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Original Article

The Effect of Different Surfactants on Dissolution Rate of Recrystallized Indomethacin

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Abstract

The effects of crystallization of indomethacin as a poorly water-soluble drug in aqueous surfactant solutions (using the basket method), on the drug dissolution behavior was investigated.A significant enhancement of drug dissolution was observed for for the dissolution rates of crystals treated with hydrophilic surfactants, Tween 80 and sodium lauryl sulfate (SLS). However, asing Arlacel 60 as a hydrophobic surfactant incrystallization medium decreased the indomethacin dissolution rate. Differential scanning calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FT-IR) indicated the existence of both α and γ- polymorphs of indomethacin (with different percentages). The FT-IR results also showed that, only the α-form could be detected in indomethacin crystals without any surfactant. These results were also confirmed by X-ray powder diffraction and scanning electron microscopy (SEM). The nuclear magnetic resonance (NMR) studies demonstrate the presence of a small amount of Tween 80 and the absence of SLS in the treated crystals. In this study, we concluded that, the presence of small amounts of surfactant, adsorption of surfactant onto the crystal surface and the decrease in powder bulk density could be the possible mechanisms of alteration in the dissolution rate of crystals treated with Tween 80, Arlacel 60 and SLS respectivelyAntioxidant.

Keywords : Surfactant; Dissolution; Indomethacin.

Introduction

Several methods for increasing the dissolution rate of poorly water-soluble drugs are known. A common approach is to reduce the drug's particle size, in order to expose a greater surface area to the dissolution medium. Reducing the particle size leads to an increase in particle-particle interactions and may lead to greater problems with wetting and liquid penetration into the dosage form (1). It has been shown that incorporation of small amounts of hydrophilic excipients, such as surfactants, alongside with hydrophobic drugs could significantly improve its dissolution rate (2). Donald et al. used different adsorbent, such as fumed silicon dioxide to enhance drug dissolution (3). Enhancement of dissolution rates of poorly water-soluble drugs (Sulfathiazole, Prednisone and Chloramphenicol) by crystallization in aqueous surfactant solutions was investigated by Chiou et al. (4). Their results showed that the dissolution rates of crystals prepared in the presence of polysorbate 80 were significantly higher than untreated crystals. They concluded that the presence of surfactant during the crystallization process does not result in a different polymorphic form. They also concluded

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that the presence of small amounts of surfactant-treated drugs could result in the depression of final melting points by approximately 0.5-1.0 °C. A polymorph is defined as a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements in the solid state. Different polymorphs of a given compound can differ so greatly in structures that the properties of the crystals behave like two completely different compounds in terms of solubility, melting point, density, hardness, crystal shape, as well as optical and electrical properties (5). Garti et al, investigated the influence of surfactants on the crystallization process of fatty acids. The mechanisms related to their adsorption on the surfaces of growing crystals, as well as their effect on crystal structure modifications and transformation in solution and solid state, were elucidated. They determined that surfactants could influence the morphology of crystals. The inhibitory effects of surfactants on polymorphism was suggested as a possible mechanism of action of surfactants on the surface of glutamic acid crystals (6). Surfactant addition and/or formation of solid dispersion (7) significantly improved the dissolution rate of SP-210661 (a potent inhibitor of 5-lipoxygenase, poorly water soluble). The possibility of solving various dosage forms problems by using the principles of crystal chemistry has been investigated in a review article by Haleblian and Macrone. They explained the applications of polymorphism in different pharmaceutical dosage forms such as suspensions, creams, solutions and suppositories. They also mentioned the thermodynamic activity, solubility and therapeutic blood levels of different polymorphs (8). Different methods have been used to investigate the indomethacin polymorphs. Royall et al used modulated temperature differential scanning calorimetry (MTDSC), localized thermal analysis (LTA) and microthermal analysis (MTA) methods for investigation of amorphous, crystalline and partially crystalline forms of indomethacin, as a model low molecular weight material (9). Various methods, including FT-NIR spectroscopy, DSC and X-ray diffraction were used to evaluate indomethacin crystallinity and polymorphism by Otsuka et al. (10). The polymorphic transformation of indomethacin under high pressures was studied by Okumura et al. (11). It had been shown earlier that indomethacin has five true polymorphs with only two of them, form I (γ) and II (α), being more important and all data regarding melting temperature, IR, NMR, and X-ray information could be obtained regularly (12). The γ form has a melting temperature (Tm) of 161 °C, where as the α- form has a Tm of 155 °C and a higher aqueous solubility than the γ -form. In γ-form the dominating feature is the crystal packing within the hydrogen bonding of carboxylic acid groups, in order to form molecular dimmers. But in the α form, the asymmetric unit consists of three molecules with the third molecule hydrogen-bonded to the molecular dimer formed by the remaining two molecules (13). In the present study dissolution rate, glass transition temperature, Fourier transform infrared spectra, X-ray diffraction profiles and thermal characterization of indomethacin as a hydrophobic model drug with different polymorphic forms were studied after recrystallization in the presence of different concentrations of Arlacel 60, sodium lauryl sulfate and Tween 80. The findings of this study could be found useful for determining a rapidly indomethacin sample as a raw material in pharmaceutical industry.

