Triboelectrification and dissolution property enhancements of solid dispersions

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Abstract

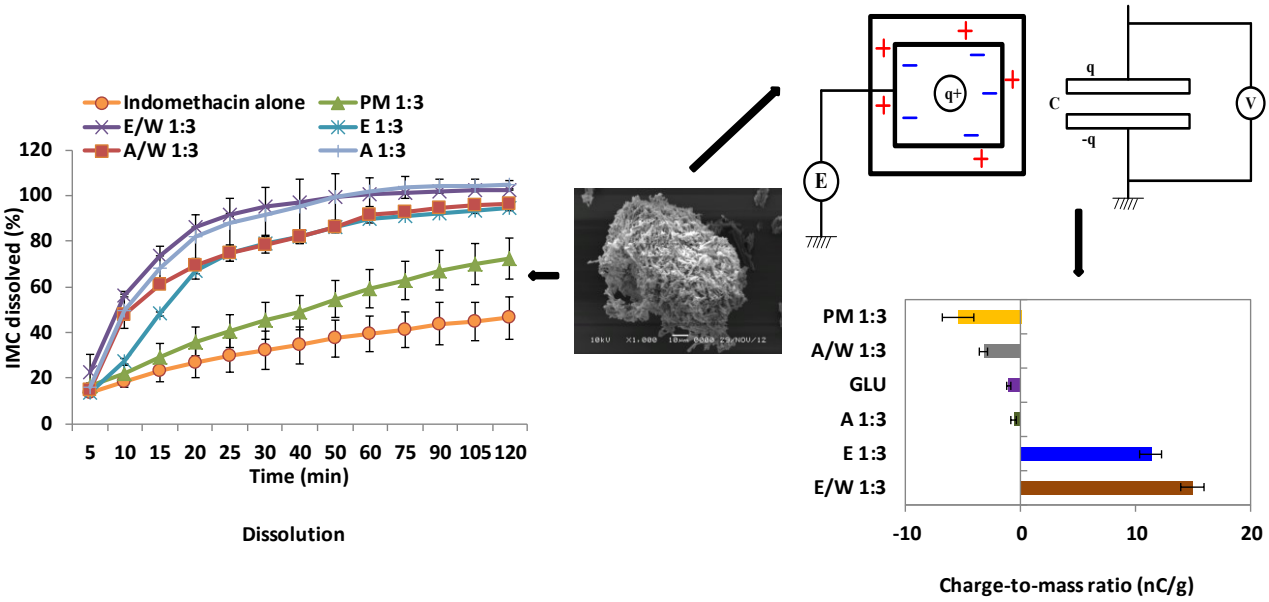
The use of solid dispersion techniques to modify physicochemical properties and improve solubility and dissolution rate may result in alteration to electrostatic properties of particles. Particle triboelectrification, plays an important part in powder processing, affecting end product quality due to particle deposition and powder loss. This study investigates the use of glucosamine hydrochloride (GLU) in solid dispersions with indomethacin. Solvents selected for the preparation of the dispersions were acetone, acetone-water, ethanol and ethanol-water. Solid state characterizations (DSC, FTIR and XRPD) and dissolution were conducted. Dispersions were subjected to charging using a custom built device based on a shaking concept, consisting of a Faraday cup connected to an electrometer. All dispersions improved the dissolution rate of indomethacin. Analysis showed the method of preparation of the dispersion induced polymorphic forms of the drug. Indomethacin had a high propensity for charging (-411 nC/g). GLU had a very low charge (-1 nC/g). All dispersions had low charges (-1 to 14 nC/g). Acetone as a solvent, or in combination with water, produced samples with an electronegative charge in polarity. The same approach with ethanol produced electropositive charging. The results show the selection of solvents can influence powder charge thereby improving powder handling as well as dissolution properties.

Keywords: Electrostatics; Solid dispersions; Triboelectrification; Indomethacin; D-glucosamine HCl; Polymorphism.

Abbreviations: GLU, glucosamine hydrochloride; DSC, differential scanning calorimetry; XRPD, x-ray powder diffraction; FTIR, Fourier transform infra-red; BCS, biopharmaceutical classification system; CBZ, carbamazepine; PXM, piroxicam; IBU, ibuprofen; IND, indomethacin; NSAID, non-steroidal anti-inflammatory drug; A, acetone; A/W, acetone-water; E, ethanol; E/W, ethanol-water; SEM, scanning electron microscopy; DE, dissolution efficiency; MDT, mean dissolution time; MDR, mean dissolution rate; ATR, attenuated total reflection; RH, relative humidity; PSD, particle

size distribution; USP, United States pharmacopeia; PM, physical mixture**; VIBRI, vibratory feeder; HELOS, Helium-Neon laser Optical System.**

Graphical Abstract



Dissolution and tribo-electrification of indomethacin: glucosamine solid dispersions

1. Introduction

Biopharmaceutical Classification System (BCS) class II drugs are characterized by high membrane permeability and low aqueous solubility. This poor aqueous solubility is problematic in pharmaceutical development and seems to be more prevalent with new drug entities (Al-Hamidi et al., 2010a; Baird and Taylor 2012; Fahr and Liu 2007). The solubility and dissolution rate of drugs in this category are key factors in determining their rate and extent of absorption from the gastrointestinal tract. As dissolution rates are typically the rate limiting step for bioavailability, their enhancement is often vital to attaining suitable blood concentrations for therapeutic effect.

There are several methods employed to aid the improvement of the dissolution rate of BCS class II drugs. The most common method involves particle size reduction using high pressure milling methods with the view of increasing the surface area (Rabinow, 2004; Valizadeh et al., 2004). The drawback with this method is the requirement for high energy input. Moreover, the product obtained after such high energy input is likely to increase affinity for electrostatic charging, leading to particle agglomeration and broad particle size distributions. Other methods used include complexation (Loftsson and Duchene, 2007), liquisolid techniques (Javadzadeh et al., 2007; Nokhodchi et al., 2005), salt formation (Berge et al., 1977; David et al., 2012) and solid dispersions (Al-Hamidi et al., 2010a). Despite limitations such as cost and scale up with solid dispersions, adoption of cost-effective solvents along with method modifications can be selected to minimise these.

Solid dispersion formation is one of the most effective methods of improving dissolution and has had much interest in recent years (Al-Hamidi et al., 2010a, Baird and Taylor 2012). The increased solubility and dissolution rate of drugs in solid dispersions could be **the** result of a reduction in particle size down to submicron **(1-100 nm)** levels **(Manikandan et al., 2012)**, conversion from crystalline to amorphous form and the improved wettability of the drug particle by the dissolved hydrophilic carrier (Leuner and Dressman 2000).

Glucosamine is a popular nutritional supplement for both humans and dogs and naturally occurring glucosamine has been shown to decrease pain and improve mobility in osteoarthritic joints of humans when given orally (da Camara and Dowless 1998; Pujalte et al., 1980). The incorporation of glucosamine HCl (GLU) into formulations may give additional benefit to patients requiring anti-inflammatory drugs, due to glucosamine's ability to decrease pain and improve mobility in osteoarthritic joints. Al-Hamidi et al. (2010a) showed it enhanced the dissolution rate of carbamazepine (CBZ) from solid dispersion formulations when used as a hydrophilic carrier. Al Hamidi et al. (2014, 2013, 2010b) also showed that the incorporation of glucosamine in ground piroxicam (PXM), ibuprofen (IBU) or CBZ mixtures co-ground together, significantly increased the dissolution rates of the respective drugs. They also showed that increasing the grinding time resulted in polymorphic transformation of the drugs (CBZ and PXM). Indomethacin (IND) is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs are widely used for rheumatoid arthritis, osteoarthritis and a variety of other acute and chronic musculoskeletal disorders, dysmenorrhea and as ordinary analgesics (Andersson et al., 1998; Montvale 2002). Indomethacin was selected as a model BCS class II compound due to its low solubility to establish the efficiency of the solid dispersion method employed in this work.

The use of solid dispersion techniques to modify physicochemical properties to improve solubility and dissolution rate may also result in changes in the electrostatic properties of particles. Particle triboelectrification plays an important part in powder processing affecting end product quality due to particle deposition and powder loss. It has been shown to give rise to segregation of binary mixtures (Šupuk *et. al.,* 2011); however, very little work has been done to understand electrostatic charging characteristics of powders produced from solid dispersions.

In pharmaceutical processes, triboelectrification refers to a method of particle electrification which can take place during powder handling operations. Such charging can be regarded as a solid state electrochemistry, where there is no transport medium (electrolyte) and their action depends solely on physical contact (Matsusaka et al., 2010). **Although, the exact charge transfer mechanisms in**

dielectric materials are still ambiguous, fundamental studies on charge transfer between an elastic sphere and a metal plate have shown the charge transfer to be completed during the unloading stage of the elastic deformation following the impact (Matsusaka et al., 2000). Therefore, essential pharmaceutical processes such as high-shear granulation are likely to influence the magnitude of charge generated as processing parameters are shown to affect the strength and size distribution of resulting granules (Rahmanian et al., 2008, 2011). Furthermore, pharmaceutical powders are usually insulators and have a relatively small particle size and low bulk density, thus providing ideal conditions for tribo-electric charging (Šupuk et. al., 2012). Supuk et al. (2013) studied the impact of the counter ion on electrostatic charge of flurbiprofen salts. The results showed the magnitude of charge and polarity of the flurbiprofen salts to be highly dependent on the type of counter ion selected for the salt formation. Ghori et al. **(**2014**)** also found cellulose ethers to reduce the charging of flurbiprofen thereby improving its flow and compaction properties.

The objective of this study was to produce indomethacin:glucosamine solid dispersions to investigate the role of solvent (ethanol and acetone and their binary mixtures with water) on dissolution enhancement and electrostatic properties. Triboelectric properties of the solid dispersions were investigated using a custom built tribo-electric device based on a shaking concept. The present work was conducted to determine whether solid dispersions could improve the dissolution profiles and to understand their effect on charging characteristics of the indomethacin-glucosamine dispersions.

