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RESEARCH ARTICLE

Dissolution enhancement of poorly water-soluble APIs processed by hot-melt extrusion using hydrophilic polymers

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Abstract

The aim of this study was to investigate the efficiency of hydrophilic polymers to enhance the dissolution rate of poorly water-soluble active pharmaceutical ingredients (APIs) processed by hot-melt extrusion (HME). Indomethacin (INM) and famotidine (FMT) were selected as model active substances while polyvinyl caprolactam graft copolymer, soluplus (SOL) and vinylpyrrolidone-vinyl acetate copolymer grades, Kollidon VA64 (VA64) and Plasdone S630 (S630) were used as hydrophilic polymeric carriers. For the purpose of the study, drug–polymer binary blends at various ratios were processed by a Randcastle single screw extruder. The physicochemical properties and the morphology of the extrudates were evaluated through X-ray diffraction (XRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). Increased drug loadings of up to 40% were achieved in the extruded formulations for both drugs. INM and FMT exhibited strong plasticization effects with increasing concentrations and were found to be molecularly dispersed within the polymer blends. The *in vitro* dissolution studies showed increased INM/FMT release rates for all formulations compared to that of pure APIs alone.

Keywords: Hot-melt extrusion, dissolution enhancement, solid dispersions, hydrophilic polymers, insoluble drugs

Introduction

With the recent start of high throughput screening of potential therapeutically active ingredients, the number of poorly soluble drug candidates has increased sharply (about 25–40%). The availability of water insoluble active pharmaceutical ingredients (APIs) into systemic circulation is highly controlled and dependant on its aqueous solubility and therefore increasing the solubility/dissolution of poorly soluble compounds for oral delivery is a challenging task in pharmaceutical processing and development. The manufacture of solid dispersions is considered one of the most attractive approaches to increase solubility and bioavailability of poorly soluble APIs[1]. Solid dispersions have been prepared by employing various approaches such as coevaporation[2], hot spin mixing[3], roll-mixing or comilling[4], freeze-drying[5], spray drying[6,7] and supercritical fluid processing (SFP)[8].

Hot-melt extrusion (HME) is considered an effective process in pharmaceutical industry for the formation of molecular dispersions in order to improve the bioavailability of drug components which have low water solubility[9]. The melt extrusion process offers various advantages over conventional approaches such as it is a solvent-free process and therefore environmental friendly. Heat sensitive substances can be easily processed by HME as the exposure of the APIs is very short and processing temperatures can be lowered by selecting the appropriate drug carrier. In addition, HME is regarded as a continuous and easy to scale-up production process. Moreover, the melt extrusion process helps to convert crystalline active substances into the amorphous state as well as offers a chance to dissolve the drugs in the inert polymer matrix through the formation of solid solutions.

Different case studies have been reported to increase solubility of various poorly soluble drugs[10] by HME including nifedipine, tolbutamide, lacidipine[11,12], itraconazole[13,14] and nitrendipine[15].

Famotidine (FMT) is a histamine H2-receptor antagonist (H2RA) mainly used for the treatment of gastric-duodenal ulcers, symptomatic gastro-oesophageal reflux disease (GERD), erosive oesophagitis, management of hypersecretory conditions[16,17] and for

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pediatric populations[17]. According to Biopharmaceutical Classification System (BCS), FMT is classified as a Class IV drug (low solubility, low permeability)[18]. INM is a nonsteroidal anti-inflammatory drug (NSAID) used to treat rheumatoid arthritis, osteoarthritis, alkylosing spondylitis, tendinitis and headaches[19,20]. It is known as a Class II active substance which exerts high permeability and weak bioavailability[19] due to the poor water solubility. The two drugs were chosen to represent the two classes and to compare the effect of HME on increasing their percent loading, solubilities and dissolution properties which are important for improving their bioavailability. To the best of our knowledge, this is the first study comparing two different poorly water-soluble drugs from two BCS classes for drug loading, solubility and drug dissolution properties.

Both FMT and INM have been reported to be molecularly dispersed in various polymer matrices in order to provide quick release profiles[16,19–21]. In the present study, solid dispersions of higher loadings of INM and FMT embedded in hydrophilic polymers such as SOL, VA64 and S630 were prepared using HME in order to achieve faster dissolution profiles. The *in vitro* dissolution properties and physicochemical properties of the solid dispersions were investigated and compared with the physical mixtures and the pure APIs alone.

Materials and methods

Materials

Indomethacin (INM) was purchased from Sigma Aldrich (London, UK) and FMT was donated by Colorcon Ltd (Dartford, UK). Soluplus and Crosslinked polyvinylpyrrolidone Kollidon VA64 were kindly donated by BASF (Ludwigshafen, Germany). Plasdone S630 was obtained from ISP (International Speciality Products (ISP),Surrey, UK). The HPLC solvents were analytical grade and purchased from Fisher Chemicals (Loughborough, UK).

Drug–polymer miscibility study by solubility parameters (δ)

The Hansen[22] solubility parameters (δ) of both drugs as well as the polymers were calculated by considering their chemical structural orientations. In order to determine the theoretical drug/polymer miscibility, the solubility parameters were calculated by using the Hoftyzer and van Krevelen method[23] according to the following equation:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

Where,

$$\delta_d = \frac{\Sigma F_{di}}{Vi},\ \delta_p = \frac{\sqrt{\Sigma F_{pi}^2}}{Vi},\ \delta_h = \sqrt{\frac{\Sigma E_{hi}}{Vi}}$$

i, structural groups within the molecule; δ, the total solubility parameter; F_{di}, molar attraction constant due to molar dispersion forces; F_{pi}^2, molar attraction constant due to molar polarization forces; E_{hi}, hydrogen bonding energy; *V*i, group contribution to molar volume.