Experimental

Known concentrations of different surfactants, Arlacel 60 (ICI, France), SLS and Tween 80 (Merck, Germany) in water were used. Indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) (Medichem, Spain) was used as a model hydrophobic drug. A certain amount (0.5 g) of indomethacin was initially dissolved in 5 mL of acetone and then added to 100 mL of an aqueous solution with or without Tween 80, SLS, and Arlacel, (5/0.3 and 1% respectively) at 0 °C. The precipitated crystals were immediately collected by filtration, washed with 50 ml of distilled water and then dried in a desiccator. After sieving, crystals remaining between sieves No. So. and 60 (250-300 μm) were collected.

Dissolution studies

The dissolution studies were conducted

using the basket method with a stirring rate of 100 rpm, 750 ml pH 6.2 phosphate buffer at 37 °C, and the DT 80 Erweka dissolution tester. The amount of dissolved indomethacin was measured after filtration, using a UV-visible spectrophotometer (Genesys 2, USA). Set at λ max 318nm. The drug release rates were calculated by fllowing equation:

$$Cn = Cnmass + \frac{V}{Vt}\sum_{s=1}^{n-1} Cmass$$

Bulk density measurement

The bulk density of different crystals is equal to the mass of powder divided by the bulk volume. A 50 cm^3 sample of each powder, previously been passed through a No. 20 sieve, was carefully introduced into a 100 ml graduated cylinder. The cylinder was hit at 2 second intervals onto a hard wood an surface, three times from a height of 1 inch. The bulk density was then obtained by dividing the weight of the sample in grams by the final volume in cm^3 (14).

Crystal characterization

Crystals were evaluated using different methods:

For differential scanning calorimetry studies, 2.6 mg of each sample in loosely covered aluminum pan were heated from 50 to 250 °C at a rate of 10 °C/min. An empty loosely covered aluminum pan was used as the reference. DSC studies were performed with a type 3100 Polymer Laboratories Co. instrument, England.

FT-IR absorbance spectra were measured by the KBr disk method, using a Bruker vector 22 FT-IR spectrometer. The scan range was 500-4000 cm^{-1}. Each spectrum was automatically averaged over 100 scans obtained at a spectral resolution of 4 cm^{-1}.

X-ray powder diffraction profiles were taken with an X-ray refractometer (XRD Simens-Kristalloflex D5000), and were as follows: target, Cu; filter, Ni; voltage,30 kV; current, 5 mA; receiving slit, 0.1 mm; time constant, 1 second; scanning speed, 4 °C 20 min^{-1}.

A model 2360 scanning electron microscope, England was used to analyze the surface and shape characteristics of particles, after being coated with gold.

A DRX 500 Avance NMR, Bruker, Germany was used in this study. For this purpose d6-DMSO was used at a concentration of 20% w/v.

Results

Dissolution

The results of dissolution studies are expressed in term of percent drug dissolved as a function of time for different crystals, using linear part of curve (Figure1). One way analysis of variance (ANOVA) indicated that the dissolution rates of crystals prepared in the presence of different hydrophilic surfactants (SLS and Tween 80) were significantly higher ($p<0.05$), and lower for the hydrophobic surfactant (Arlacel 60) than indomethacin crystals prepared under the same condition without surfactant.