2. Materials and Methods

2.1. Materials

Indomethacin (γ-form) and D-(+)-glucosamine hydrochloride (GLU) were purchased from Sigma (UK). The solvents were of analytical grade and all the materials were used as obtained. The

dissolution medium (pH 7.2) was prepared according to the USP 2003 method using the following materials: potassium phosphate monobasic-white crystals and sodium hydroxide (Sigma (UK)).

2.2. Hansen's solubility parameter

The Hansen solubility parameter (δ) was calculated for indomethacin and glucosamine by considering their chemical structure (Hansen 1969). This was used to predict the miscibility of both the drug and carrier. The Hoftyzer-Van Krevelen method described below was used in the determination of the drug/carrier miscibility (Gupta et al., 2011; Hansen 1969; Hoftyzer and Krevelen, 1976; Manniruzziman **et al.,** 2014).

$$\delta_d = \frac{\Sigma F_{di}}{V}, (\textbf{Equation 1}); \quad \delta_p = \frac{(\Sigma F_{pi})^{0.5}}{V}, (\textbf{Equation 2}); \quad \delta_h = (\frac{\Sigma E_{hi}}{V})^{0.5}, (\textbf{Equation 3})$$

and

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2, (\textbf{Equation 4})$$

Where F_{di} and F_{pi} are molar attraction constants due to dispersion **($J^{1/2}.cm^{3/2}.mol^{-1}$)** and polar **($J^{1/2}.cm^{3/2}.mol^{-1}$)** components respectively and E_{hi} is the hydrogen bonding energy **(J/mol)**. δ_d, δ_p and δ_h are the dispersive **($MPa^{1/2}$)**, electrostatic polar **($MPa^{1/2}$)** and hydrogen bonding forces **($MPa^{1/2}$)** respectively with V being the molar volume **(cm^3/mol)**. δ_t is known as the total solubility parameter also known as the Hansen solubility parameter. The molar volume of the drug and carrier were calculated based on their density and molecular weight, as determined from literature.

2.3. Preparation of physical mixtures of drug-carrier

Physical mixtures of indomethacin were prepared by mixing indomethacin and D-(+)-glucosamine hydrochloride in a Turbula blender (Type T2 C, Switzerland) for 10 min. Different ratios of

drug:carrier (2:1, 1:3, 1:5 and 1:10) were prepared for comparison. The powders were stored in screw-capped glass vials in a desiccator until required after the mixing process.

2.4. Preparation of solid dispersions of drug-carrier

The conventional solvent evaporation technique was employed in the preparation of the different ratios of drug to carrier (2:1, 1:3, 1:5 and 1:10). The drug was dissolved in either acetone (A) or ethanol (E) (30 ml) followed by the dispersion of GLU at appropriate amounts. The solvents were removed during continuous stirring at 200 rpm at 40 ^{o}C for 24 hours. A second technique used involved dissolving the drug in 20 ml of solvent (either acetone or ethanol) and the carrier in 10 ml of water (abbreviations used are A/W for acetone and water binary mixture and E/W for ethanol and water binary mixture). The carrier solution was then added to the drug solution under the same conditions described previously until the dry solid dispersions were obtained. The dispersions obtained were again stored in a desiccator until required.

2.5. Electrostatic properties of physical mixture and solid dispersions

A triboelectric device based on a shaking concept, previously described by Šupuk and co-workers (2009) and detailed elsewhere (Asare-Addo et al., 2013a; Supuk et al., 2013), was used to investigate the triboelectrification of drug, glucosamine and solid dispersion powders by determining the charge-to-mass ratio. In this work, the charge-to-mass ratio of drug, glucosamine and solid dispersion powders was measured following shaking using a custom made Faraday cup connected to an electrometer (Keithley Model 6514).

In brief, a 100 mg indomethacin-glucosamine sample was weighed and initial charge (at time 0 min) obtained using the Faraday cup and an electrometer. The sample was then placed inside a stainless steel container and subjected to shaking for a predetermined time (0.5, 2, 5 or 10 minutes) at 20 Hz to induce the triboelectrification effect. The final charge and polarity post tribo-electrification were measured by the Faraday cup and an electrometer. The container was then

tapped to remove any particles adhered to the walls. The weight of the sample was measured to account for mass loss to the container walls due to adhesion. Tests were carried out under ambient temperature (22 ± 1ºC) and relative humidity of 35-47 %RH.

2.6. Solid State Studies

Particle Size Analysis

The Sympatec laser diffraction particle size analyser (Clausthal-Zellerfeld, Germany) was used in the determination of the particle size distribution of the formulations. The procedure was as follows: about 2‑3 g of the sample was transferred into the funnel of the VIBRI **(vibratory feeder)**. The sample container was cautiously tapped against the funnel to ensure all the content was transferred. A test reference measurement was performed with the **Helium-Neon laser Optical System (**HELOS**) (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany)** sensor using WINDOX software **(version 5.4.0.0, Sympatec GmbH, Clausthal-Zellerfeld, Germany)** followed by a standard measurement.

Scanning electron microscopy (SEM)

Electron micrographs were obtained using a scanning electron microscope (Jeol JSM-6060CV SEM) operating at 10 kV. The samples were mounted on a metal stub with double-sided adhesive tape and were sputter-coated with an ultra-thin coating of gold/palladium (80:20) for 60 s using a Quorum SC7620 Sputter Coater under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were taken to facilitate the study of the morphology of the solid dispersions.

Fourier transform infrared (FTIR)

A 5-10 mg sample of drug, carrier and solid dispersions (ratio 1:3 in acetone and in ethanol) and those of the binary mixtures (acetone and water or ethanol and water) were placed on an Attenuated Total Reflection (ATR) plate and analysed using FTIR spectroscopy (Nicolet 380 FT-IR spectrometer, ThermoElectron Corporation, USA). All samples were analysed by measuring the transmittance of infrared wavelengths of the electromagnetic spectrum of the sample in the range of 400–4000 cm^{-1}.

Differential scanning calorimetry (DSC)

Samples of solid dispersions or physical mixtures of drug:carrier (3-6 mg) was placed in standard aluminium pans (40 µL) with a vented lid. The crimped aluminium pans were heated from 20 to 250 ˚C at a scanning rate of 10 °C/min using nitrogen gas as a purge gas in a DSC 1 (Mettler-Toledo, Switzerland). The enthalpy, onset temperatures and melting points of the samples were obtained using the software provided.

X-ray powder diffraction (XRPD)

The XRPD patterns of pure indomethacin, glucosamine and indomethacin-glucosamine solid dispersions were obtained using a Bruker D2 Phaser XRPD diffractometer. The samples were scanned from 5° to 100° 2 θ at a rate of 1.5° min^{-1}.

2.7. Dissolution studies

USP dissolution apparatus I was used to monitor the dissolution profiles of indomethacin, indomethacin-glucosamine physical mixtures and solid dispersions. All formulations for the dissolution process contained the same amount of indomethacin (25 mg). The powder samples, after weighing, were introduced into the dissolution basket. The baskets had filter paper placed at the base to prevent the powder falling through the pores of the basket. The dissolution medium was a pH 7.2 buffer (900 mL) equilibrated to 37 °C ± 0.5 °C. The baskets were rotated at 50 rpm.

Samples were withdrawn at selected time intervals (5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105 and 120 min) using a peristaltic pump and the concentrations of indomethacin in the samples determined by UV spectrophotometer at 318 nm. All dissolution tests were carried out in triplicate.

2.8. Dissolution parameters

As an independent metric, the mean percentage of drug dissolved in the first 10 min (Q_{10min}) and 30 min (Q_{30min}) were used to represent the dissolution rate from various preparations. The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to the time, *t*, expressed as the percentage of the area of the rectangle (Khan, 1975) as detailed elsewhere (Asare-Addo et al., 2013b; Siahi-Shadbad et al., 2011).

$$\text{DE (\%)} = \frac{\int_0^t y\,dt}{y_{100}\,t} \times 100 \quad \textbf{(Equation 5)}$$

where *y* is the percentage **(%)** of drug dissolved at time *t* **(min)**.

Another approach to obtain a parameter that describes the dissolution rate is the mean dissolution time (MDT). This parameter is the most likely time taken for a molecule to be dissolved from a solid dosage form. In other words, MDT is the mean time for the drug to dissolve under *in vitro* dissolution conditions and is calculated using the following equation:

$$\text{MDT (min)} = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad \textbf{(Equation 6)}$$

where *j* is the sample number, t_j is the midpoint of the *j*th time period (calculated with ((t + t-1)/2) and ΔM_j is the additional amount of drug dissolved between t_j and t-1.

The mean dissolution rate (MDR) can be calculated according to the following equations:

$$\text{MDR } (\%\text{min}^{-1}) = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n} \quad \textbf{(Equation 7)}$$

where n is the number of dissolution sample times, Δt is the time at the midpoint between t and t-1 (easily calculated with $[t + (t\text{-}1)/2]$.

3. RESULTS AND DISCUSSION

3.1. Solubility parameters and SEM

The Hansen solubility parameter was estimated using the Hoftyzer-Van Krevelen approach to predict the miscibility of indomethacin and glucosamine (Table 1). Several other authors have used this method in predicting the miscibility of drugs and excipients (Forster et al., 2001; Greenhalgh et al., 1999; Hancock et al., 1997; Manniruzziman et al 2014; Suzuki and Sanada, 1997). Compounds with similar values of δ or $\Delta\delta < 7$ $MPa^{1/2}$ are likely to be miscible with compound with $\Delta\delta > 10$ $MPa^{1/2}$ immiscible (Forster et al., 2001). The Δδ value obtained for indomethacin and glucosamine was 15.93 $MPa^{1/2}$ suggesting that the two components were immiscible. This further evidenced in the SEM images in Figure 1(d and g) where indomethacin particles can be seen in pockets or adhering to the surfaces of glucosamine.