The average molecular weight was used to determine the solubility parameter of different polymeric excipients while Bagley advanced solubility parameter equation and diagrams[24] were used to investigate the effect of the hydrogen bonding compared to the combined solubility parameters (dispersion forces and polarization forces).

Preparation of formulation blends

The dry drug/polymer powders (100 g) were blended properly in a Turbula TF2 mixer (Glen Mills Inc, NJ, USA) for 10 min. As shown in Table 1 the drug content for the binary blends varied from 20 to 40%. For the FMT/VA64, FMT/S630 and INM/S630 the drug content did not exceed 20% due to the difficulty with extruding the powdered formulations.

HME process

Extrusion of all INM and FMT formulations was performed using a single screw Randcastle extruder (Model RC 0750, Randcastle Extrusion Systems Inc. Cedar Grove, NJ, USA) with a 0.2 mm rod die. The temperature profile from the feeding zone to die was 105°C/113°C/118°C/122°C/120°C for all formulations with 15 rpm screw speeds. The extrudates (strands) were milled for 5 min to produce granules using a Pulverisette 6 ball mill (Fritsch, Rudolstadt, Germany) with 400 rpm rotational speed. The micronized particles were then passed through a 500 μm sieve in order to use the fraction below this threshold.

Thermal analysis

A Mettler-Toledo 823e (Mettler Toledo International Inc., Greifensee, Switzerland) differential scanning calorimeter (DSC) was used to carry out DSC runs of pure actives, physical mixtures and extrudates. A 2–5 mg of sample was placed in sealed aluminium pans with pierced lids. The samples were heated at 10°C/min from 0°C to 220°C under dry nitrogen atmosphere. In addition, modulated temperature scanning calorimetry (MTDSC) studies were performed from 30°C to 150°C temperature range

Table 1. Drug/polymer percentages of the HME processed formulations.

Drug	Polymer	Drug (%, w/w)	Polymer (%, w/w)
FMT	SOL	20	80
FMT	SOL	40	60
FMT	VA64	20	80
FMT	S630	20	80
INM	SOL	20	80
INM	SOL	40	60
INM	VA64	20	80
INM	VA64	40	60
INM	S630	20	80

FMT, famotidine; HME, hot-melt extrusion; INM, indomethacin; SOL, soluplus.

with an underlying heating rate of 1°C/min to further analyze the samples. The pulse height was adjusted to 1–2°C with a temperature pulse width of 15–30 s.

X-ray powder diffraction

X-ray powder diffraction (XRPD) was used to determine the solid state of pure active substances, physical mixtures and extruded materials using a Bruker D8 Advance (Bruker AXS GmbH, Karlsruhe, Germany) in 2θ mode. For the purpose of the study, a Copper anode at 40 kV and 40 Ma, parallel beam Goebel mirror, 0.2 mm exit slit, LynxEye Position Sensitive Detector with 3° opening (LynxIris at 6.5 mm) and sample rotation at 15 rpm were used. Each sample was scanned from 2 to 40° 2θ with a step size of 0.02° 2θ and a counting time of 0.2 s per step; 176 channels active on the PSD making a total counting time of 35.2 s per step.

Particle size morphology and distribution

SEM was used to study the surface morphology of the hot-melt extrudates. The samples were mounted on an aluminium stage using adhesive carbon tape and placed in a low humidity chamber prior to analysis. Samples were coated with gold, and microscopy was performed using a Jeol 5200, SEM operating at an accelerating voltage of 5 kV.

The particle size distribution of the micronized extrudate granules of all formulations was measured by dry sieving. The method involved stacking of the sieves on top of each other and then placing the test powder (100 g) on the top sieve. The nest of sieves was subjected to a standardized period of agitation (20 min) and then the weight of the material retained on each sieve was accurately determined to give the weigh percentage of powder in each sieve size range.

In vitro drug release studies

In vitro drug release studies were carried out in 750 mL of 0.1 M hydrochloric acid for 2 h using a Varian 705 DS dissolution paddle apparatus (Varian Inc., Raleigh, NC, USA) at 100 rpm and 37 ± 0.5°C. After 2 h operation, 250 mL of 0.20 M solution of trisodium phosphate dodecahydrate were added into the vessel (buffer stage, pH 6.8) that had been equilibrated to 37°C. At predetermined time intervals, samples were withdrawn for HPLC assay. All dissolution studies were performed in triplicate.

The difference factor[25] *f*2 was used to compare the obtained release profiles. The *f*2 value (Eq. 2) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all time points ($n = 5$). According to the FDA guidelines, release curves are considered similar when the calculated *f*2 is 50–100.

$$f2 = 50x\log\left[\left\{1+\left(\frac{1}{n}\Sigma_{j=1}^{n}(R_j - T_j)^2\right)^{-0.5}\right\}\times 100\right] \quad (2)$$

HPLC analysis

The release of INM and FMT was determined by using HPLC, Agilent Technologies system 1200 series. A HYCHROME S50DS2-4889 (5 µm × 150 mm × 4 mm) column was used for both active substances. The wavelength was set at 260 nm and 267 nm for INM and FMT, respectively. The mobile phase consisted of methanol/water/acetic acid (64/35/1 v/v) and the flow rate was maintained at 2 mL/min and the retention time was 4–5 min. For INM and FMT, calibration curves were prepared with concentrations varying from 10 µg/mL to 50 µg/mL and 20 µL injection volumes.

Results and discussion

Miscibility studies by calculating solubility parameters (δ)

The estimation of the solubility parameter (δ) was used to predict the miscibility of the active substances and the polymeric carriers[12,26,27]. Calculated solubility parameters indicate the probability of a drug molecule to be miscible with a large polymer molecule. In the calculation of solubility parameters, three different forces are considered. It is believed that the compounds with similar values for solubility parameters are likely to be miscible because the miscibility is caused by balancing the energy of mixing released by inter molecular interactions between the components and the energy released by intramolecular interactions within the components[27]. The Hansen dimensional solubility parameters are calculated by group contributions of dispersion forces, polar forces and hydrogen bonding forces using the van Krevelen/Hoftyzer (1976) method.

