co-workers (Barzegar-Jalali et al., 2010).

Table 1: *Effect of formulation on the melting point of IBU in the PM and CMSD (mean ± SD, n =3)*

Formulations	Melting points (˚C)
Pure IBU	77.39 ± 0.14
PM 4:1	78.63 ± 0.55
PM 1:1	77.37 ± 0.01
PM 1:4	76.86 ± 0.01
1 min CMSD 4:1	78.17 ± 0.01
5 min CMSD 4:1	76.01 ± 0.30
10 min CMSD 4:1	75.47 ± 0.00
1 min CMSD 1:1	76.41 ± 0.28
5 min CMSD 1:1	74.79 ± 0.13
10 min CMSD 1:1	74.96 ± 0.11
1 min CMSD 1:4	75.12 ± 0.00
5 min CMSD 1:4	72.38 ± 0.14
10 min MSD 1:4	71.97 ± 0.23

Fourier transform-infrared (FT-IR) studies

The FT-IR spectra of IBU, SRG, and PM are presented in Figure 3, while the spectra for the CMSD formulations are presented in Figure 4A-C. The FT-IR spectrum of IBU has been assigned (Chatwal et al., 2009; Chen et al., 2012; Wahab et al., 2013). The peaks in the region between 2700-3300 cm^{-1}, 2954.2 cm^{-1}, 2922.7 cm^{-1} and 2868.5 cm^{-1} are attributed to C-H stretching vibrations (Chatwal et al., 2009), which overlapped with the broad peak of the hydroxyl group of propionic acid at the same region.

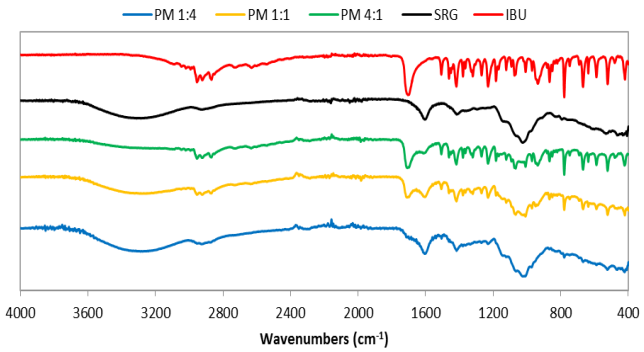

Fig.3: *FT-IR spectrum of IBU, SRG and the physical mixtures (PM 4:1, PM 1:1 and PM 1:4*

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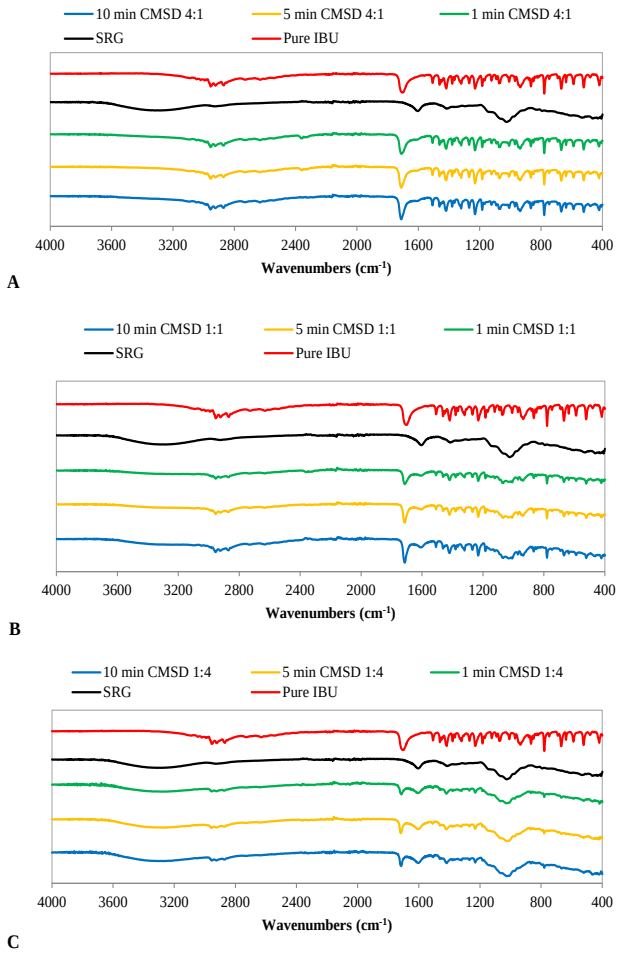

Fig.4: *FT-IR spectra IBU, SRG and CMSD (A) 4:1, (B) 1:1 and (C) 1:4 milled for 1 min, 5 min and 10 min.*

