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Original article

Design of Agglomerated Crystals of Ibuprofen During Crystallization: Influence of Surfactant

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Abstract

Objective(s)
Ibuprofen is a problematic drug in tableting, and dissolution due to its poor solubility, hydrophobicity, and tendency to stick to surface. Because of the bad compaction behavior ibuprofen has to be granulated usually before tableting. However, it would be more satisfactory to obtain directly during the crystallization step crystalline particles that can be directly compressed and quickly dissolved.

Materials and Methods
Crystallization of ibuprofen was carried out using the quasi emulsion solvent diffusion method in presence of surfactant (sodium lauryl sulfate (SLS), Tween 80). The particles were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD) and were evaluated for particle size, flowability, drug release and tableting behavior.

Results
Ibuprofen particles obtained in the presence of surfactants consisted of numerous plate- shaped crystals which had agglomerated together as near spherical shape. The obtained agglomerates exhibited significantly improved micromeritic properties as well as tableting behavior than untreated drug crystals. The agglomerates size and size distribution was largely controlled by surfactant concentration, but there was no significant influence found on the tableting properties. The dissolution tests showed that the agglomerates obtained in presence of SLS exhibited enhanced dissolution rate while the agglomerates made in the presence of Tween 80 had no significant impact on dissolution rate of ibuprofen in comparison to untreated sample. The XRPD and DSC results showed that during the agglomeration process, ibuprofen did not undergo any polymorphic changes.

Conclusion
The study highlights the influence of surfactants on crystallization process leading to modified performance.

Keywords: Direct compression, Emulsion solvent diffusion method, Ibuprofen, Surfactant

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Introduction

Direct tableting has been renewed as a preferable process by simply mixing and compressing powder to save time and cost in comparison with granule tableting. The direct compression of a powder depends on its flowability and mechanical properties (1). Some drug crystals exhibit appropriately such properties, but many materials have very poor flowability and compactability.

Direct tableting of latter materials has been successfully industrialized by coformulating higher amounts of fillers (≥75%). However, direct compression in the production of high-dose formulations is limited, since large quantities of excipients are ordinarily required to produce suitable tablets (2). In these cases, the micromeritic properties such as flowability, packability, compactability, etc. of the drug must be improved.

Ibuprofen is a high-dose nonsteroidal anti-inflammatory agent which has poor flowability and compaction characteristics owing to its needle-like (acicular) crystalline structure and viscoelastic properties, respectively. Another problem in manufacturing is the high tendency for sticking to the punches (3, 4).

It is known that crystallization techniques provide a rout towards the control of the characteristics of pharmaceutical raw materials to such an extent that the properties of powders can be optimized to suit particular processing applications. The properties of a drug can be affected by choosing a suitable polymorphic form, by choosing a suitable crystal habit, by using special crystallization techniques, and by using a suitable preparation with appropriate excipients.

In the literature several methods for improving the properties of ibuprofen are described. Usually excipients are used to optimize the substance properties. A coprecipitation with Eudragit S100 is described by Khan *et al* (5). Kachrimanis *et al* (6) also describe spherical crystal agglomerates obtained by crystallization by the solvent change technique in the presence of Eudragit S100. A powder with a drug-load of 90% (m/m) is obtained. Flowability and compressibility are improved because of the Eudragit S100 and the drug release is sustained. Pawar *et al* (7) describe agglomerates of ibuprofen with talc prepared by crystallo-co-agglomeration technique to obtain directly compressible agglomerates of ibuprofen.

In the present work, agglomeration of ibuprofen crystals was performed by employing the quasi emulsion solvent diffusion method using isopropyl alcohol and surfactant (SLS and Tween 80) in water as solvent and antisolvent, respectively. Moreover, the effect of the surfactant on physicomechanical properties such as size, flowability and tableting and dissolution behavior of the resultant crystal agglomerates was studied.

Materials and Methods

Materials

Ibuprofen (Boots Limited, UK), Tween 80 (Merck Schuchardt OHG, Hohenbrunn, Germany), SLS (Scharlau Chemie SA, the European Union), isopropyl alcohol (Merck, Germany) were used.