The estimated solubility parameters are depicted in Table 2 and it can be seen that for all drug–polymer combinations, the Δδ values vary from 3.2 to 5.2 $MPa^{0.5}$ derived by the van Krevelen/Hoftyzer approach. Greenhalgh[26] classified compounds according to their difference in solubility parameters. The authors found out that compounds with a Δδ < 7 $MPa^{0.5}$ were likely to be miscible, but likely to be immiscible with a Δδ > 10 $MPa^{0.5}$. Since the determined solubility parameters differences between each drug and polymer are less than 7 $MPa^{0.5}$, all three polymers are likely to be miscible with both of the APIs. Interestingly, the Δδ values for INM and the two vinylpyrrolidone copolymer grades are slightly different although both appear to be miscible. This was attributed to the different molecular weights and the degree of crosslinking of the two polymers. Similar differences can be observed for FMT and the vinylpyrrolidone copolymers.

Furthermore, by means of thermodynamic considerations, Bagley *et al.*[24] concluded that the effects of δ_d and δ_p show close similarity and so introduced the combined solubility parameter δ_v, where

$$\delta_v = \sqrt{\delta_d^2 + d_p^2} \quad (3)$$

Table 2. Calculated solubility parameters of drug/polymers and compounds distances in Bagley diagram.

Sample	δ_d (MPa$^{0.5}$)	δ_p (MPa$^{0.5}$)	δ_v (MPa$^{0.5}$)	δ_h (MPa$^{0.5}$)	$\delta_{average}$ (MPa$^{0.5}$)	$\Delta\delta_{(INM)}$ (MPa$^{0.5}$)	$\Delta\delta_{(FMT)}$ (MPa$^{0.5}$)	$R_{a(v)}$ INM (MPa$^{0.5}$)	$R_{a(v)}$ FMT (MPa$^{0.5}$)
INM	18.99	7.37	20.34	10.34	22.84	–	–	–	–
FMT	11.93	15.00	19.17	13.49	23.44	–	–	–	–
VA64	18.0	0.64	18.01	7.73	19.60	3.24	3.84	3.49	5.87
SOL	15.14	0.45	15.15	12.18	19.43	3.41	3.99	5.54	4.23
S630	13.0	8.80	15.70	9.17	18.18	4.66	5.26	4.79	5.54

Solubility parameters in MPa$^{0.5}$.
FMT, famotidine; INM, indomethacin; SOL, soluplus.

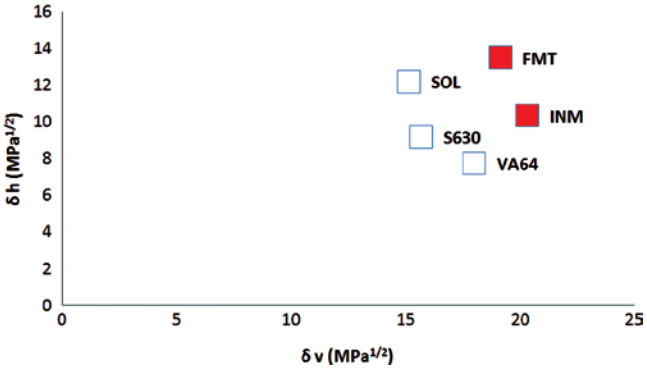

Figure 1. Location of polymers (open symbols) and APIs (closed symbols) within the Bagley plot. API, active pharmaceutical ingredient.

The parameter for components of intermolecular hydrogen bonding δ_h and the combined parameter δ_v are plotted in a diagram to project the three-dimensional solubility parameter space into a two-dimensional plot to produce a Bagley diagram (Figure 1).

The two-dimensional approach through plotting the Bagley diagram can provide more accurate prediction of the drug–polymer miscibility. The drug–polymer miscibility can be predicted by the distance ($R_{a(v)}$) using the Pythagorean Theorem in the Bagley diagram and the two components are likely to be miscible when $R_{a(v)}$ is ≤5.6 MPa$^{0.5}$[28], where

$$R_{a(v)} = \sqrt{(\delta_{v2} - \delta_{v1})^2 + (\delta_{h2} - \delta_{h1})^2} \quad (4)$$

In Figure 1, the Bagley diagram projects the three-dimensional solubility parameter into a two-dimensional plot against the hydrogen bonding δ_h. Only small differences can be observed for FMT and INM and all three polymers where the $R_{a(v)}$ values are less than 5.6 MPa$^{0.5}$ suggesting again drug–polymer miscibility for each formulation. The estimated $R_{a(v)}$ value for the FMT/VA 64 is 5.87 MPa$^{0.5}$ suggesting immiscibility of the two components. However, the difference from the value given by Albers et al. (2008) is marginal and the components were considered miscible.

Nevertheless, both approaches confirmed the miscibility of the binary mixtures for all formulations. It is worth mentioning that the manufacturing of solid dispersions via HME depends also on the processing parameters such as temperature profile and screw rotation speed which are not taken into account in the estimated solubility parameters by van Krevelen/Hoftyzer or Bagley. Thus, further process optimization is required for the manufacturing of solid dispersions in order to increase drug solubility.

As it can be seen in Table 1, no plasticizer was incorporated in the binary mixtures due to low glass transition temperatures of the selected polymers. All formulations were easily extruded at temperatures around 120°C even at high drug loadings.