Differential scanning calorimetry (DSC)

In figure 2 the DSC scans obtained for different samples of indomethacin have been shown in five sections. The DSC thermogram (2-A) of indomethacin powder before crystallization shows a very broad endothermic peak, wich could not be related to a specific polymorph. The indomethacin powder resulted after crystallization in water, in the absence of any surfactant produced thermogram 2-B. This thermogram presents a sharp endothermic peak at 159.24 °C. For α polymorph, different melting points had been reported (152-159 °C). However, a melting temperature of over 160 °C is mentioned for the γ polymorph(10-12). Based on the references and considering the IR and X-ray spectra, our findings could be related to the presence of α polymorph of indomethacin. The DSC thermo gram 2-C (SLS treated) exhibits an initial small endothermic peak at 155.85 °C, followed by another big endothermic peak at 164.99 °C, which corresponds, to the melting of α and γ forms, respectively (15, 16). On the other hand, thermogram 2-D (Tween treated) demonstrates the presence of a large amount of α and a small amount of γ polymorph, based on the two endothermic peaks observed at157.65 and 162.91 °C, respectively. Figure 2-E shows a thermogram with three clear endothermic peaks at 60.14, 146.71 and 158.13 °C, being due to the

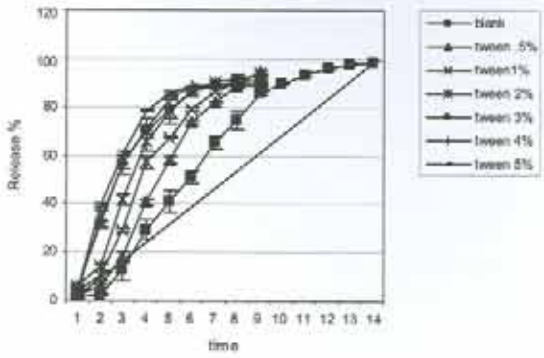

Figure 1a. Dissolution profiles of indomethacin crystals after crystallization in the presence of different concentration of Tween, (n=6) and blank, after crystallization without surfactant.

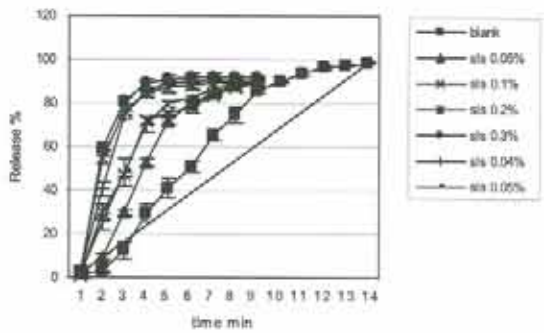

Figure 1b. Dissolution profiles of indomethacin crystals after crystallization in the presence of different concentration of SLS, (n=6) and blank, after crystallization without surfactant.

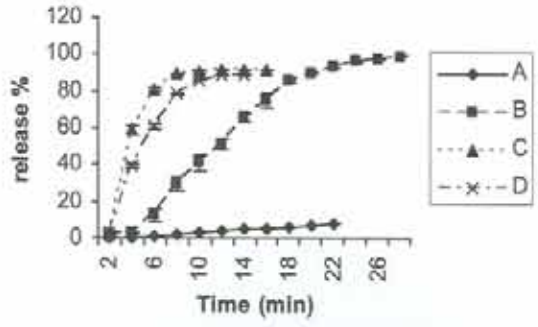

Figure 1c. Dissolution profiles of indomethacin crystals prepared in different condition. n=6 a- after crystallization in the presence of 1% Arlacel 60. b- after crystallization without surfactant. c- after crystallization in the presence of 0.3% SLS. d- after crystallization in the presence of 5% Tween 80.

melting points of Arlacel, α and γ polymorphs of indomethacin.