3.2. Solid state studies of solid dispersions and physical mixtures

FTIR spectra for indomethacin samples are shown in Figure 2. It has been shown that indomethacin has two monotropic polymorphs, γ (which is the most stable form) and α (which is a metastable form) (Borka 1974; Yamamoto, 1968). FTIR spectroscopy was carried out on several formulations to ascertain whether any possible structural changes occurred at the molecular level. According to

existing literature, the most characteristic difference between the two main polymorphic forms of indomethacin is at the 1700 cm^{-1} region, where CO-bonds shift within the spectrum of each polymorph (Greco and Bogner, 2010). This suggested involvement of the carbonyl group in different types of hydrogen bonds in the establishment of the crystal lattice of the two structures. The spectrum of commercial untreated indomethacin proves the characteristic bands of the drug at 3000 cm^{-1} (aromatic C-H stretch), 1719 cm^{-1} (ketone C=O stretch), 1593 cm^{-1} (aromatic C=C stretch), 1457 cm^{-1} (O-CH_3 deformation), 1230 cm^{-1} (C-O stretch plus O-H deformation), 927 cm^{-1} (carboxylic O-H deformation), and 754 cm^{-1} (C-Cl vibration). The solid dispersion of indomethacin:glucosamine prepared from ethanol/water exhibited similar IR spectra to untreated indomethacin (Figure 2e). The same peaks at the same wavenumbers are seen for untreated indomethacin while solid dispersions prepared from acetone, ethanol and acetone/water exhibited different IR spectra. This indicates that the solid dispersions prepared from ethanol/water were not associated with changes at the molecular level, whereas extra bands between 1600 and 1800 cm^{-1} appeared for the solid dispersions prepared from acetone, ethanol and acetone/water (Figure 2). It has been shown that α-form exhibits absorption events at 1735, 1688, 1681 and 1649 cm^{-1}, whereas γ-form shows bands at 1717 and 1692 cm^{-1}. In case of the presence of amorphous form, two bands at 1710 and 1684 should appear (Taylor and Zografi, 1997). FT-IR results showed that solid dispersions prepared from acetone, ethanol and acetone/water are mixtures of α and γ forms.

To confirm the results obtained by FTIR, XRPD was carried out on **pure** indomethacin, solid dispersions of indomethacin-glucosamine prepared from the different solvents and the physical mixtures of indomethacin-glucosamine HCl. The results are presented in Figure 3. It has been shown that major distinctive peaks for identification of γ-form are 11.6, 16.8, 19.6, 21.8 and 26.6° 2θ, whereas these 2θ for α-form are 8.4, 14.4, 18.5 and 22°. The peaks shown in Figure 3 indicate that the pure indomethacin is γ-indomethacin. These spectra are in agreement with the corresponding polymorph reported elsewhere (Kaneniwa *et al.,* 1985; Okumura *et al.,* 2006). The

presence of some peaks relating to the γ-form in the solid dispersion samples prepared from acetone, ethanol and acetone/water is indicative of the formation of mixtures of γ- and α- forms.

DSC can be used to reflect miscibility by a shift in the melting endotherm of drug, glass transition temperature changes for amorphous systems or both as reported by several authors (Ford and Timmins 1987; Gupta et al., 2011; Mura et al., 1998; Shamblin et al., 1998) and can be used to identify different polymorphs of indomethacin (Crowley and Zografi 2002). Figure 4 depicts the DSC traces of indomethacin, its physical mixture with glucosamine and solid dispersions of indomethacin:glucosamine at scanning rate of 10 ºC/min for the 1:3 ratio. Indomethacin displayed an endothermic peak at ~161.26 ºC corresponding to its melting point. Glucosamine melted at ~210 ºC and the DSC traces for the physical mixture of indomethacin and glucosamine showed no changes in their thermal behaviour (Figure 4). The same was observed for the solid dispersion sample prepared from ethanol/water. This was similar to the results obtained by FTIR or XRPD. Figure 4 shows the sharp endothermic peak at ~210 ºC corresponding to the melting of glucosamine for all formulations indicating immiscibility. The absence of any melting point depression was expected due to the immiscible nature of the solid dispersions as the chemical potential of the indomethacin remained unchanged or unaltered in the glucosamine (Gupta et al., 2011). This was true for all the ratios of the drug studied. The results also showed that in the case of solid dispersions prepared from acetone, ethanol and acetone/water, an extra endothermic peak was observed before the main endothermic transformation for the γ-form (Figure 4). This small peak around 154 ºC is an indication of the presence of α-form of indomethacin as a result of the solvent used. This polymorphic form could impact dissolution (covered under dissolution section) and triboelectrification.

3.3 Triboelectrification studies

The triboelectrification results showed pure indomethacin to have a great propensity for tribo-electric charging (-411 nC/g) and a resulting particle adhesion to stainless steel wall (82 %) (Figures

5 and 6). Pure glucosamine had practically no charge (-1 nC/g). The net charging behaviour of the physical mixture, and all the solid dispersions of indomethacin:glucosamine, was shown to be low regardless of the type of solvent used or the method used in generating the solid dispersions. The low net charge of the physical mixture (-5 nC/g) implied ordered mixing so that particles of opposite charges adhered to each other. This also shows glucosamine's potential to reduce the high charge of indomethacin thereby improving its handling. The results also showed that acetone as a solvent, or in combination with water, produced samples with a charge that was electro negative in polarity. On the other hand, when ethanol was used with the same approach, the polarity of charge was electro positive (Figure 5). The net charges of the resultant solid dispersions were however slightly increased when water was used as a binary solvent for both acetone and ethanol. The results suggest that one can manipulate the charge of solid dispersions, depending on the solvent used, to improve triboelectrification properties. The mass loss of all samples tested was shown to be low regardless of the type of solvent (Figure 6). The lowest level of net charge, and particle adhesion, of the solid dispersions tested was obtained when acetone was used as a single solvent. As a result, further work is in progress to analyse the effect of different solvents and solvent mixture compositions in generating solid dispersions on the electrostatic properties of other drug-glucosamine dispersions (with other carriers being investigated to determine if this phenomenon occurs with both miscible and immiscible systems).

3.4. Dissolution studies

Indomethcin:glucosamine solid dispersions, prepared under different conditions, were subjected to dissolution testing and the results are shown in Figs. 7–10, according to the type of solvent used during the preparation of solid dispersion formulations. The solvents used have differ**ent** polarity which can be ranked as follows: ethanol:water (2:1) > ethanol > acetone:water (2:1) > acetone. The dissolution behaviour of pure IND and IND solid dispersions prepared with GLU using acetone (A) as the solvent are shown in Figure 7. It is clear that the IND has the slowest dissolution and all solid

dispersions have a higher dissolution. Despite the prediction of immiscibility from the Hansen solubility parameters, all solid dispersions produced had a significant impact on dissolution compared to IND alone or their physical mixture counterparts. The dissolution parameters for the solid dispersions of indomethacin are shown in Table 2. Increasing the contribution of carrier from 2:1 to 1:10 (indomethacin:G-HCl) did not induce any significant dissolution enhancement, as Q_{30min}, DE_{120min}, MDT, and MDR had not changed significantly (ANOVA-test, $p > 0.05$). This indicates that the ratio of drug to carrier in the solid dispersion is not one of the main parameters controlling the performance of these solid dispersions, and a direct relationship between the amount of carrier and indomethacin dissolution could not be established.

The dissolution profiles of solid dispersions using ethanol with various ratios of drug to carrier are shown in Figure 8. The highest dissolution was observed at higher concentration of carrier (drug to carrier 1:3, 1:5 and 1:10). No further improvement in dissolution of indomethacin occurred when the amount of carrier was increased from 75 % (ratio of drug to carrier 1:3) to 90.9 % (ratio of drug:carrier 1:10) (Figure 7 and 8). By comparing the solid dispersions samples produced from acetone (Figure 7), with the samples prepared from ethanol (Figure 2), there is no significant difference observed in the dissolution of indomethacin when a high concentration of carrier used (1:5 or 1:10). When the amount of carrier used was further reduced (2:1 and 1:3), solid dispersion samples produced from acetone dissolved faster than the solid dispersion samples produced from ethanol.

At high concentrations of glucosamine, solubility issues meant that it was difficult to dissolve all of the glucosamine in acetone or ethanol for preparation of solid dispersion. Water was incorporated in the preparation of solid dispersion samples to improve solubility as glucosamine has a high solubility in water (320 mg/mL). To prepare this solvent combination, IND was dissolved in acetone or ethanol and GLU was dissolved in water (for more details refer to preparation of solid dispersions). The dissolution behaviours of indomethacin from these solid dispersions prepared

from binary mixtures of A/W and E/W are shown in Figures 9 and 10, respectively. In contrast to solid dispersions samples produced from single solvent (Figures 9 and 10), those prepared using binary solvents generally had their highest dissolution observed at higher concentration of carrier (drug to carrier 1:10), particularly evident for those produced using E/W (Figures 9 and 10). The dissolution of indomethacin from physical mixtures showed that, like solid dispersion formulations, the presence of glucosamine significantly increased the dissolution of indomethacin (Figure 11). The fastest dissolution for physical mixtures of indomethacin:glucosamine was observed when the ratio of drug:carrier was 1:10, but was not as enhanced as equivalent solid dispersions, as demonstrated by the DE values in Table 2. The use of the various solvents induced polymorphic transformations in some of the solid dispersion samples (A, A/W and E). Hancock and Parks, (1999) studied the solubility of the different polymorphic forms of indomethacin by inducing the metastable α-polymorph of indomethacin from its stable γ-polymorph by precipitation from saturated methanol solution with water. They showed the α-polymorph to have an improved solubility over the stable γ-polymorph. This shows that the formation of the metastable polymorphic may have also contributed to the dissolution enhancement of the solid dispersions.