Particle size morphology and particle size analysis

SEM was used to examine the surface morphology of the drug and extrudates. The particle morphology of INM and FMT is illustrated in Figure 2. The particles size range for all extruded materials varied from 50 to 200 μm after optimizing the milling process. The extrudates containing SOL, VA64 and S630 exhibited no drug crystals on the extrudate surface at 20 and 40% drug loading with INM. Similarly, no FMT crystals were observed on the surface of polymeric extrudates at all drug concentrations. The particle size distribution depicted in Figure 3 shows particle sizes lower than 500 μm for most formulations ranging from 40 to 400 μm. A small percentage can be seen at sizes <40 μm as the milling process was optimized to reduce fines in the final extruded batches

X-ray powder diffraction

The drug–polymer extrudates, including pure drugs and physical mixtures of the same composition were studied by X-ray analysis and the diffractograms were recorded to examine INM and FMT crystalline state. As can be seen from Figure 4a–4b, the diffractogram of pure INM and FMT showed distinct peaks at 10.17, 11.62, 17.02, 19.60, 21.82, 23.99, 26.61, 29.37, 30.32, 33.55 2θ and 5.97, 11.59, 15.73, 17.97, 20.03, 20.83, 24.04, 30.15, 32.19, 35.27 2θ, respectively. As shown in Figure 4a, the physical mixtures of all INM formulations showed identical peaks at lower intensities suggesting that both drugs retain their crystallinity at loads of 20–40%. In contrast, no distinct intensity peaks were observed in the diffractograms of the extruded formulations even at high drug loadings. The absence of INM and FMT intensity peaks indicates the formation of a solid dispersion where the drugs are present in amorphous state or molecularly dispersed into the polymer matrix.

The diffraction patterns of all FMT physical mixtures exhibited crystalline peaks (Figure 4b) with

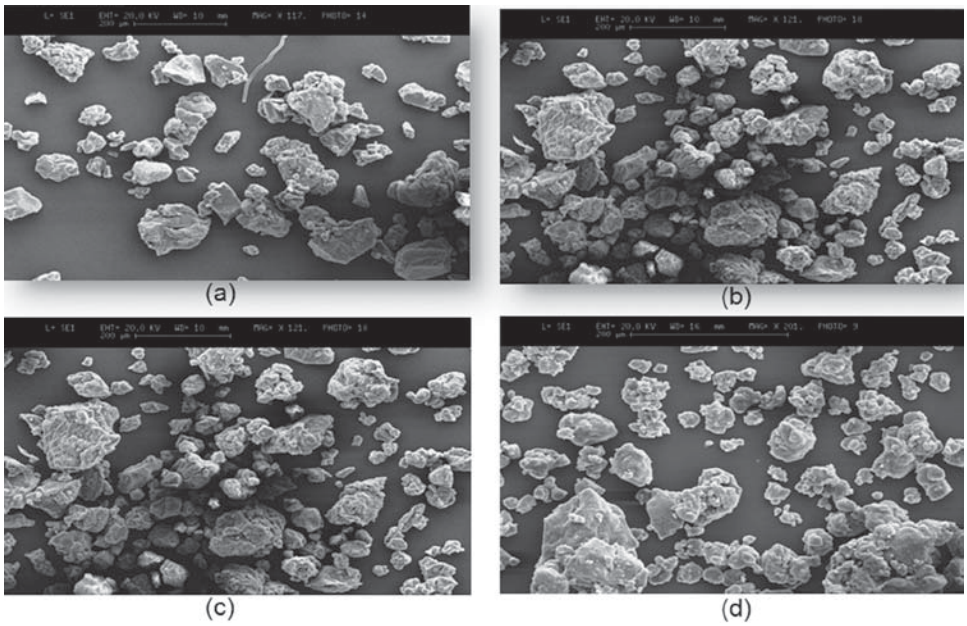

Figure 2. SEM images of extruded formulations: (a) SOL/INM 20%, (b) SOL/INM 40%, (c) FMT/VA64 20% and (d) FMT/S630 20%. FMT, famotidine; INM, indomethacin; SOL, soluplus.