Fourier transform infrared spectroscopy (FT-IR)

According to the existing literature, the most characteristic difference between the two main polymorphs of indomethacin exists at the 1700 cm^{-1} region, of the spectrum where the CO- bonds shift within the spectrum of each polymorph (12, 17). This suggests the involvement of carbonyl group in different types of hydrogen bonds, in the built up of the crystal lattice of the two modifications. The dimerization of the carboxylic acid groups of indomethacin at 1700 cm^{-1} is assigned to asymmetric stretch of carboxylic acid in a dimer structure. Figure 3 shows the FTIR spectra of indomethacin powder prepared by different routes (a: without surfactant, b: in presence of Tween, c: in presence of SLS and d: in presence of Arlacel) at 1700 cm^{-1} region. The main absorption peaks are seen at:

1650, 1690 and 1735 cm^{-1} for A

1650, 1690, 1735 and shoulder at 1715 and cm^{-1} for B

1650, 1690, 1715 cm^{-1} for C

and 1650, 1690, 1715 and 1735 cm^{-1} for D

Based on IR spectra of pure α and γ forms of indomethacin (17, 18), the main differences detected in the FT-IR spectra of polymorphs α and γ could be summarized as follows:

The peaks at 1650, 1690 and 1735 cm^{-1}, which correspond to the carbonyl group, and present in both polymorphs.

The presence of both 1690 and 1715 cm^{-1} peaks show another way of arrangement of indomethacin molecules and different crystal morphology, which could be related to the γ-form. This arrangement is expected to be due to the presence of anhydride groups, formed from the interaction of acidic hydrogen with an amide-carbonyl group of another indomethacin molecule. The peak seen at 1715 cm^{-1} is only present in the γ-form, because of its' dimer structure. This bond could be clearly seen in Figures 3C and D However, it exhibits a shoulder in figure 3B, because of the small amounts of γ-form available in these crystals. Nevertheless, it seems that α-form is formed when there is no surfactant present in the aqueous solution (Figure 3A). But different percentages of both

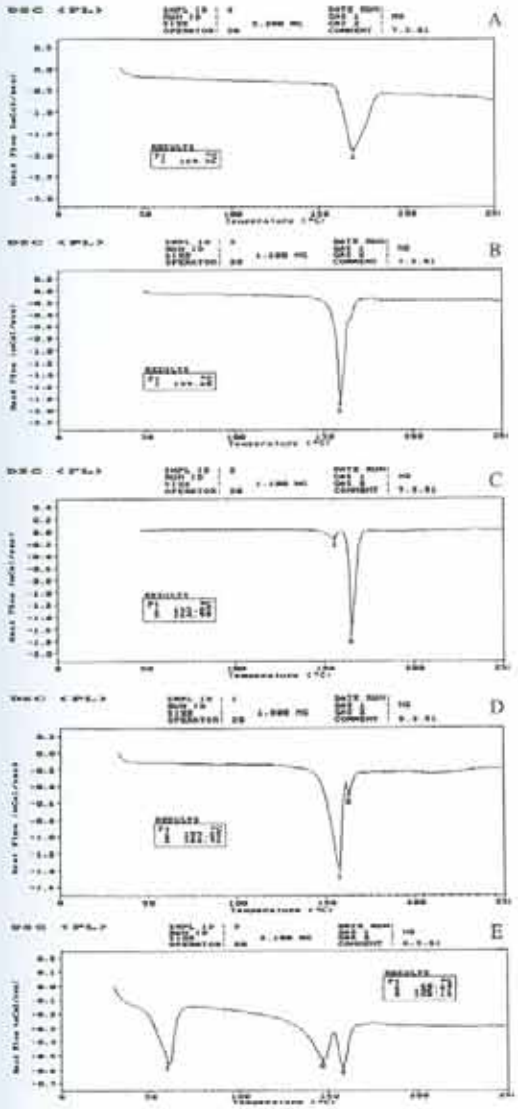

Figure 2. Differential scanning calorimetry thermograms of indomethacin crystals. A: before crystallization, B: after crystallization without surfactant, C: after crystallization in the presence of 0.3% SLS, D: after crystallization in the presence of 5% Tween 80, E: after crystallization in the presence of 1% Arlacel 60.

forms (α and γ) are formed, when known amounts of surfactant within the aqueous solution are used (Figures 3B, C and D).