Preparation of agglomerates

Six different modified particles of ibuprofen were prepared and denoted as SLS (w/v %) and Tween 80 (w/v %). Samples were prepared by dissolving 5 g of drug in 20 ml of isopropyl alcohol at 40 ^{o}C, the concentration was below the saturation concentration to avoid any crystal remaining that would affect the crystallization process, then inducing a crystallization process by gradually adding 100 ml water at 5 ^{o}C over 20 min under continuous stirring (450 rpm). The separated materials were filtered off and washed with two successive portion of cold water. The harvested crystals were evenly spread on an oversized petri dish and were dried for 12 hr in an oven (60 °C). The dried crystals were stored in a desiccator at room temperature before use.

Three different concentrations of surfactant, 0.1, 0.5, and 1% w/v were employed to study the effect of surfactant concentration on crystallization.

The yields of production were calculated as the weight percentage of the final product after

drying, with respect to the initial amount of ibuprofen was used for the preparations.

Micromeritic properties

Size distribution and mean diameter were determined by the sieving method. A total of 25 g of material was sieved using an Erweka vibration sieve (Erweka, Germany) through a nest of sieves. The vibration rate was set at 200 strokes/min and the sieving time was 10 min. The powder fractions retained by the individual sieves were determined and expressed as mass percentages.

To determine the primary particle size, the agglomerates obtained in presence of surfactants were disintegrated in an aqueous solution of Tween 80 (0.05%) using ultrasonicator (VC 130, Sonics and Materials Inc., USA) for 30 sec at 100 W before determining the particle size.

A small amount of obtained powder (about 20 mg) was suspended in mineral oil (Sigma Chemical Co., St. Louis, USA) and the suspension was spread onto a microscope slide. A cover slip was applied, allowing the suspension to settle homogeneously between the two glass surfaces. Particle size was assessed by an optical microscope (Nikon Labophot, Tokyo, Japan) via a miniature video camera. Hundred of particles were measured in each sample and the surface volume mean diameter was recorded.

Flowability and packability of untreated crystals and agglomerated samples was assessed by determination of angle of repose and Carr's Index (CI) (8, 9). The angle of repose was measured according to the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip 2.5 cm height, H, above graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel (H). The mean diameter ($2R$) of the powder cone, was determined and the tangent of the angle of repose was given by:

$$\tan \alpha = H/R$$

where α is the repose angle. The mean of 6 determinations was obtained.

The compressibility index is a measure of the propensity of a powder to consolidate. The bulk density and tap density of particles were determined. The bulk density was determined for each sample from a weighed 5 g sample, carefully poured into a 25 ml cylinder. The samples were tapped 1250 times to obtain constant volume. Changes occurring in packing arrangement during the tapping procedure are expressed as the compressibility index according to the following equation.

$$CI = [(\text{Tapped density} - \text{Bulk density})/\text{Tapped density}] \times 100$$

In vitro release studies

The dissolution of samples was studied using USP rotating paddle method. Two hundred mg of samples were dispersed in dissolution vessel containing 900 ml phosphate buffer (pH 7.4) maintained at 37±0.5 °C and stirred at 50 rpm. At preset time intervals, aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. After suitable dilution, the samples were analyzed spectrophotometrically at 221.6 nm.

Preparation and characterization of the compacts

The agglomerates and the untreated sample were directly compacted using 10 mm flat-faced punches on a hydraulic press (Riken Seiki Co, Japan). Each tablet is made out of one type of material. The material for each tablet was weighed (200 mg), introduced into the die and compacted at various compression pressures of 200, 300 and 500 Kg/cm^2. The compaction surfaces were lubricated with 1% w/w magnesium stearate in ethanol before compaction. The compacts were held under load for 30 sec, ejected and stored in screw-capped bottles for 24 hr before using, to allow for possible hardening and elastic recovery.

In this study a consistent sieve fraction (200-350 μm) of all agglomerated particles was used.

The force required to fracture the compacts on a motorized tablet hardness tester (Erweka, Germany) was measured to determine tablet

crushing strength. The tensile strength of the compact was calculated using the following equation (10):

$$T = {}^{2F}/_{\pi Dt}$$

in which D and t are the diameter and thickness of the compact, respectively, and F is the force fracturing the compact. Experiments are repeated five times for statistical reliability and the mean values of five determinations are reported.

X-ray powder diffraction (XRPD)

In order to investigate polymorphism X-ray was used. The cavity of the metal sample holder of the X-ray diffractometer was filled with the ground sample powder and then smoothed with a spatula. X-ray diffraction pattern of ibuprofen samples was obtained using the X-ray diffractometer (Seimens, Model D5000, Germany) at 40 kV, 30 mA and a scanning rate of 0.06°/min over the range 2θ= 5–40, using CuKα1 radiation of wavelength 1.5405 A°.