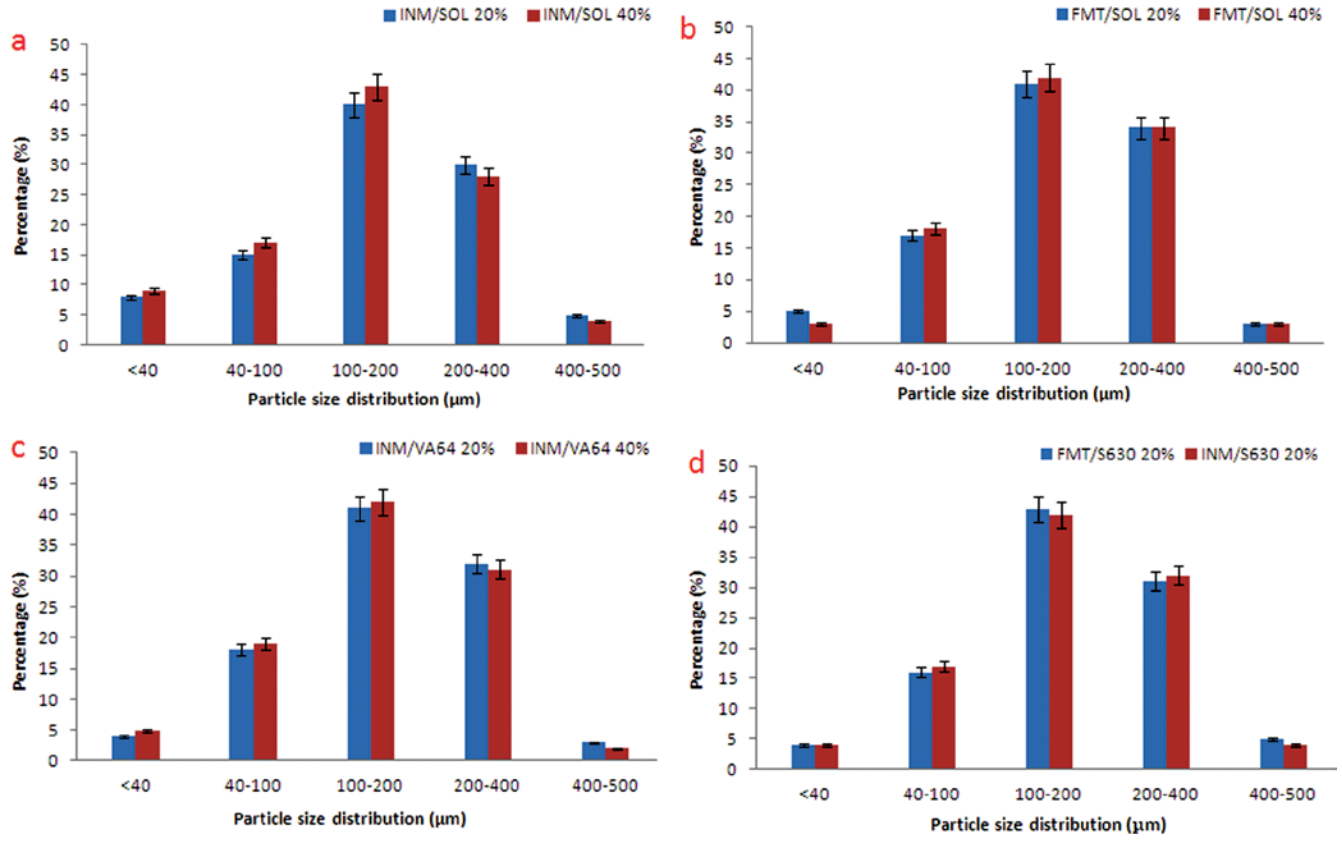

Figure 3. Particle size distribution of extruded formulations after milling: (a) INM/SOL 20–40%, (b) FMT/SOL 20–40%, (c) INM/VA64 20–40% and (d) INM/S630 20%, FMT/S630 20%. FMT, famotidine; INM, indomethacin; SOL, soluplus.

reduced intensities corresponding to FMT. Similar to INM the diffractograms of the extruded FMT formulations were characterized by the absence of drug intensity peaks indicating amorphous or molecularly dispersed state.

Differential scanning calorimetry

DSC was used to determine the state of both drugs, within the extruded formulations and compared with those of the physical mixtures. The DSC thermograms of pure INM and FMT showed sharp melting endothermic