X- Ray powder diffraction

Both X-Ray diffraction profiles of both the α-form and γ-form showed a halo pattern, with two very broad peaks at 2θ of about 10° and about 18°(19). These two halo peaks can be attributed to the heterogeneous structure existing in the

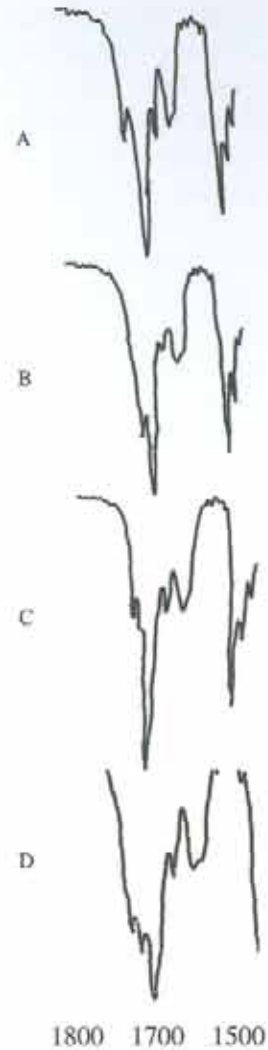

Figure 3. The FT-IR spectra of indomethacin crystals. [A:without surfactant, B:in presence of Tween 80, C: in presence of SLS, and D: in presence of Arlacel 60].

solid state and reflect distances of about 4.43 and 2.49 A°. Therefore it seems that the peaks are attributable to the indole (4.43 A°) and benzene (2.49 A°) rings in the indomethacin molecule. In comparison to the X-Ray diffraction profiles of pure polymorphs of indomethacin (19- 20), our results show different X-Ray patterns. Figure 4A shows a pure α-form pattern for recrystallized indomethacin (without surfactant), but the pure form profiles are not seen for any other samples

Scanning electron microscopy (SEM)

Crystal's morphological evaluations were carried out by photomicrographic studies. The SEM photomicrograms show (Figures 5A, B, C, and D), depending on the process parameters, two

different crystal habits. SEM photomicrographs of crystal morphologies are displayed in different references. As it has been already shown (11), there is a significant shape difference for the two polymorphs of indomethacin. The -form has needle-like crystals, while the polymorph has cubic-like crystals. In this study, the SEM micrographs clearly show the difference in the crystal habit. Figure 5A shows the presence of acicular crystals for untreated crystals, but Figures 5B, C and D show the presence of both cubical and acicular shaped crystals. The amount of each shape in each photomicrogram confirms the to ratio reported from previous results (DSC and FT-IR).

Nuclear magnetic resonance (NMR)

The presence of small amounts of Tween 80 and SLS were investigated from the proton NMR spectrum of treated indomethacin crystals (Figures 6A and B). In comparison with the pure proton NMR spectrum of Tween 80 and SLS, the results show the presence of detectable amounts of Tween 80, but it has not shown any SLS in the Tween and SLS-treated crystals.

Bulk density measurement

The bulk density of SLS treated indomethacin crystals (0.069 g/cm^3 ± 0.002), compared to the recrystallized forms with no surfactant (0.086 g/cm^3 ± 0.003), Tween treated crystals (0.077 g/cm^3 ± 0.002) and Arlacel treated crystals (0.082 g/cm^3 ± 0.004) of indomethacin shows lower bulk density for SLS treated crystals than the recrystallized forms with no surfactant.

Discussion

Various theories could explain the above effects. Some surfactant molecules could be either or both adsorbed or absorbed on the hydrophobic surface of the crystals. This adsorption for hydrophilic surfactants increases the wettability of the crystals and also their dissolution rate (4). Based on our method, the crystals were washed with 50ml distilled water after filtration. This water could wash the hydrophilic surfactants (SLS and Tween), but not the hydrophobic surfactant (such as Arlacel). The DSC thermograms also show the presence of a large amount of Arlacel in the crystals. The hydrophobic surfactant could be adsorbed onto