The distinct peak at 1704.4 cm^{-1} represents the stretching of carbonyl group of propionic acid (Chen et al., 2012), while the little peaks in the area between 1200-1000 cm^{-1} indicate the presence of a benzene ring (Wahab et al., 2013). The FT-IR spectrum of SRG has also been assigned (Ngwuluka et al., 2014). Briefly, the spectrum consist of bands and peaks that include 3300 cm^{-1} (-OH), 2930 cm^{-1} (C-H bonds of methyl groups (Ma and Pawlik, 2007), 1603 cm^{-1} (free carboxyls), 1400 cm^{-1} (COO^- symmetric stretching), 1380 cm^{-1} (C-H bending), 1300-1000 cm^{-1} (C-O stretching). The FT-IR spectrum of PM 4:1 showed a broadening of the OH band of SRG and a slight shift of the IBU peaks in the region 2700-3300 cm^{-1} to the left at 2954.4 cm^{-1}, 2923.8 cm^{-1}, and 2869.4 cm^{-1}. The carbonyl group of IBU shifted to the left at 1708.6 cm^{-1}, and overlapped with free carboxyls of SRG, which showed up as a shoulder at the carboxylic acid group of galacturonic acid residues, which shifted to the left as well at 1614.0, cm^{-1}. IBU peaks at the same region overlapped the finger print region of the carbohydrate; this was more visible for the SRG peak at 1024.5 cm^{-1}. From the FTIR spectra of the PM 1:1 and PM 1:4, it can be seen that the increasing proportion of SRG corresponded to an increasing expression of the spectra of SRG in the mixes with the OH band, the free carboxyls and the peak at 1024.5 cm^{-1} becoming more pronounced. The result shows that the relative proportions of IBU and SRG were critical in determining the predominant spectra, but IBU did not become amorphous. The FT-IR spectra of CMSD formulations with drug : polymer ratios of 4:1, 1:1 and 1:4 at the different co-milling times (Figure 4A-C) showed that no obvious difference exists between different co-milling times, but the carbonyl groups of IBU shifted to the left at 1709.6 cm^{-1}, 1711.5 cm^{-1}, and 1711.4 cm^{-1} for CMSD 4:1 formulations at 1 min, 5 min, and 10 min co-milling times respectively, indicating that milling is the main factor to cause this shift attributed to the formation of intermolecular hydrogen bonds or esterification between the carboxylic acid group in the IBU and the hydroxyl group in the SRG. For the CMSD formulations with drug:polymer ratio of 1:1, there was reduced intensity of the band due to hydroxyls when compared to the PM 1:1 (Figure 3). The CMSD at a drug:polymer ratio of 1:4 at 1 min, 5 min and 10 min co-milling times (Figure 4C) exhibited no visible differences in the spectra at the different co-milling. The milling process brings out the characteristic peak of the carbonyl group of IBU when compared with their physical mixture (PM 1:4) (Figure 3). The shift of carbonyl groups and hydroxyl groups of IBU and the carboxylic groups of galacturonic acid residues of SRG increased as the co-milling time increased as well as the peaks of IBU in the area 2700 - 3300 cm^{-1}.

X-ray powder diffraction (XRPD) studies

The XRPD of the physical mixtures (PM) are shown in Figure 5. Three characteristic crystalline diffraction peaks were visible at 16°, 20° and 22° angles for the IBU (indicated by black arrows) (Giri et al., 2010; Pang et al., 2011). The diffractogram of pure SRG (Figure 5) has no sharp intense peaks, but diffused peaks, indicating that the gum is amorphous in nature (Choudhary et al., 2012). The PM (4:1, 1:1 and 1:4) showed decreasing intensity of the peaks as the ratio of the SRG increased.

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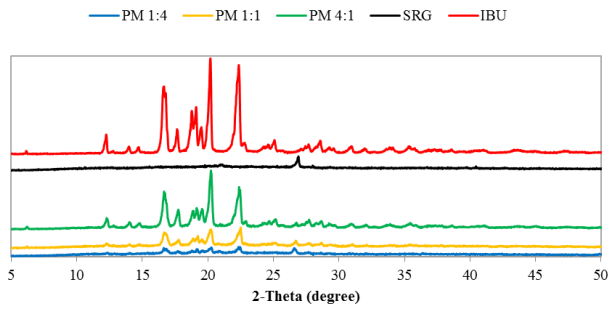

Fig.5: *Diffractograms of IBU, SRG, and the physical mixtures (4:1, 1:1 and 1:4)*