Differential scanning calorimetry (DSC)

In order to determine polymorphic composition of pharmaceutical powders, when the polymorphs present different melting points, DSC was used. After calibration with indium a lead standards, samples of the crystals (3–5 mg) were heated (range 25- 170 °C) at 10 °C/min in crimped aluminum pans under a nitrogen atmosphere. The enthalpy of fusion and melting point were automatically calculated (Shimadzu, Japan).

Statistical evaluation of data

Significance was taken at 95% confidence levels ($P< 0.05$). The mean values of the various parameters determined, i.e., micromeritic properties, dissolution rate (between t_0- t_{10} min) and tensile strength were compared for significant difference using one-way or two-way analysis of variance (ANOVA) for single factor and two factors comparison, respectively.

Results

Micromeritic properties

The morphologic features of the untreated crystals and the samples crystallized in the presence of surfactant were visually examined using light microscopy. Figure 1e and f showed that the primary crystals of the agglomerates were plate-shaped, as compared to needle like crystals in the untreated sample. Also according to this Figure and Table 1 the primary crystal size of the agglomerates was much lower than that of untreated crystals. The effect of surfactant concentration on the particle size of the agglomerates is also shown in Figure 1a, b, c and d. Increasing surfactant concentration led to a smaller mean size and standard deviation of the agglomerates (Table 1). For example, the mean sizes of particles obtained under three SDS concentrations were 310 µm (0.1 %), 282 µm (0.5 %) and 268 µm (1 %), respectively. As well as standard deviation decreased from 190 to 116 on increasing in the amount of SLS from 0.1% to 1%, respectively. Table 1 also indicates that the practical yield was found satisfactory and ranged from 83% to 95% for agglomerate obtained in the presence of surfactants. The angle of repose of the agglomerates was smaller than that of untreated crystals (Table 1). The packing properties of the agglomerates are also listed in Table 1, agglomerates were easily packed by tapping, the process of which was evaluated based on percent compressibility (8). Table 1 also shows that an increase in concentration of surfactant in the crystallization medium produced a significant change in the bulk and tapped densities ($P< 0.05$).

Dissolution

Results of the dissolution study are reported in Figure 2. The agglomerates obtained in presence of SLS showed faster dissolution rate in comparison to the agglomerates obtained in presence of Tween 80. On the other hand, there was no significant difference between dissolution rate of the agglomerates obtained in the presence of Tween 80 and the untreated crystals.