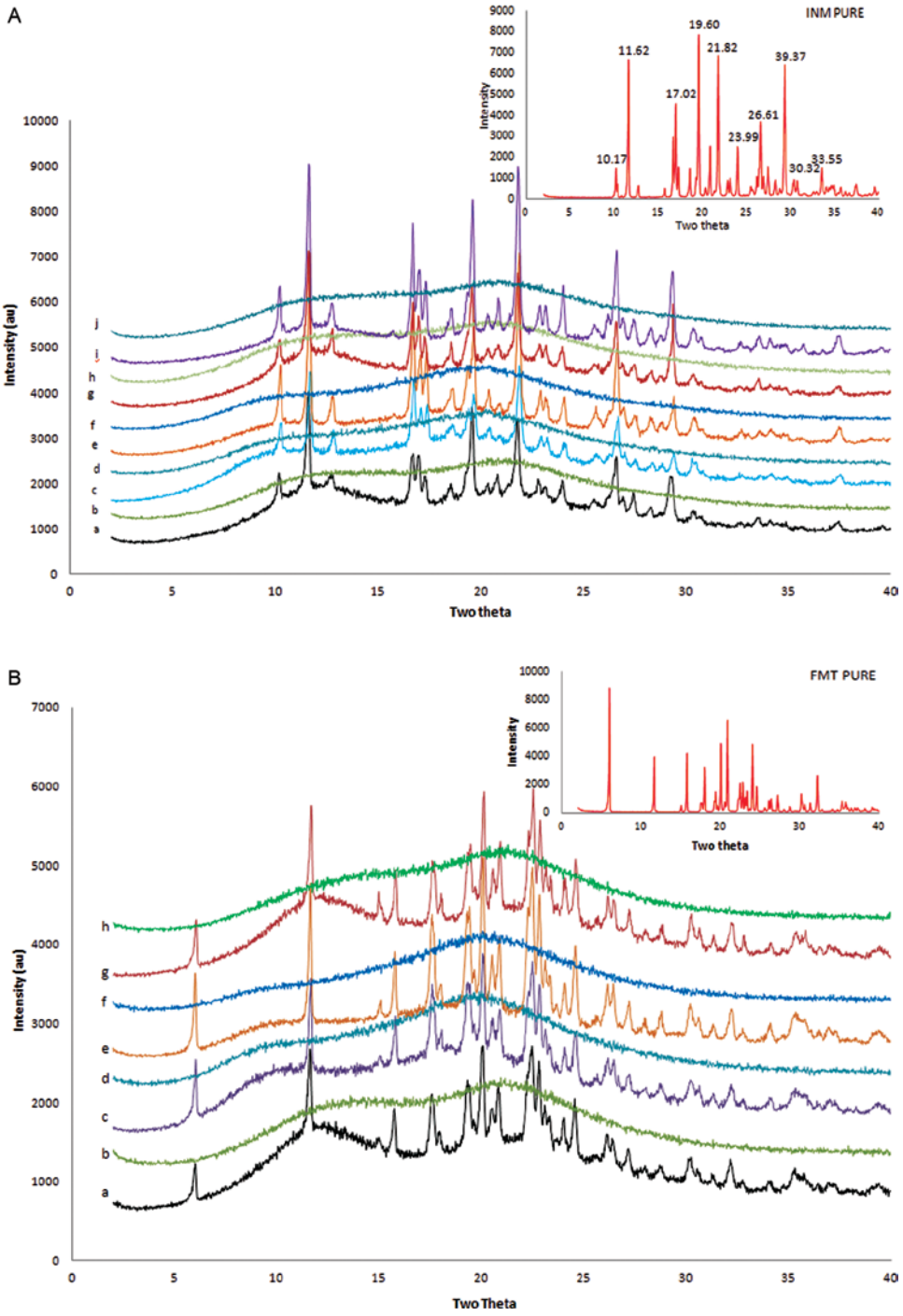

Figure 4. XRD profiles showing (A) Diffractograms of INM formulations: INM pure (inset), (a) INM/S630 20% PM, (b) INM/SC30 20% extrudates, (c) INM/ SOL 20% PM, (d) INM/SOL 20% EF, (e) INM/SOL 40% PM, (f) INM/SOL 40% extrudates, (g) INM/VA64 20% PM, (h) INMO/VA64 20% extrudates, (i) INM/VA64 40% PM and (j) INM/VA64 40% EF. EF, extruded formulations; FMT, famotidine; INM, indomethacin; PM, physical mixtures; SOL, soluplus. (B) Diffractograms of FMT formulations: FMT pure (inset), (a) FMT/S630 20% PM, (b) FMT/S63020% extrudates, (c) FAM/SOL 20% PM, (d) FMT/SOL 20% extrudates, (e) FMT/SOL 40% PM, (f) FMT/SOL 40% extrudates, (g) FMT/VA64 20% PM and (h) FMT/VA64 20% extrudates. FMT, famotidine; INM, indomethacin; PM, physical mixtures; SOL, soluplus.

peaks at 162°C and 165.5°C respectively with a fusion enthalpy (ΔH) of about 109.6 J/g and 158.5 J/g (Figure 5a). Modulated temperature DSC (MTDSC) was used to analyze reversible heat flow of the pure polymers where amorphous SOL, VA64 and S630 exhibited glass transitions (T_g) at 68.7, 105.0 and 105.5°C (Figure 5a), respectively. As can be seen in Table 3, all drug–polymer physical mixtures exhibited melting peaks of INM and FMT at lower temperatures and reduced ΔH values as the ratio of carrier increased. However, the DSC thermograms of the physical mixtures showed broad endothermic peaks from 127 to 163°C and from 124 to