To facilitate comparison between solid dispersion and physical mixtures and identification of the optimal solvent to prepare indomethacin solid dispersions, DE, MDT and MDR were calculated (Table 2). Solubility parameters were not useful in predicting the miscibility of the IND and GLU in the solvent systems. For example, the solubility parameters suggested IND to be soluble in water and GLU not to be soluble in water. The results however from Table 2 clearly show that the highest dissolution efficiency belongs to the samples prepared from acetone at a ratio of drug to carrier of 1:3. For the binary solvent solid dispersions, when the ratio of glucosamine was increased, a significant increase in dissolution rate of drug was observed (the higher DE and MDR or the lowest MDT). Therefore, for the solid dispersions prepared using binary solvents, a high concentration of carrier should be used to enhance the dissolution of indomethacin. Generally, the dissolution of

indomethacin is faster from solid dispersion samples produced in the presence of binary solvents. However, interesting results were obtained when differences in DE were calculated between solid dispersion formulations prepared in the presence of acetone or ethanol with those prepared in the presence of additional solvent (water) at the same ratio of indomethacin:carrier. These results showed that the difference reduces as the contribution of carrier in the solid dispersion increases. For example, when the ratio of indomethacin:carrier was 2:1, the difference in DE between solid dispersion produced in presence of acetone and acetone:water was +8.9%, whereas at the ratio of 1:10 this difference was reduced to -9.5%, while in case of ethanol and ethanol/water it increased from -27.5 to -11.5 % (Figure 12). This indicated that in order to increase the dissolution of indomethacin from solid dispersions prepared from acetone-water or ethanol-water, the contribution of carrier should be high. Independent dissolution parameters (DE, MDR and MDT) usually give an overview of the dissolution of a sample throughout the dissolution process, but they do not give an insight into the dissolution changes for each time interval. Therefore, Q_{10min} and Q_{30min} (percent drug dissolved within 10 and 30 minutes respectively) were calculated (Table 2).

From Table 2 it is evident that the dissolution of pure indomethacin is very low (less than 32 % within 30 min). It can be concluded that all solid dispersions of indomethacin-glucosamine showed considerable enhancement in dissolution compared to the physical mixtures. However, the dissolution of all physical mixtures was higher compared to pure indomethacin. Possible explanations of the increased dissolution rate of solid dispersions have been proposed by Ford (1986) and Craig (2002) and include: reduction of drug crystallite size (Table 3, Figure 1 (e and f) as evidenced in the SEM images); a solubilisation effect of the carrier; absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug; dissolution of the drug in the hydrophilic carrier; inhibition of fine particle aggregation; conversion of the drug to the amorphous state; and finally a combination of the above mentioned mechanisms.

Table 2 again shows that in the first 10 min of the dissolution run, solid dispersion samples prepared from ethanol/water with ratio of 1:5 produced the fastest dissolution. This is similar to the

DE data reported in the same table. When the dissolution data was compared for 30 min dissolution (Q_{30min}), the same ratio 1:5 had the fastest dissolution.

4. CONCLUSIONS

Despite the solubility parameters predicting immiscibility of IND with GLU, the use of GLU had significant impact on the triboelectrification and dissolution properties of the dispersion formed. GLU significantly enhanced the dissolution rate of indomethacin formulated as solid dispersions. The type of solvent used also influenced the rate of dissolution of the solid dispersion, with solid state characterization also showing that the method used in producing the solid dispersion had an effect on inducing different polymorphic forms of the parent drug. Triboelectrification showed indomethacin to have a high propensity for charging with glucosamine having practically no charge and being able to form ordered mixtures in its PMs resulting in the PMs of drug and carrier having a very low charge. The solid dispersions also exhibited very low net charges with an interesting phenomenon observed regarding its charging. Dispersions made from acetone or acetone/water mix had an electronegative charge with dispersions from ethanol or ethanol/water displaying electropositive charging. As a result of these findings, further studies are being carried out simultaneously investigating several solvent effects on solid dispersion charging (also investigating polymorphic form contribution to charging as this was outside the scope of this study) and dissolution improvement.

5. ACKNOWLEDGEMENTS

The authors would like to acknowledge the University of Huddersfield for financial support and Nyasha Chawira and Hamzah Ali for performing the dissolution experiments.

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Table 1. Calculated Hansen solubility parameters for indomethacin and glucosamine

Sample	δ_d (MPa$^{1/2}$)	δ_p (MPa$^{1/2}$)	δ_h (MPa$^{1/2}$)	δ_t (MPa$^{1/2}$)	$\Delta\delta$
IND	18.82	5.06	8.68	21.30	-
GLU	16.49	17.79	28.24	37.23	15.93

Table 2. Solvent type and its effects on the dissolution parameters of solid dispersions and physical mixtures (mean ± SD, $n \geq 3$).

IND:GLU	Solvent	DE_{120min} (%)	MDT (min)	MDR (% min^{-1})	Q_{10min} (%)	Q_{30min} (%)
IND		36.01	21.24	0.37	18.5 ± 2.2	32.2 ± 8.1
PM 2:1	-	48.36	27.40	0.54	16.6 ± 0.2	37.6 ± 5.5
PM 1:3	-	53.26	24.38	0.60	22.1 ± 3.4	45.3 ± 8.0
PM 1:5	-	46.06	24.47	0.50	18.9 ± 0.5	38.4 ± 5.0
PM 1:10	-	56.36	22.58	0.71	26.0 ± 2.7	50.7 ± 2.1
E 2:1	Ethanol	54.51	27.37	0.66	17.8 ± 2.3	42.2 ± 3.4
E 1:3	Ethanol	78.51	17.99	1.11	27.5 ± 0.9	79.3 ± 3.4
E 1:5	Ethanol	80.95	17.99	1.10	38.8 ± 0.0	78.7 ± 0.0
E 1:10	Ethanol	84.11	18.68	1.15	43.2 ± 7.8	79.5 ± 15.3
E/W 2:1	Ethanol/water	82.03	16.85	1.13	41.6 ± 4.9	81.4 ± 3.0
E/W 1:3	Ethanol/water	91.22	12.52	1.16	56.1 ± 0.5	95.0 ± 0.5
E/W 1:5	Ethanol/water	94.54	8.10	1.17	78.8 ± 0.0	99.6 ± 0.0
E/W 1:10	Ethanol/water	95.65	9.29	1.28	74.5 ± 0.0	100.00 ± 0.0
A 2:1	Acetone	88.54	16.27	1.11	47.8 ± 0.0	87.6 ± 0.0
A 1:3	Acetone	90.85	15.46	1.26	49.7 ± 0.0	91.7 ± 0.0
A 1:5	Acetone	85.59	15.28	1.21	44.7 ± 6.7	88.1 ± 5.6
A 1:10	Acetone	81.58	16.00	1.10	52.7 ± 8.4	80.2 ± 9.1
A/W 2:1	Acetone/water	79.63	18.31	1.10	35.3 ± 3.0	78.3 ± 5.3
A/W 1:3	Acetone/water	81.10	17.42	1.10	47.7 ± 8.1	78.6 ± 11.8
A/W 1:5	Acetone/water	77.88	20.48	1.03	39.5 ± 1.4	71.3 ± 0.3
A/W 1:10	Acetone/water	91.69	14.02	1.30	57.1 ± 2.5	96.5 ± 7.1

PM = Physical mixture of drug and carrier

Table 3. Particle size analysis of physical mixtures and solid dispersion samples of indomethacin and glucosamine

IND:GLU	Solvent	$D_{10\%}$ (μm)	$D_{50\%}$ (μm)	$D_{90\%}$ (μm)
IND	-	5.11	27.11	127.38
GLU	-	36.20	252.30	518.39
PM 2:1	-	6.26	39.54	284.80
PM 1:3	-	6.74	53.23	224.62
PM 1:5	-	7.47	58.29	210.9
PM 1:10	-	30.98	438.44	790.28
E 2:1	Ethanol	2.16	12.72	232.69
E 1:3	Ethanol	2.57	20.28	220.45
E 1:5	Ethanol	6.47	62.17	343.81
E 1:10	Ethanol	3.68	24.14	136.61
E/W 2:1	Ethanol/water	1.9	9.82	63.65
E/W 1:3	Ethanol/water	2.72	24.04	183.56
E/W 1:5	Ethanol/water	2.79	25.89	179.74
E/W 1:10	Ethanol/water	2.54	25.65	158.34
A 2:1	Acetone	2.07	12.33	188.03
A 1:3	Acetone	6.09	542.32	808.05
A 1:5	Acetone	3.97	22.8	147.81
A 1:10	Acetone	6.12	84.4	365.72
A/W 2:1	Acetone/water	2.80	19.57	145.65
A/W 1:3	Acetone/water	2.33	18.73	213.91
A/W 1:5	Acetone/water	2.33	14.18	66.66
A/W 1:10	Acetone/water	3.85	42.19	330.8

Figure 1. SEM images of a) indomethacin, b) glucosamine HCl, c) physical mixture of indomethacin-DG (1:3) and solid dispersion of indomethacin:glucosamine HCl (1:3) d) acetone, e) ethanol, f) acetone and water, g) ethanol and water. All images are at the same magnification (x500 with scale bar indicating 50 μm). IND = indomethacin. GLU = glucosamine.

Figure 2. FT-IR spectra of glucosamine, indomethacin and solid dispersions of indomethacin:glucosamine of ration 1:3, a) glucosamine, b) indomethacin and solid dispersions from c) ethanol 1:3, d) acetone 1:3, e) ethanol in water 1:3, f) acetone in water.

Figure 3. XRPD pattern of the unprocessed Indomethcin, solid dispersions and physical mixtures (PM) of indomethacin:glucosamine ratio 1:3 and solid dispersions of indomethacin:glucosamine prepared from ethanol (E), ethanol/water (E/W), acetone (A) and acetone/water (A/W) ratio 1:3.