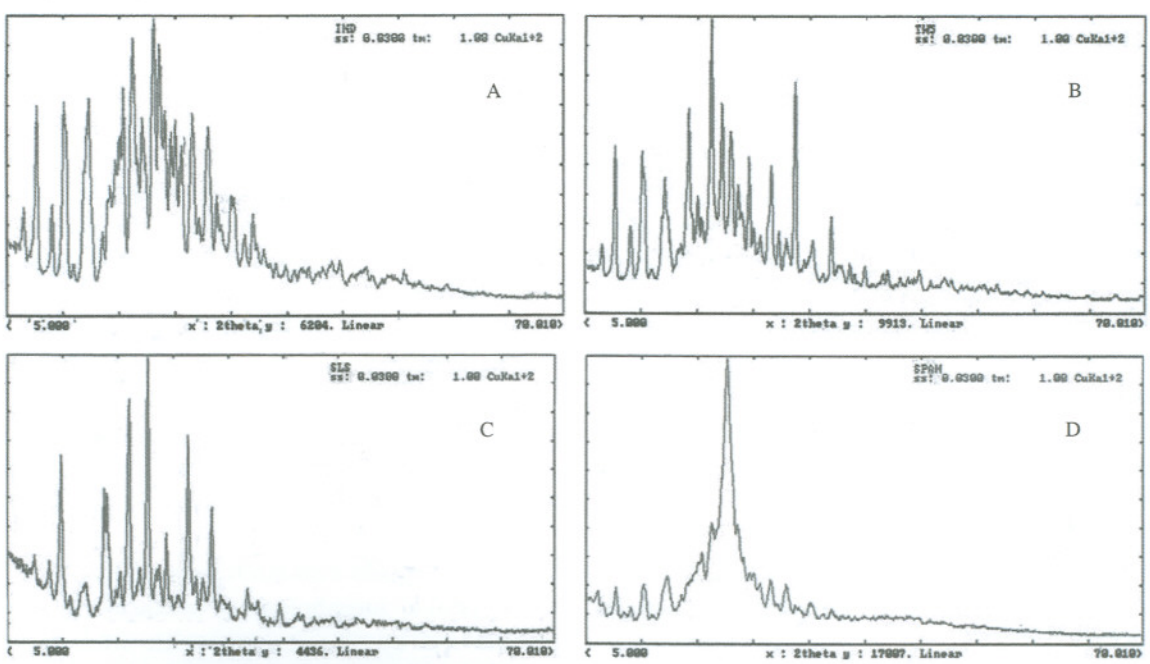

Figure 4. The X-Ray diffraction profiles of indomethacin crystal [A:without surfactant, B: in presence of SLS, C: in presence of Tween 80, and D: in presence of Arlacel 60].

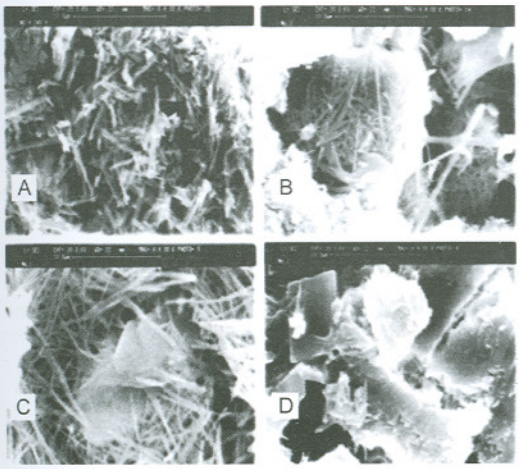

Figure 5. Scanning electron micrographs of indomethacin crystals. A- after crystallization without surfactant. B- after crystallization in the presence of 0.3% SLS. C- after crystallization in the presence of 5% Tween. D- after crystallization in the presence of 1% Arlacel.

the crystal surfaces and remain there during the crystallization process. The adsorption of Arlacel onto the crystal surface could either affect the crystal polymorphism or decrease the crystal dissolution rate by making a hydrophobic layer around the crystals. On the other hand, presence of surfactant during the crystallization process could result in a defect within the crystal structure and their instability, leading to a faster dissolution rate (15). In this study, this effect was investigated by different methods, which could clarify the mechanism of action of and hydrophobic surfactants in the treated crystals. The results of differential scanning calorimetry studies indicate the formation of different indomethacin polymorphs (α and γ) (5) in all surfactant-treated crystals. Since the formation of pure α-form (metastable and higher soluble) has been proven by different analytical methods for the untreated crystals, regarding the polymorphic forms, it was expected that as a metastable form, the α-form should have a higher dissolution rate than the treated crystals consisting both the α and γ forms. In contrary to the expectation, the results show a faster dissolution rate for Tween and SLS treated crystals. These crystals contain α and γ forms (γ is the major form in SLS- treated and α the major form in Tween-treated crystals). Hence, a so the faster dissolution rate could not be explained by the crystal polymorphism. This observation should be explained by another mechanism. The