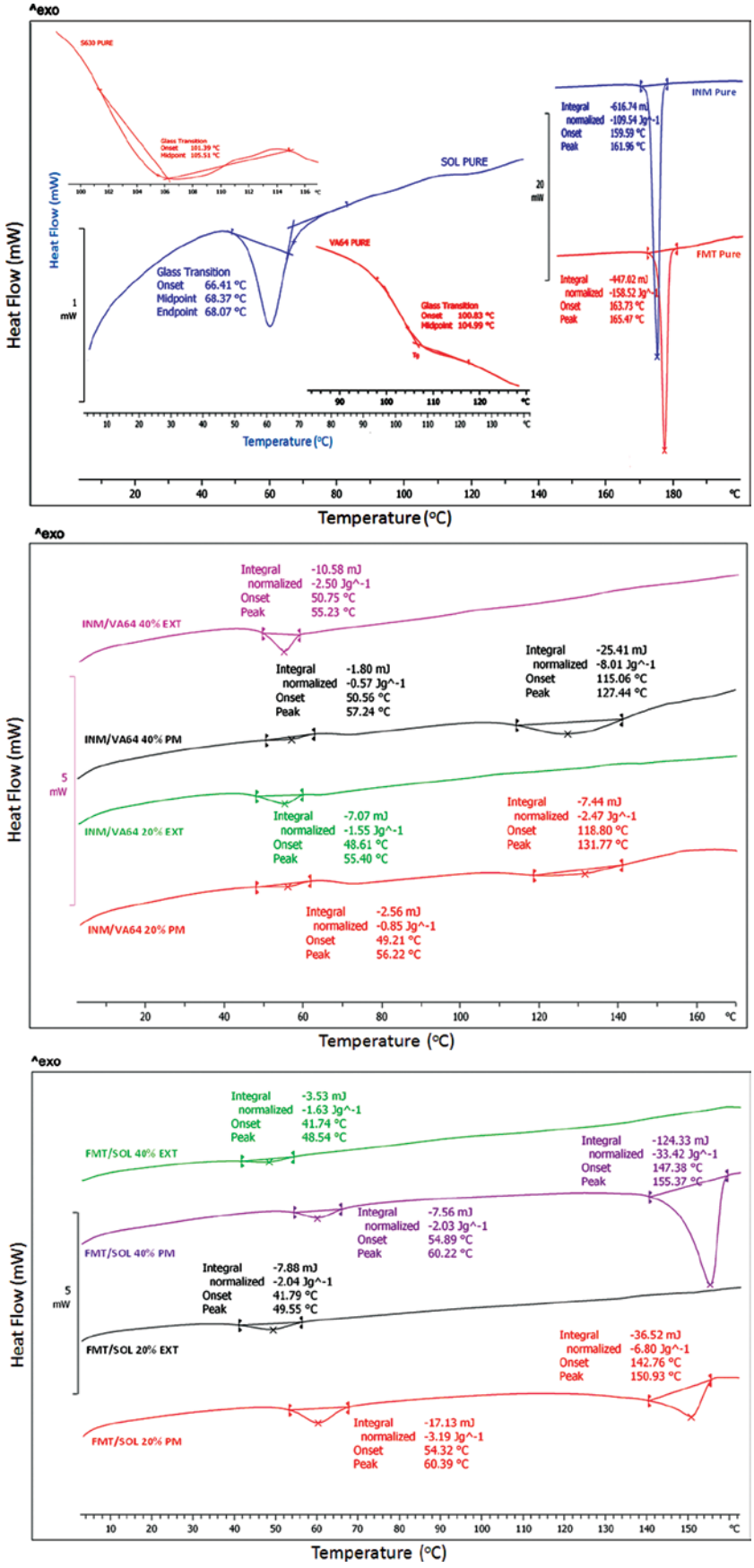

Figure 5. Thermal analysis results showing (A) Modulated temperature scanning calorimetry thermograms of pure polymers and pure drugs. (B) DSC thermograms of INM and VA64 (physical mixtures and extrudates). DSC, differential scanning calorimetry; INM, indomethacin. (C) DSC thermogram of FMT and SOL (physical mixtures and extrudates). DSC, differential scanning calorimetry; FMT, famotidine; SOL, soluplus.

Table 3. DSC peaks for drugs, polymers and active formulations.

Formulations	Glass transition/ enthalpy (°C/ΔH, Jg^{-1})	Melting endotherm/ enthalpy (°C/ΔH, Jg^{-1})	
INM	–	162.0/109.6	
FMT	–	165.5/158.5	
SOL	68.7	–	
VA64	105.0	–	
S630	105.5	–	
PM and EF			
	PM (°C/ΔH, Jg^{-1})	EF (°C/ΔH, Jg^{-1})	PM (°C/ΔH, Jg^{-1})
INM/SOL 20%	60.6/3.7	52.7/2.1	162.4/12.8
INM/SOL 40%	60.6/2.6	51.7/2.3	154.6/15.9
INM/VA64 20%	56.2/0.9	55.4/1.6	131.8/2.5
INM/VA64 40%	57.2/0.6	55.2/2.5	127.4/8.0
INM/S630 20%	70.8/0.7	56.6/2.1	130.8/2.7
FMT/SOL 20%	60.4/3.2	49.6/2.0	150.9/6.8
FMT/SOL 40%	60.2/2.1	48.5/1.6	155.3/33.4
FMT/VA64 20%	55.3/0.5	53.9/2.0	124.3/4.3
FMT/S630 20%	69.2/0.5	51.9/1.4	143.8/3.4

DSC, differential scanning calorimetry; EF, extruded formulations; FMT, famotidine; INM, indomethacin; PM, physical mixtures; SOL, soluplus.

151°C that correspond to INM and FMT respectively. The absence of sharp melting endotherms in the active formulations suggests that both drugs are partially dissolved in the melted polymers.

In the case of INM/VA64 extrudates, a single T_g was observed for both loadings indicating drug–polymer miscibility. When the two components are miscible the T_g of the extruded sample should be between their T_gs according to Gordon-Taylor equation[29]. For INM 20% and 40% loadings, the T_gs were lowered at 56.2°C and 57.2°C respectively denoting INM–VA64 miscibility. The INM glass transition temperature has been previously estimated at 42.3°C. The presence of a single T_g for the INM/VA64 extrudates suggests the presence of a glassy solid solution where INM is molecularly dispersed within the polymer matrices. In addition, the determined T_g values (Figure 5b) showed plasticization effect for INM as T_g decreased with increase in drug concentration. This phenomenon was also observed for INM/soluplus extrudates where a single T_g was detected at 52.70°C and 51.71°C for 20% and 40% INM loadings as shown in Table 3. The drug plasticization effect indicates intense intermolecular mixing during HME processing where the drug distribute itself between the polymer chains and interact with functional groups, thereby reducing the interaction between the polymer chain and softening the matrix[30]. Both T_gs were found between the INM and polymer T_gs indicating the presence of molecularly dispersed INM. By comparing the T_gs at different loadings, INM showed a plasticization effect for soluplus. By analyzing the thermograms of the INM/S630 extrudates it was concluded that INM was also molecularly dispersed in the carrier due to the single T_g at 56.57°C and the absence of the drug melting endotherm.

Further evaluation of the DSC thermograms for the FMT–polymer extrudates confirmed the existence of glassy solid solutions for all formulations. For each binary mixture only a single T_g was observed without any endothermic peak related to FMT (Figure 5c). The T_gs of FMT/SOL at 20% and 40% loadings were detected at 49.55°C and 48.54°C respectively suggesting plasticization effect of FMT. In contrast, the thermograms of physical mixtures showed distinct FMT melting endotherms shifted at lower temperatures.

The DSC analysis confirmed the predicted Hansen miscibility of the drug–polymer blends by demonstrating the presence of molecularly dispersed drugs within the extruded polymer matrices.

In vitro dissolution studies

The dissolution profiles of INM and FMT from SOL, VA64 and S630 extruded granules are shown in Figure 6a and 6b. The dissolution rates of pure APIs were also investigated to signify the increase of the dissolution rates of the extruded formulations.

Due to its low water solubility, the bulk INM powder showed very slow dissolution rates up to 5% within 5 h. In contrast, the dissolution profiles of INM extruded formulations exhibited enhanced dissolution rates compared to the bulk INM powder as shown in Figure 6b. The extrudates of SOL, VA64 and S630 polymers at 20% INM loading exhibited increased dissolution rates where 30–40% was released in 120 min and 55–70% in 300 min. SOL showed slightly increased released rates compared to VA64 and S630 without significant differences as shown by a Kruskal–Wallis nonparametric test (GraphPad, InStat, Software, CA, USA). Interestingly, the INM loading level was shown to have an effect on the dissolution rates. The drug dissolution rate at high drug loadings tended to increase with an increase in the INM level. This phenomenon was attributed to the plasticization effect of INM on VA64. Therefore, at 40% INM loadings the drug release rate of INM/SOL and INM/VA64 granules was 55–65% in 120 min and 75–80% in 300 min.