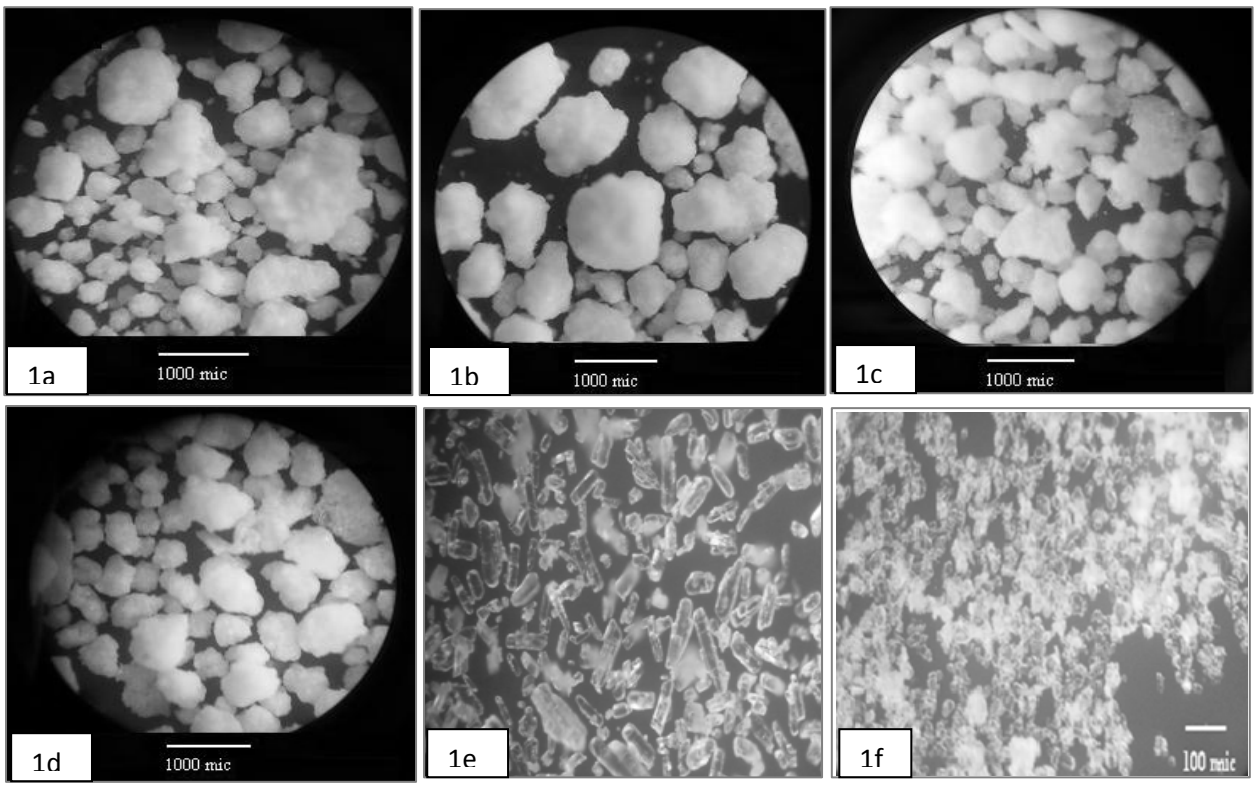

Figure 1. Photomicrographs of the samples; a: SLS (0.1%), b: SLS (1%), c: Tween 80 (0.1%), d: Tween 80 (1%), e: untreated crystals, f: constituent crystals of Tween 80 (1%).

Table 1. Micromeritics properties of the agglomerates and untreated crystals (Mean±SD).

Formulations	Yield (%)	Bulk density (g/cm^3) (n= 3)	Tapped density (g/cm^3) (n= 3)	Carr index (%) (n= 3)	Angle of repose (^{o}) (n= 6)	Arithmetic mean diameter±σ (μm)
Tween 80 (0.1%)	95.0±1.5	0.27±0.01	0.32±0.01	14.9±0.8	21.3±0.8	543±234
Tween 80 (0.5%)	92.3±1.4	0.25±0.02	0.29±0.01	12.6±0.9	21.4±0.5	489±187
Tween 80 (1%)	89.6±1.3	0.25±0.01	0.29±0.01	14.1±1.2	22.1±0.6	365±135
SLS (0.1%)	93.9±0.9	0.27±0.02	0.31±0.01	10.8±0.9	22.5±0.4	310±190
SLS (0.5%)	89.5±0.9	0.25±0.02	0.29±0.01	12.7±1.1	23.7±0.5	282±141
SLS (1%)	83.1±1.5	0.27±0.01	0.32±0.01	15.2±0.8	27.1±0.8	268±116
Agglomerates obtained without surfactants	95.6±1.2	-	-	-	-	150±120
Conventional crystals	-	0.30±0.02	0.51±0.02	41.7±1.5	53.7±1.3	120±20/20±4 (length/breadth)
Constituent crystals of the agglomerates	-	-	-	-	-	20±6

Tabletability

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure and is represented by a plot of tablet tensile strength against compaction pressure (11). The effect of compression force on the tensile strength of tablets made from ibuprofen agglomerates is reported in Table 2. Compression of untreated ibuprofen crystals at all compaction pressure produced weak compacts with a high tendency to cap, however, the agglomerated crystals possessed superior tensile strength characteristics in comparison to the untreated single crystals. According to results, there was no significant difference between tensile strength of tablets from various agglomerates, in other words the tensile strength of the tablets from agglomerates was unaffected by

the type and concentration of surfactant in crystallization medium. Untreated ibuprofen crystals has also severe problem of sticking to the punches during compression, however, sticking was not observed for the agglomerated samples. The photomicographs of surface of the tablets made of untreated crystals and the agglomerates are shown in Figure 4. It revealed that crystalline drug tablet has rough surface with large cracks in between due to sticking whereas surface of the agglomerates tablet was smooth and devoid of any cracks indicating non-sticking nature.