Figure 4. DSC traces of glucosamine ; indomethacin; physical mixture (PM) of indomethacin-glucosamine and solid dispersions of indomethacin:glucosamine prepared from ethanol (E), ethanol/water (E/W), acetone (A) and acetone/water (A/W) ratio 1:3.

Figure 5. Specific charge and polarity for unprocessed indomethacin (IND), glucosamine (GLU), physical mixture (PM) of indomethacin-glucosamine and solid dispersions of indomethacin:glucosamine prepared from ethanol (E), ethanol/water (E/W), acetone (A) and acetone/water (A/W) all with ratio 1:3.

Figure 6. Percentage of mass loss for unprocessed indomethacin (IND), glucosamine, (GLU), physical mixture (PM) of indomethacin-glucosamine and solid dispersions of indomethacin:glucosamine prepared from ethanol (E), ethanol/water (E/W), acetone (A) and acetone/water (A/W) all with ratio 1:3 against stainless steel surface after charging.

Figure 7. Dissolution profiles of indomethacin–glucosamine HCl solid dispersions with different ratios of drug:carrier where acetone (A) used as solvent (data are mean and standard deviations of three determinations).

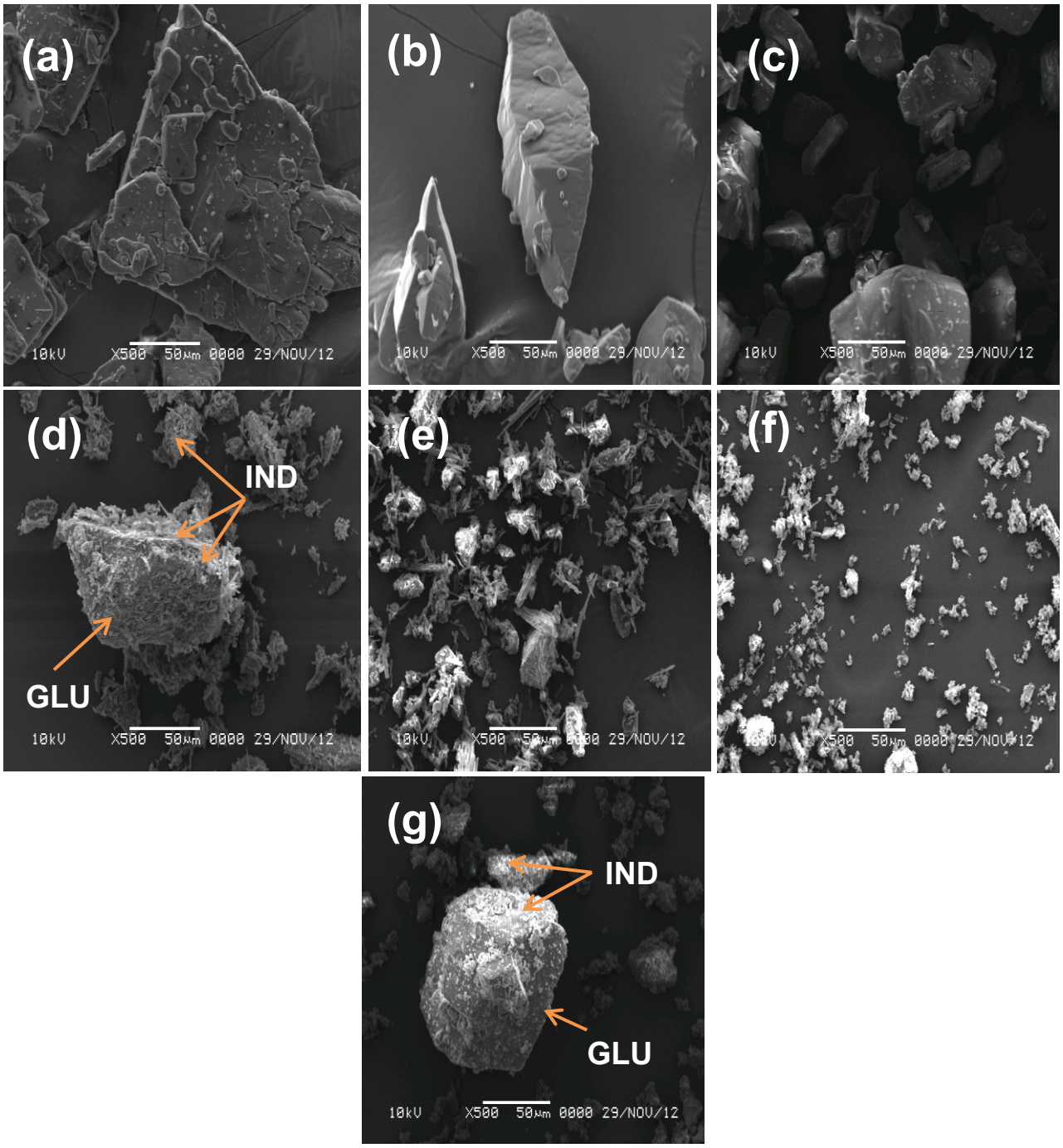
Figure 8. Dissolution profiles of indomethacin–glucosamine HCl solid dispersions with different ratios of drug:carrier where ethanol (E) used as solvent (data are mean and standard deviations of three determinations).

Figure 9. Dissolution profiles of indomethacin–glucosamine HCl solid dispersions made from binary mixtures of acetone–water (A/W) with different ratios of drug:carrier where acetone–water (A/W) used as solvent (data are mean and standard deviations of three determinations).

Figure 10. Dissolution profiles of indomethacin–glucosamine HCl solid dispersions made from binary mixtures of ethanol–water (E/W) with different ratios of drug:carrier where ethanol–water (E/W) used as solvent (data are mean and standard deviations of three determinations).

Figure 11. Dissolution profiles of indomethacin from physical mixtures (PM) with different ratios of drug–glucosamine (data are mean and standard deviations of three determinations).

Figure 12. Relationship between the differences in dissolution efficiency of solid dispersion produced from single solvent and binary solvents and amount of carrier in the formulation.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(e)
10kV X500 50µm 0000 29/NOV/12
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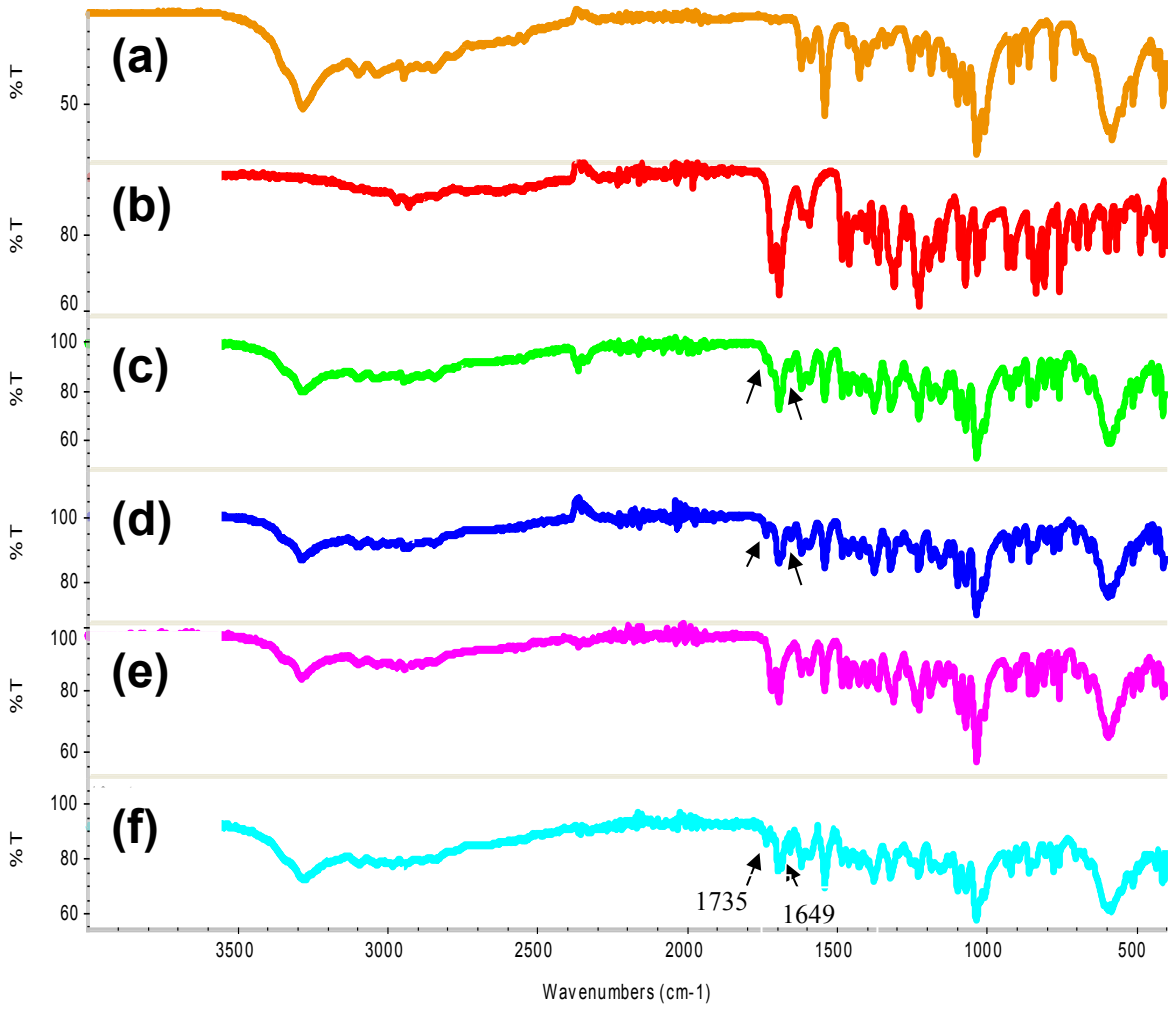
Figure 1.