FMT demonstrated low dissolution rates of about 22% in 300 min whereas FMT/SOL 20% and FMT/VA64 20% presented about six times faster dissolution rates compared to pure API with more than 70% released within 120 min. The FMT/S630 20% extrudates showed slightly lower dissolution rates compared to the other formulations but significantly higher than the pure active substance. Nevertheless, more than 80% FMT was released from all drug/polymers formulations after 300 min. Similar to INM, the FMT/SOL granules at 40% loading showed faster dissolution rates to the 20% loading which was attributed to the drug's plasticization effect.

Furthermore, the difference of the release profiles of different formulations were investigated by calculating

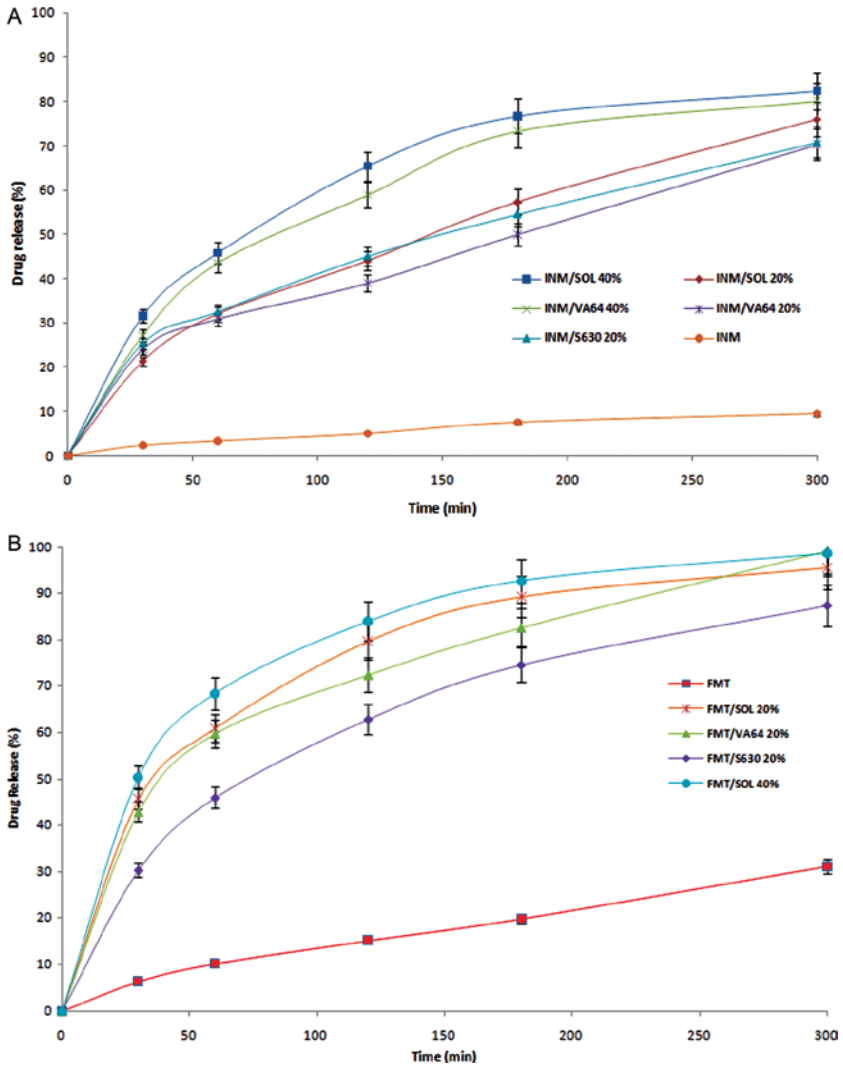

Figure 6. Dissolution studies showing: (A) Drug release profile of pure INM, INM/SOL 20%, INM/VA64 20%, INM/S630 20%, INM/VA64 40% and INM/SOL 40%. INM, indomethacin; SOL, soluplus. (B) Drug release profile of pure FMT, FMT/VA64 20%, FMT/SOL 20% and FMT/S630 20%. FMT, famotidine; SOL, soluplus.

Table 4. Difference factors ($f2$) for comparing release curves with respect to drug loading of INM and FMT formulations.

	Difference factor ($f2$)	
Formulations	INM	FMT
INM/S630 20%	18.67	–
INM/VA64 20%	20.07	–
INM/VA64 40%	13.48	–
INM/SOL 20%	17.91	–
INM/SOL 40%	12.10	–
INM PURE	Ref	–
FMT/S630 20%	–	17.27
FMT/VA64 20%	–	12.72
FMT/SOL 20%	–	11.63
FMT/SOL 40%	–	10.09
FMT PURE	–	Ref

FMT, famotidine; INM, indomethacin; SOL, soluplus.

the difference factors ($f2$). The formulations containing pure APIs differ significantly from that of the active extruded formulations as all of the calculated $f2$ values fall into 10–20.07 range (Table 4).

Conclusions

HME processing has been proved efficient to increase the dissolution rates of two water insoluble drugs. INM and FMT were extruded with SOL, VA64 and S630 at different loadings up to 40% without the presence of traditional plasticizers and optimized to produce solid dispersions of the two drugs.

Further physicochemical characterization studies confirmed the theoretical drug–polymer miscibility for all binary mixtures as predicted by Greenhalgh and Bagley approaches. HME processing facilitated API-polymer interactions and the extruded solid dispersions resulted in greater dissolution rates over the bulk drugs.

Therefore, through the appropriate selection of a polymeric carrier solid dispersions of both INM and FMT can be prepared by HME to improve the dissolution properties of the poorly water-soluble drug. Further work is warranted to determine whether the oral bioavailability of INM/FMT is increased for the solid dispersions with enhanced dissolution characteristics.

Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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