X-ray and DSC

XRPD patterns of the untreated sample and the agglomerated samples are shown in Figure 5. The XRPD patterns of the agglomerates did not show any significant difference with untreated sample. The maximum intensity peak i.e. I_0 has been shifted from 2θ value 22.4◦ to 16.5◦. There was no change observed in the d-spacing value of various samples. However, the relative intensities of their XRPD peaks were modified. DSC curves of untreated crystals and the agglomerated samples are shown in Figure 6. All samples showed a sharp melting point with flat baseline which indicated that no events such as hydration, solvation or polymorphic transition had occurred during crystallization of the particles. The mean values of the melting points and enthalpies of fusion for untreated ibuprofen and the agglomerated samples are presented in Table 3. Results indicates that the melting point and enthalpies of fusion of the agglomerated samples decreased by 1.07 1.41 °C and 2.58-5.07 cal/g, as compared to the untreated sample.

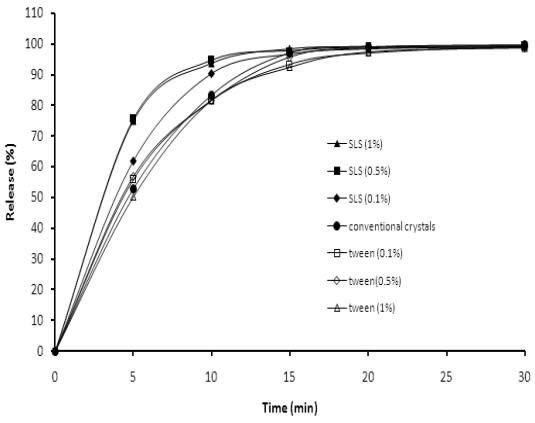

Figure 2. Dissolution profiles of the agglomerates and untreated ibuprofen powders (Mean±SD, n= 3).

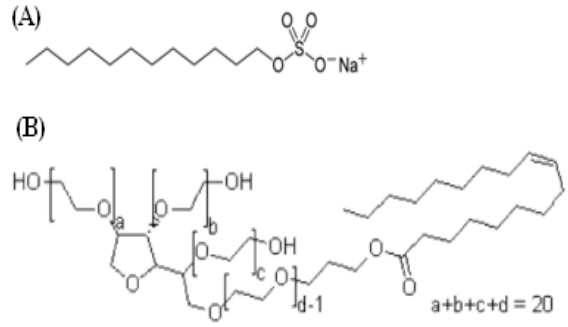

Figure 3. Molecular structure of the surfactants used in this study (A): SLS, (B): Tween 80.

Figure 4. photomicrographs of the tablet made from; (A): untreated ibuprofen crystals, (B): Tween 80 (1%).

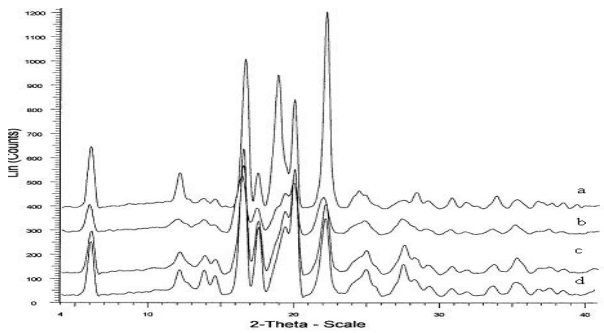

Figure 5. X-ray diffraction patterns of the sample a: untreated crystals, b: the agglomerates obtained without surfactant, c: Tween 80 (1%), d: SLS (1%).

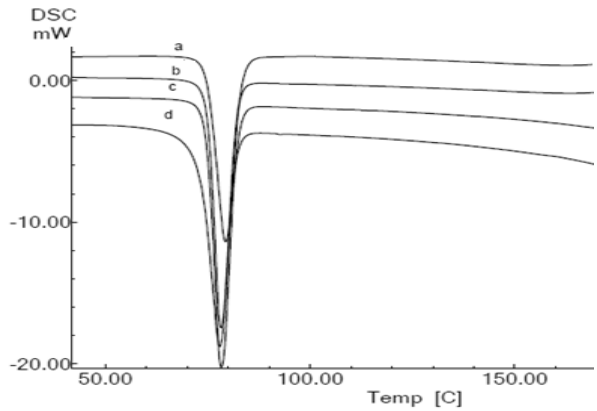

Figure 6. Thermograms of the samples; a: untreated crystals, b: Tween 80 (1%), c: SLS (1%), d: the agglomerates obtained without surfactant.

Table 2. The tensile strength of the compacts of the agglomerates (Mean±SD, n=5).