(a)
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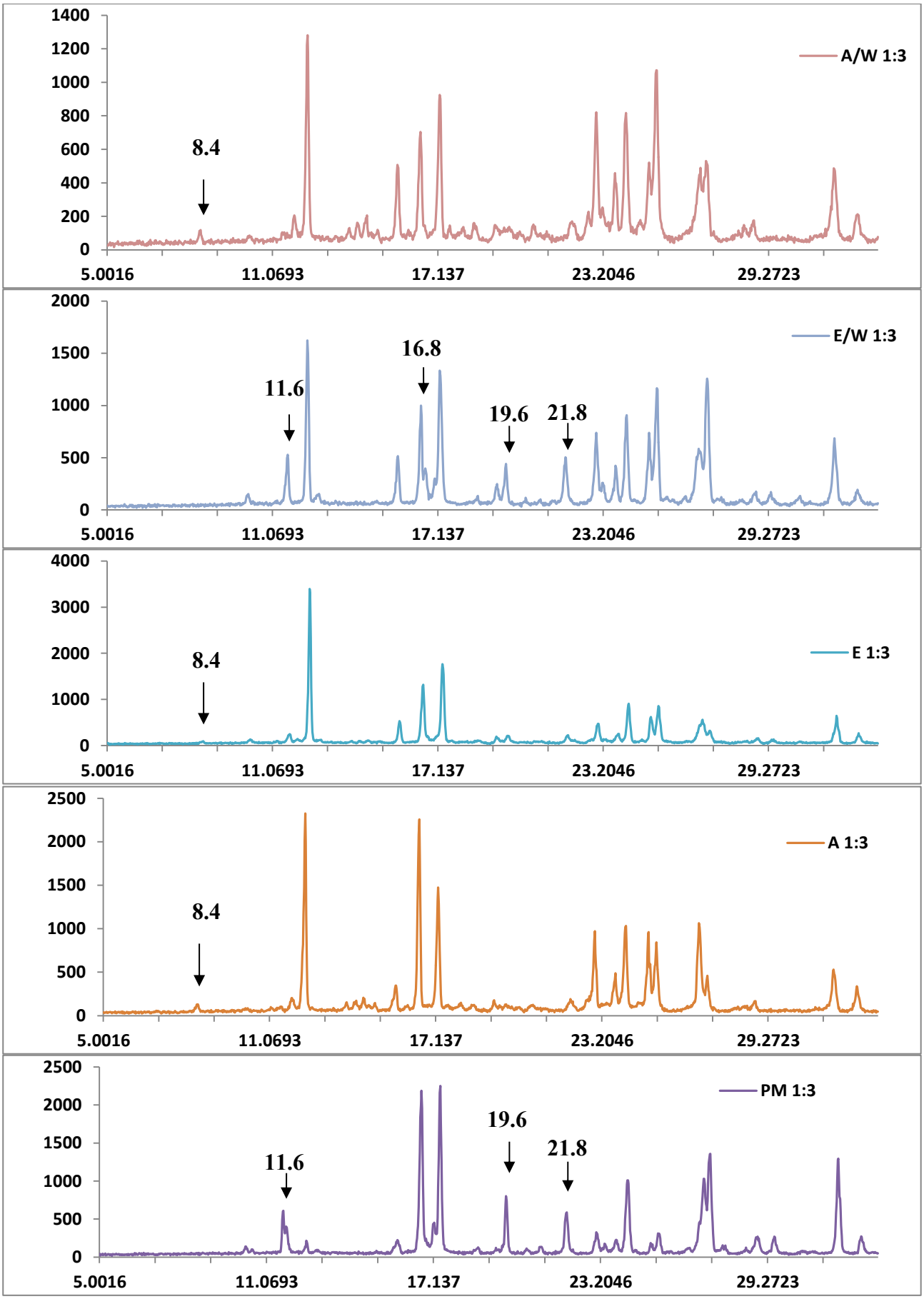
Wavenumbers (cm-1)

Figure 2.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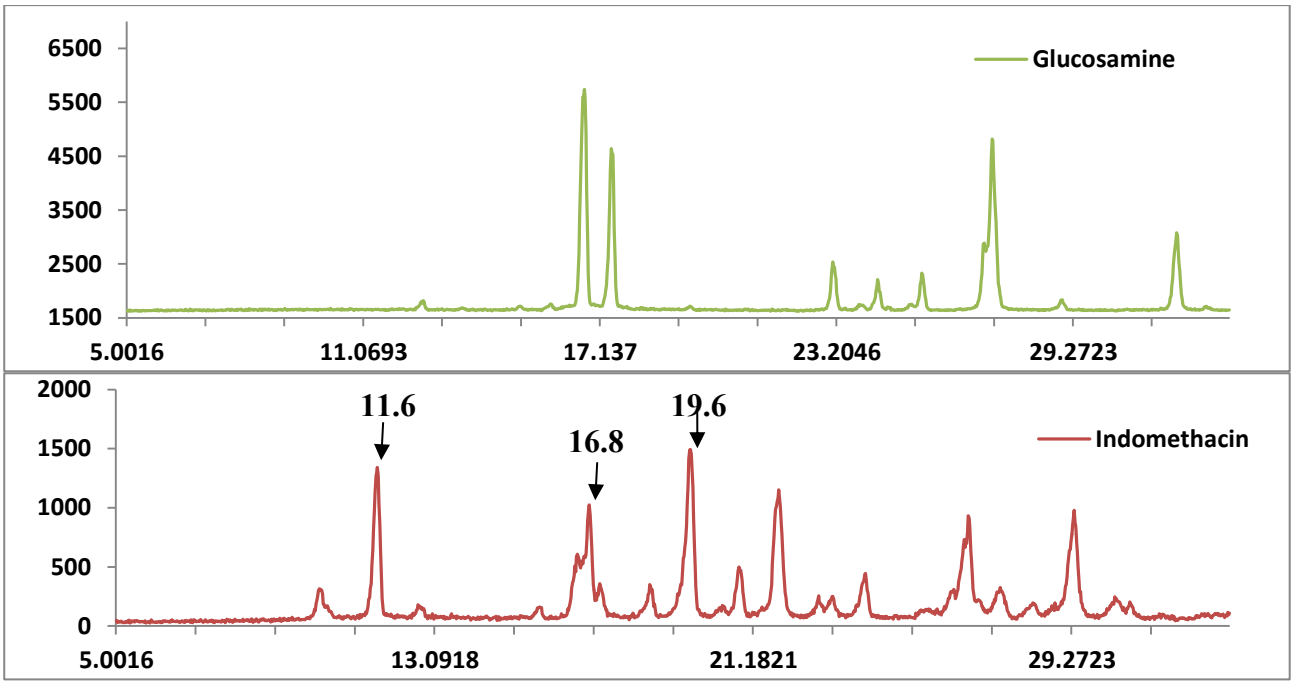
29.2723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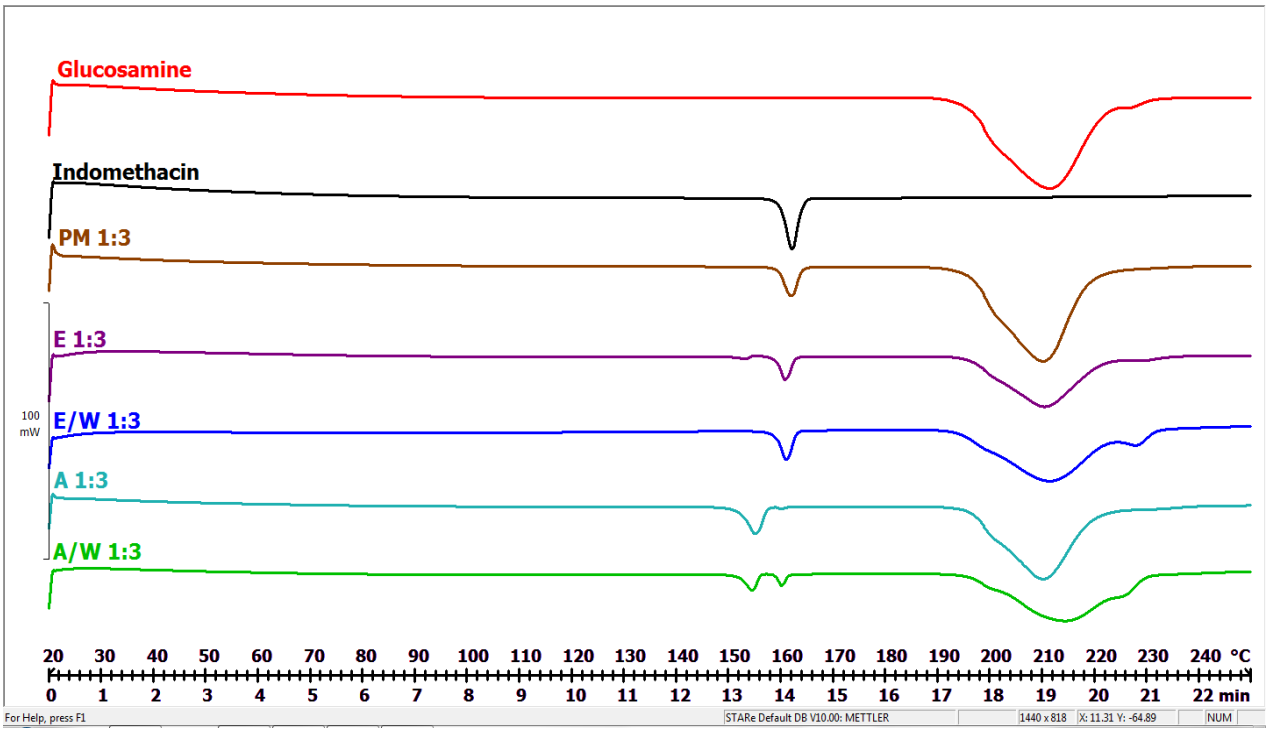
Indomethacin