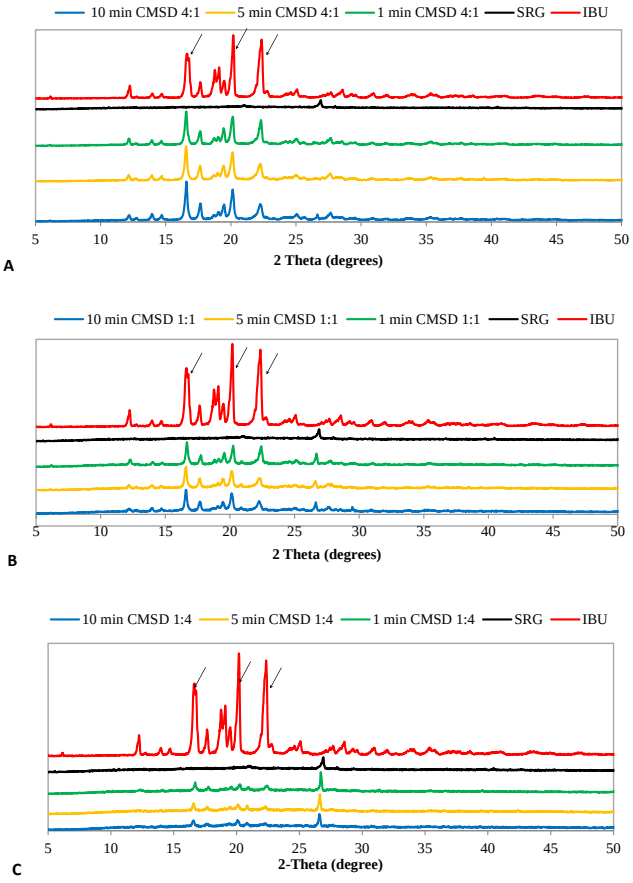

Fig.6: *Diffractograms of IBU, SRG, and co-milled solid dispersions (A) 1:4 (B) 1:1 and (C) 4:1, milled for 1 min, 5 min and 10 min.*

The XRPD of the CMSD (4:1, 1:1 and 1:4) at 1 min, 5 min and 10 min co-milling times are shown in Figure 6A-C. The diffractograms of CMSD showed that the intensity of IBU peaks decreases with increasing concentration of SRG and also with increasing co-milling times. This concurs with the DSC results.

In-vitro dissolution studies

The dissolution profile of IBU and IBU in the PM at the different drug: polymer ratios of 4:1, 1:1 and 1:4 are shown in Figure 7. The dissolution profiles of the PM showed that the release rate of IBU in the formulation was lower than the release of pure IBU in phosphate buffer pH 7.2 and indicate that the physical mixing of IBU and SRG in the ratios evaluated did not improve the dissolution of IBU. This concurs with previous sections in which we reported that physical mixing did result in the amorphization of IBU.

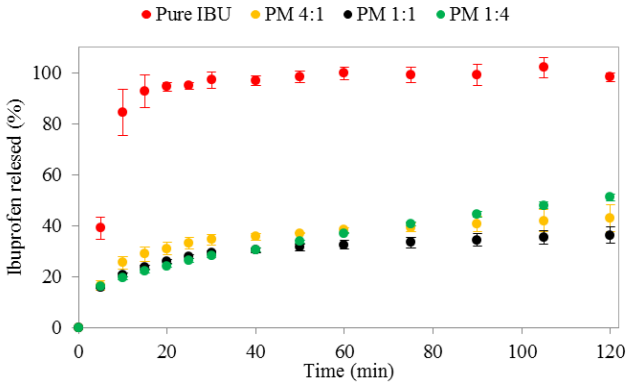

Fig.7: *Dissolution profiles of pure ibuprofen (IBU) and IBU in the PM (4:1, 1:1 and 1:4).*

The dissolution profiles of pure IBU and CMSD are presented in Figure 8A-C. When the drug:polymer ratio was 4:1, it can be seen that the release rates increased with increasing co-milling time. However, the rate of IBU release was still lower than that of pure IBU. This was more or less the case when drug:polymer ratio was 1:4. At drug-polymer ratio of 1:1, the highest dissolution was exhibited by co-milling time of 1 min and all the co-milled formulations exhibited lower release of IBU than the release rate for pure IBU. The amount of IBU released from the formulations at 10 min (Q10) and 30 min (Q30) as a % of the total drug content, is presented in Table 2. The results show that at 10 min or 30 min, the CMSD formulations release more of the drug than that of the PM, indicating the effect of co-milling. However, for all the formulations, the dissolution rate from the SDs did not exceed that of pure IBU. The results indicate that SRG did not improve the dissolution of IBU from the SD formulations; instead the polymer exhibited a retarding effect on release of the drug.