		Tensile strength (kg/cm^2)					
samples		SLS			Tween 80		
		0.1%	0.5 %	1%	0.1%	0.5 %	1%
	200	8.7±0.9	8.9±1.1	9.5±0.8	7.5±1.2	7.7±0.9	8.3±0.8
Pressure	300	7.2±1.1	6.3±1.0	6.0±0.9	7.1±1.0	7.5±1.2	6.0±1.1
(kg/cm^2)	500	4.1±1.0	4.0±0.9	4.7±0.8	5.2±0.9	5.1±0.9	4.5±1.2

Table 3. Melting peak temperature and enthalpy of fusion ΔH_f for the samples.

Samples	Conventional crystals	Agglomerates (obtained without surfactant)	Tween 80 (1%)	SLS (1%)
ΔH_f (cal/g)	-27.87±1.0	-25.29±1.8	-22.80±1.4	-25.13±1.2
Melting peak (^0C)	79.30±0.5	77.89±0.6	78.11±0.3	78.23±0.5

Discussion

In this study, the crystallization of ibuprofen from isopropyl alcohol (good solvent) was performed by the addition of water (poor solvent) containing different concentrations of surfactant. The quasi-emulsion droplets are produced, due to a measurable interfacial tension being established between the good and poor solvent. Then the diffusion of isopropyl alcohol out of the droplet and the counter-diffusion of water into the droplet induce the crystallization of the drug within the droplet due to the decreasing solubility of the drug. The presence of surfactant is likely to modify the interfacial tension between the good and poor solvent. Thus, in order to investigate the contribution of surfactant in preparation of particles, the quasi emulsion solvent diffusion method (QESD), was carried out at various concentrations of surfactant in water.

Micromeritic properties

The finding shown in Figure 1 and Tablet 1 indicated that the use of surfactant in the crystallization medium had a major effect on the size of the particles. The presence of surfactant was indispensable to yield spherical agglomerates. Without the addition of surfactant, only an irregular mass of the drug with a mean size of 150 µm and coarse surface were obtained. In contrast, larger spherical agglomerates with smooth surface could be achieved with the use of surfactant.The surfactant concentration would probably influence the final particle size of the agglomerates in modifying the initial quasi-emulsion droplet mean size and size distribution. In the other words, decreasing the interfacial tension between the good and poor solvent with the increasing of surfactant concentration might make the newly formed emulsion droplets distribute and subsequently collide more evenly, leading to the formation of more uniform particles. Also, recrystallization of ibuprofen in isopropyl alcohol/water system in the presence of surfactant changed both the size and shape of the primary drug crystals as shown in Figure 1e and f. In order to achieve uniformity in tablet weight, the feed crystals must flow and pack smoothly into the die cavity of the tablet machine. Therefore, it is essential purpose of particle design for direct compression to improve the flow and packing properties. The low values of angle of repose (21.3-27.1 ^{o}) and percent compressibility (10.8-15.2%) for agglomerates indicated their high flowability and packability, respectively. In spite of better packability of the agglomerates, the bulk and tapped density of all of the agglomerates are lower than that of the untreated sample. Therefore, these low densities should be related to the intraparticle porosity or particle density. The changes of bulk and tapped density with increasing surfactant concentration should be related to size, shape and mainly to surface roughness of the agglomerates. Smaller, less spherical and

rougher agglomerates contribute to looser packing and smaller bulk and tapped density due to greater interparticle contact area and friction (6).

Dissolution

Faster dissolution rate of the agglomerates obtained in the presence of SLS compared with those obtained in the presence of Tween 80 can be attributed to the hydrophilization of ibuprofen crystal surfaces caused by interactions with surfactants. As a common property of surfactants, SLS and Tween 80 have a hydrophilic and hydrophobic part of the molecule.

As can be seen in Figure 3, the hydrophilic part of SLS is located in a small area, in the form of an anionic sulfate group. In contrast to this structure, Tween 80 with a PEG chain has a long hydrophilic chain where the hydrophilicity is not located in such a concentrated manner. The molecules with smaller hydrophilic part should exhibit a higher probability of interacting with the hydrophobic ibuprofen particles. Thus, it would be expected that Tween 80 can weaker interact with ibuprofen crystals than SLS. Rasenack and Muller (12) has reported similar result who showed that faster drug dissolution rate occurs if ibuprofen is crystallized in the presence of surfactants without a PEG chain (sodium salts of fatty acids) in comparison with the surfactants with a PEG chain.