Figure 3.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Indomethacin
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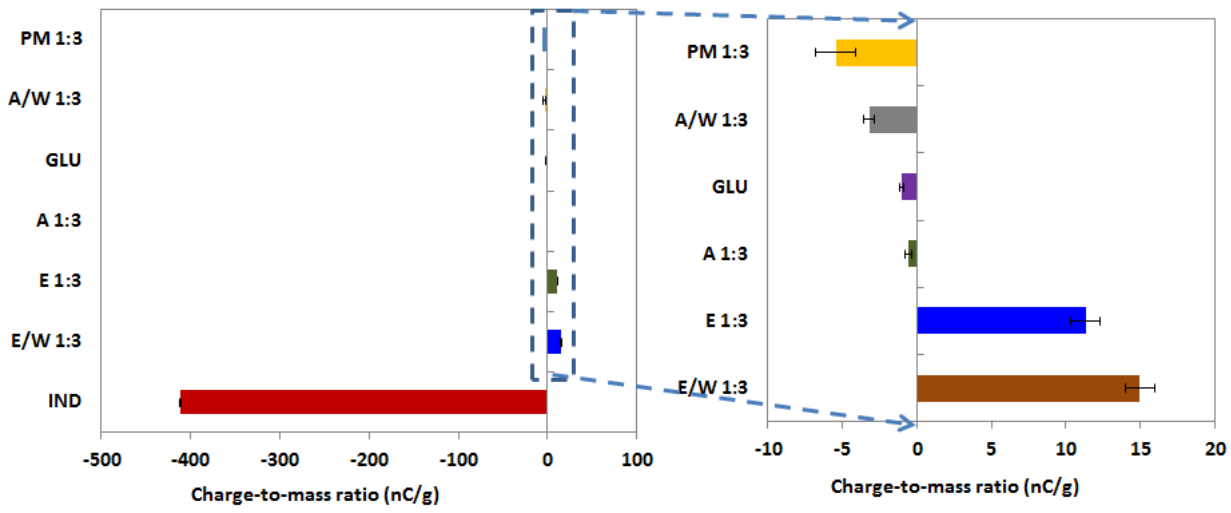
Figure 4.



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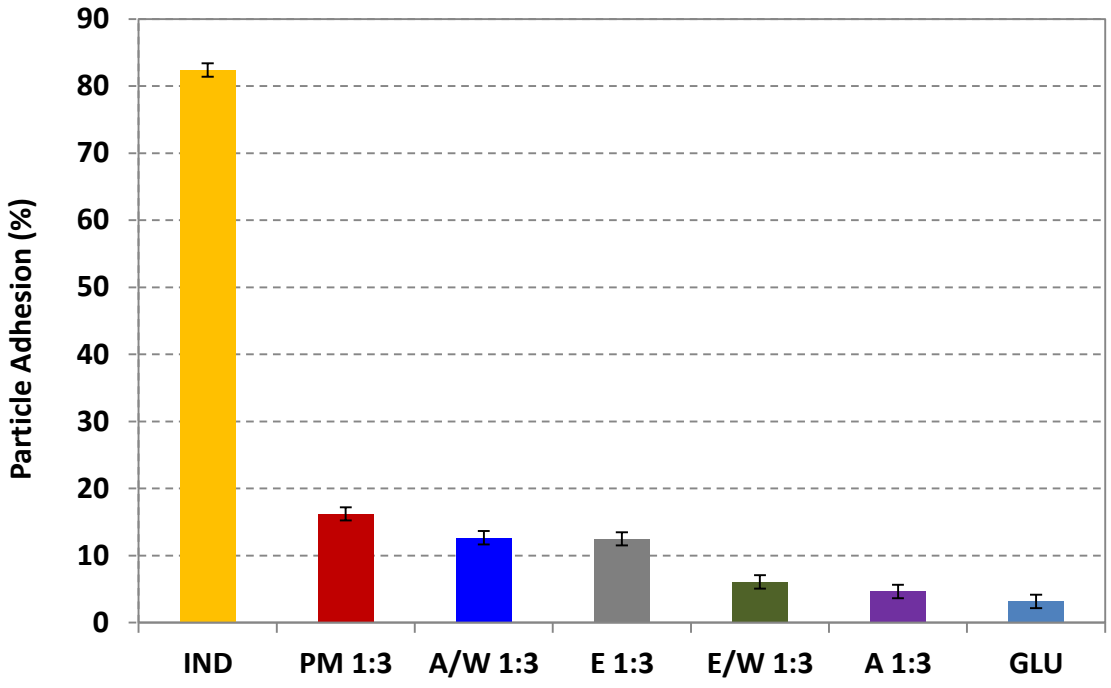

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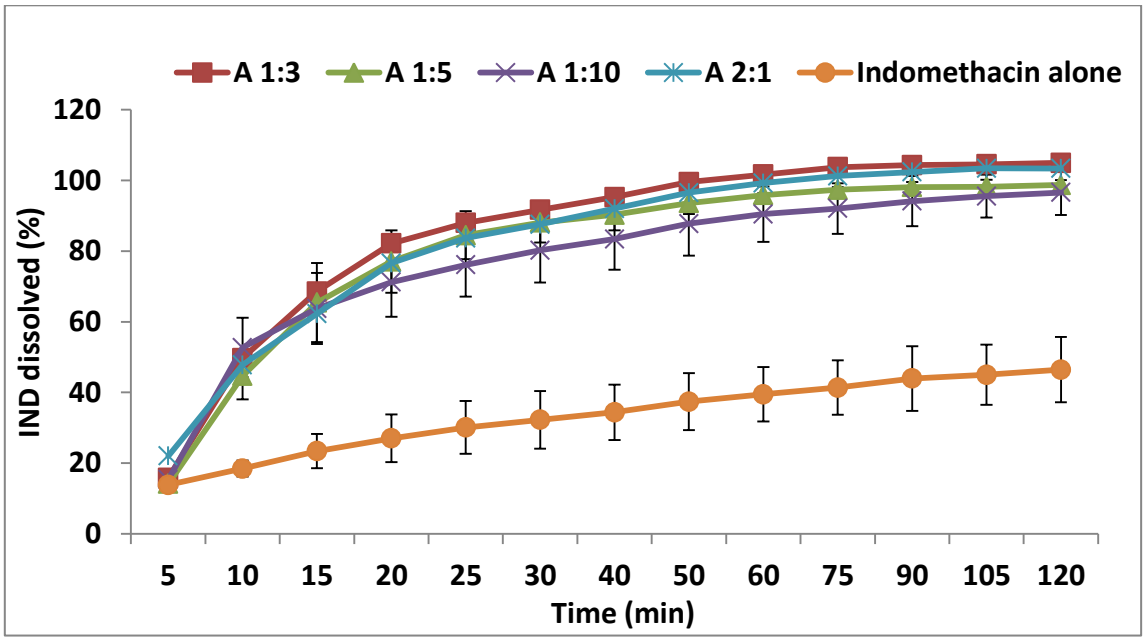
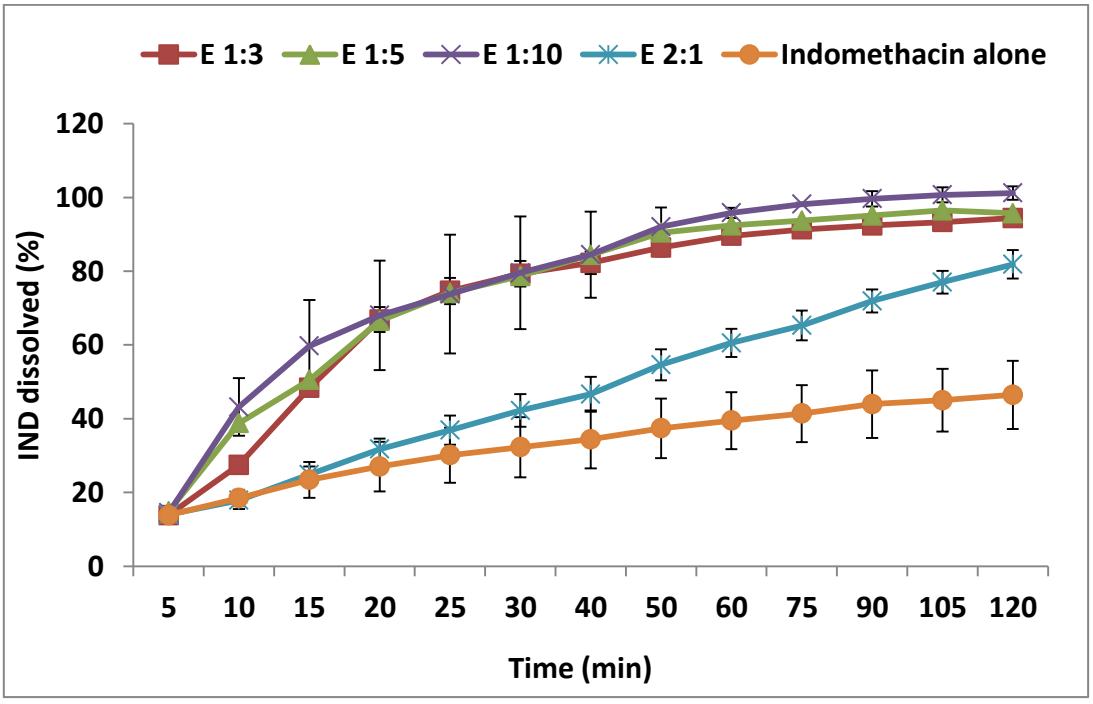


Figure 7.