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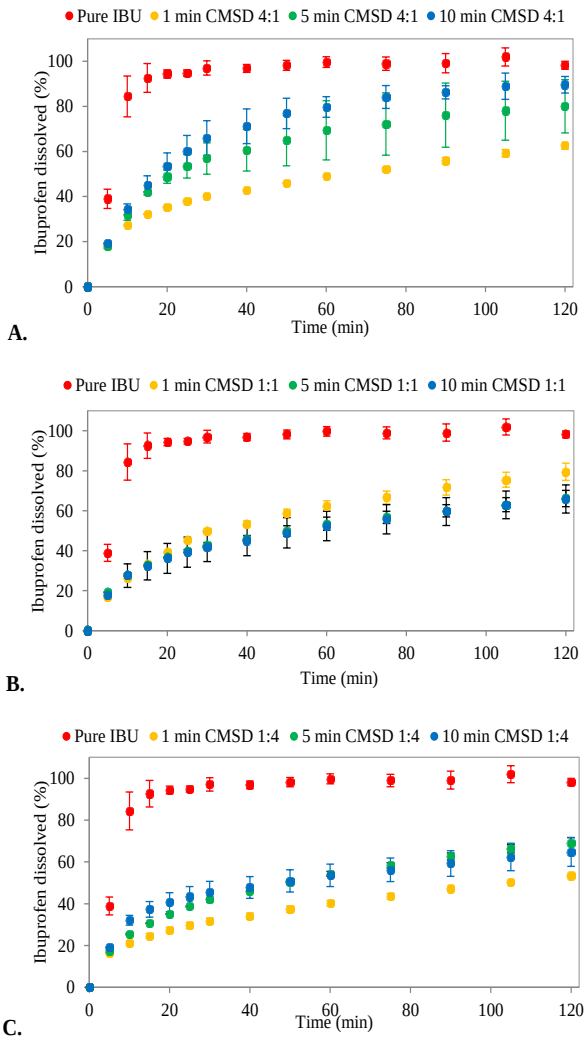

Fig.8. Dissolution profiles of pure ibuprofen (IBU) and CMSD formulations (A) 4:1, (B) 1:1 and (C) 1:4 milled for 1 min, 5 min and 10 min.

This may be attributed to the high viscosity yielding ability of the polymer (Figure 9). Amar and co-workers reported that the viscosity of many polymers limit their ability to increase the solubility of poorly soluble drugs (Amar et al., 2014). Consequently, natural polysaccharides may have to be modified by heating for specific periods of time at selected temperatures to be suitable for use in SD formulations. Such treatment on Khaya gum and Hupu gum was reported to improve the dissolution profile and solubility of nimodipine and pioglitazone HCl respectively, using a co-milling technique, as a result of reduction in the viscosity of the gel layer by heating. Viral et al. (2010) also showed that SD formulations of licofelone using a co-grinding technique with modified guar gum gave a much better dissolution profile than SD formulations with native guar gum using the same technique (Viral et al., 2010). A similar result was reported by Patel and co-workers (Patel et al., 2008).

Table 2: *The percent release of drug from co-milled solid dispersion (CMSD) formulations after 10 min and 30 min as compared with pure IBU and physical mixtures (PM).*

Formulations	Q_{10} (%)	Q_{30} (%)
Pure IBU	84.4 ± 9.05	97.1 ± 3.18
PM 4:1	25.4 ± 2.51	34.4 ± 1.96
PM 1:1	20.6 ± 0.78	29.3 ± 0.72
PM 1:4	19.4 ± 0.46	28.0 ± 0.60
1 min CMSD 4:1	27.3 ± 0.34	40.3 ± 0.35
5 min CMSD 4:1	31.8 ± 2.34	56.9 ± 6.93
10 min CMSD 4:1	34.3 ± 2.40	66.0 ± 7.69
1 min CMSD 1:1	26.4 ± 0.45	49.9 ± 0.87
5 min CMSD 1:1	27.9 ± 0.68	42.6 ± 1.51
10 min CMSD 1:1	27.6 ± 5.89	42.1 ± 7.53
1 min CMSD 1:4	21.1 ± 1.17	31.6 ± 1.46
5 min CMSD 1:4	25.5 ± 0.41	42.1 ± 0.37
10 min MSD 1:4	32.1 ± 2.30	45.7 ± 5.07

Fig.9: Viscous gel layer surrounding formulation that possibly caused the drug retardation

CONCLUSION

The results have demonstrated that IBU is compatible with SRG when used in solid dispersions. SRG slowly hydrates to form a viscous gel layer when in contact with the dissolution media, thereby retarding the dissolution of drug. Although the use of co-milling to achieve solid dispersion of the drug in SRG improved dissolution of the drug from its PM counterpart, this did not provide a superior release when compared to the dissolution of the pure drug. The role of SRG in solid dispersion formulation can be further evaluated by utilizing modified forms of the material, which are of lower viscosity.

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