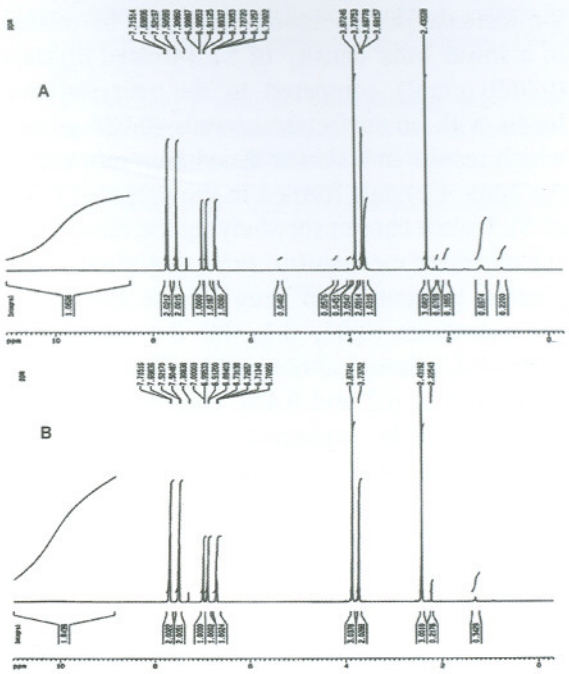

Figure 6. The proton NMR spectrum of A- Tween treated indomethacin crystal and B- SLS treated indomethacin crystal.

proton NMR results detected the presence of small amounts of Tween in Tween-treated crystals and this could strongly affect the dissolution rate (7). In this case the presence of surfactant is responsible for the dissolution rate enhancement. The absence of SLS in SLS-treated crystals was proven by the proton NMR (Figure 6B). Because of the absence of SLS and the presence of a large amount of γ-form in the SLS-treated crystals, another mechanism should be found for explaining their faster dissolution rate. It has already been shown that the bulk density is strongly affected by the agglomeration, polymorphism and morphology of the constituent elementary crystals (21-21). On the other hand it was observed that, during the recrystallization process of ASA and Mannitol, all the recrystallized forms present a lower bulk density and a faster dissolution rate, than physical mixtures which had a higher bulk density. Hence, the reduction in bulk density could be considered as an explanation for the faster dissolution rate of crystals (22). The bulk density of crystals was measured after confirming that a faster dissolution rate could not be affected by polymorphism and the presence of SLS crystals. According to these results, in here

the increase in dissolution rate could be related to a lower bulk density of SLS-treated crystals (0.069 g/cm^3) compared to the recrystallized forms with no surfactant crystals (0.086 g/cm^3) which results in a slower dissolution rate within the latter. Crystals formed in the presence 0.3% of SLS were chosen for studying the dissolution enhancement mechanism, since they showed the greatest percentage of drug release than other concentrations (0.05, 0.1, 0.2 0.4 and 0.5%) examined, although although this effect could also be seen at in 0.2 and 0.4%. concentrationsThis finding could be explained by paying attention to the ability of this concentration for making a lower bulk density crystals, compared to the other concentrations.

Conclusion

Our results indicate that the dissolution rate of indomethacin decreases by it's recrystallization in the presence of hydrophobic surfactants such as Arlacel and increases by being recrystallized in the presence of hydrophilic surfactants, such as SLS and Tween. Physicochemical properties of crystals indicate that the main factors which could explain the change of dissolution rates in surfactant-treated crystals are: the adsorption of Arlacel onto the crystals surfaces, the presence of small amounts of Tween in Tween-treated crystals and the decrease in powder bulk density in SLS-treated crystals. These results could be used in the production of more water soluble raw materials in the pharmaceutical industry. This could be pointed out for SLS-treated crystals, which showed the presence of pure indomethacin withno any SLS impurities.

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