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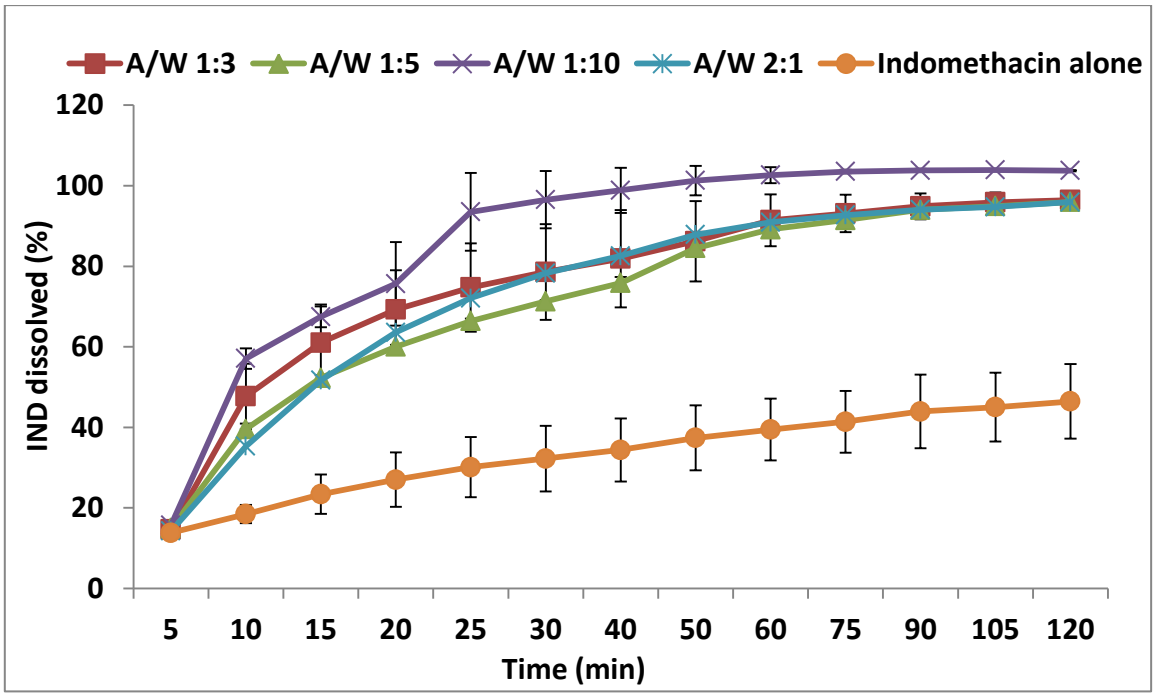

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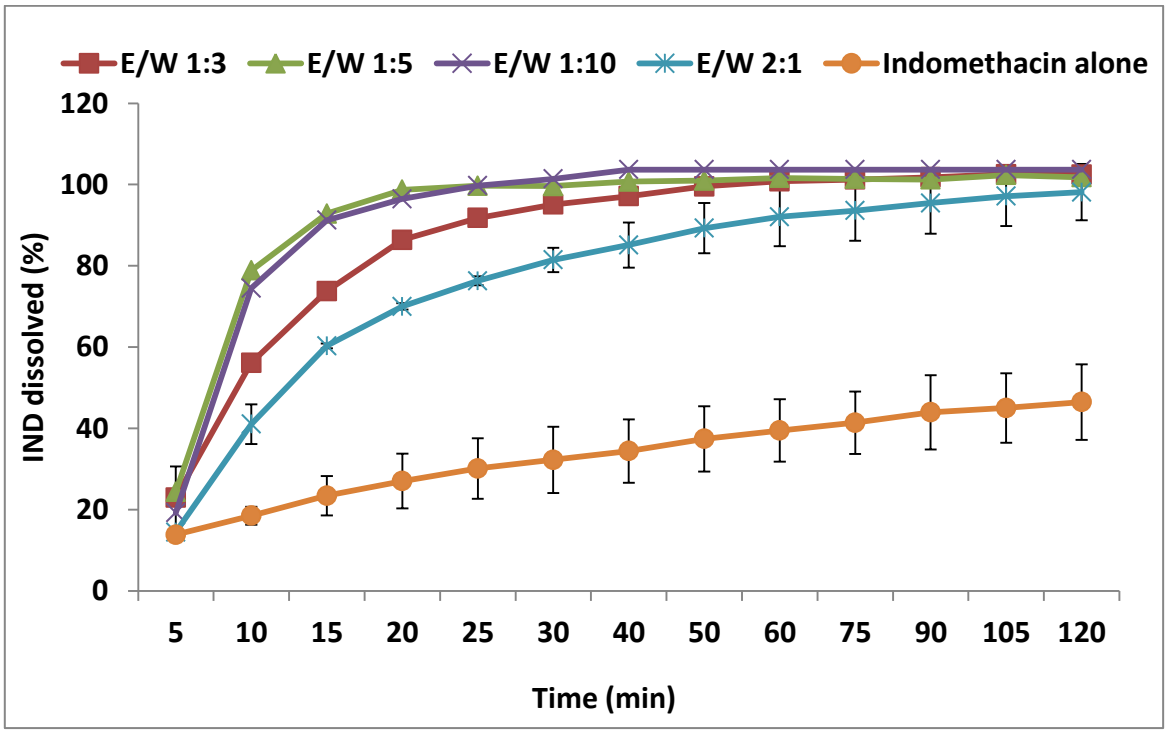

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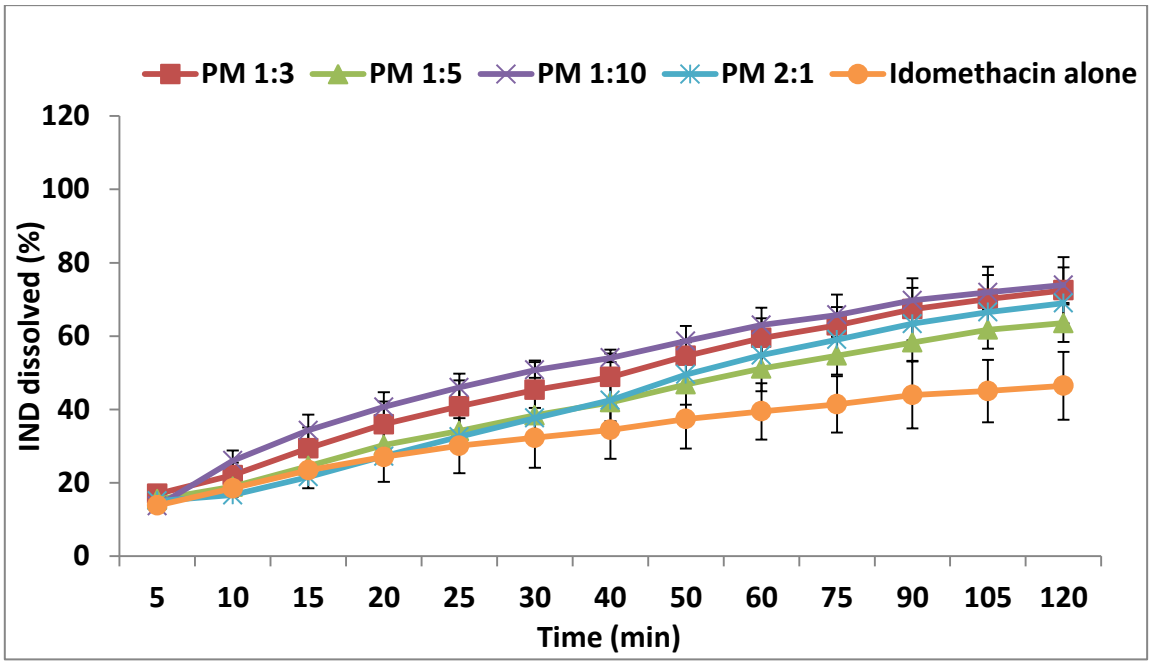

Figure 11.

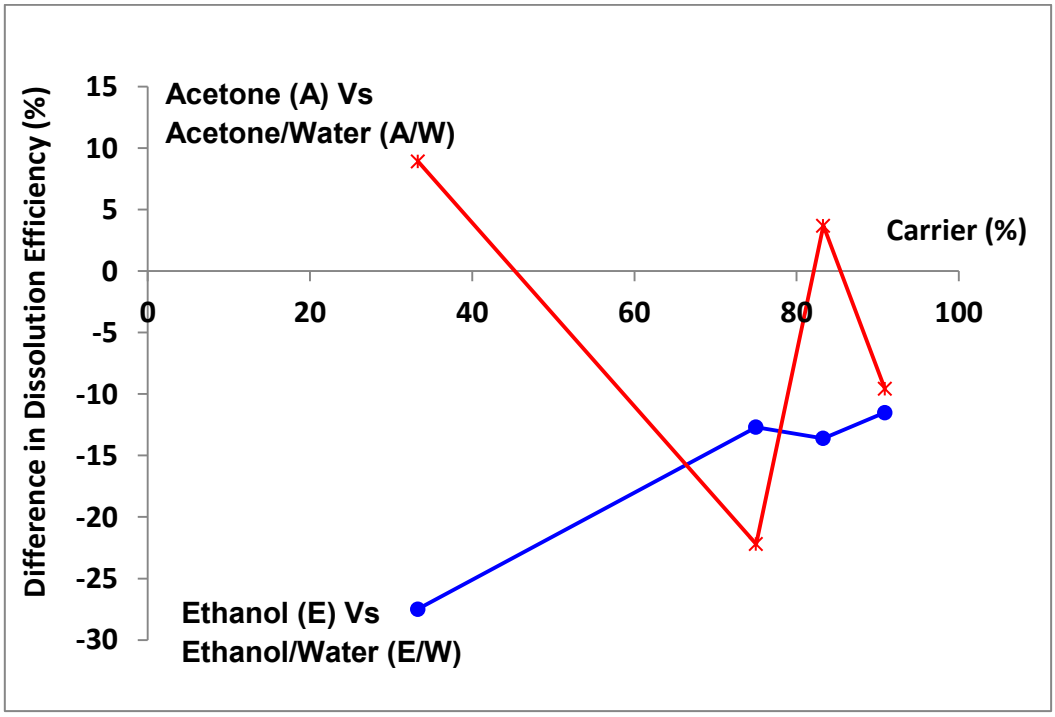

Figure 12.