Beside the hydrophilization of ibuprofen crystal surfaces caused by interactions with surfactants, slight amounts of surfactant that remain in the product can be anchored in the crystal surface. Therefore, this result may be also attributed to effect of surfactants on ibuprofen solubility. Higher ibuprofen solubility in the presence of SLS in comparison to Tween 80, as has been shown by other researchers (13) may be also responsible for the faster dissolution rate of the agglomerates obtained in the presence of SLS.

As far as the dissolution rate of the untreated crystals are concerned, no significant difference with that of the agglomerates obtained in the presence of Tween 80 are surprising. It must be recalled that the particle size of the untreated crystals is much finer than that of the agglomerates (Table 1) and results of the dissolution study are expressed as a percentage of dissolved drug without consideration of shape and particle size. Therefore, In fact, the dissolution is faster from the agglomerates in comparison to untreated crystals, when it is expressed more realistically as a function of particle size. In spite of smaller particle size of untreated crystals than agglomerates, the apparent low specific surface area of these very small crystals could be expected by their flat surface and high hydrophobicity, which can produce very dense aggregates. Indeed, the flat faces of the crystals adhere to each other during dissolution test. Aggregation of fine ibuprofen crystals has also been shown by other researchers (12, 14). Whereas hydrophilization of ibuprofen crystal surfaces in the presence of surfactants and agglomeration of these crystals as a loose structure may prevent the formation of such dense aggregates. Therefore, it would be expected that the agglomerates to have higher surface area to contact with dissolution medium, despite of larger particle size than untreated crystals. Indeed, dissolution is supposed to occur from agglomerates surface in direct contact with the dissolution medium as well as from diffusion through the water filled pores of the agglomerates.

Tabletability

Higher tensile strength of tablets made of the agglomerates in comparison with the untreated crystals may be attributed to elementary crystal size of the agglomerates. Actually, agglomerates are broken during compaction leaving small single crystals whose agglomerates were originally composed. Therefore, agglomerates could behave like small crystals, which can result from the breakage of agglomerates by the punch during compression. As a consequence of compaction, consolidation implies an increase in mechanical strength resulting from particle–particle interaction. According to Table 1 and Figure 1, the size of the individual crystals comprising the agglomerates was significantly less than the crystals of untreated ibuprofen. In

other researches, where compactability of the two different fraction sizes of crystals has been compared, it has been shown that the compactability of small size fraction was higher (11, 15). Therefore, it is possible to assume an increase in particle– particle interaction due to the smaller size and distances of elementary crystals of the agglomerates compared to untreated crystals.

An explanation for the limited variation in compactability obtained for the agglomerates obtained in presence of surfactants is that the dominant compression mechanism for this type of particles was fragmentation as shown by many other studies (16-20). A variation in the degree of fragmentation as a consequence of intra particle porosity affects the evolution in the number of inter-particulate junctions in the tablet. However, it has been proposed that a variation in the degree of fragmentation has a limited effect on the total area of contact at the inter-particulate junctions and thus on the tablet tensile strength (assuming that some proportionality exists between total inter-particulate contact area and tablet tensile strength) (21).

According to Figure 4 the agglomerates showed non-sticking characteristics in comparison with the untreated crystals which may be attributed to change in crystal habit of elementary crystals of the agglomerates. In other researches, better compressibility of plate type crystal of ibuprofen as compared to needle shaped crystals has been reported (22, 23).

As mentioned previously, in this study, the elementary crystals of the agglomerates were plate-shaped, as compared to needle like crystals in the untreated sample.

This result may be also due to differences concerning the presence of small amount of surfactants at crystal surfaces on the agglomerates in comparison with untreated crystals.

X-ray and DSC

The change in the relative intensities of the agglomerates XRPD peaks in comparison with the untreated crystals may be due to change in size and habit of constituent crystals of the agglomerates as can be seen in Figure 1e and f. Garekani *et al* (24) have attributed decrease in the intensity of XRPD peaks to the changes in crystal habit of drug. As a result of changing crystal habit, the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peaks. On the other hand, it has been shown the crystal size can have influence on the intensities of XRPD peaks (25). Little changes in DSC data of the agglomerates in comparison to the untreated sample may be an effect of crystal size (26). In summary, X-ray and DSC results show that particles crystallized in the presence of surfactants did not undergo structural modifications.

Conclusion

In this study, QESD method was employed to prepare near spherical agglomerates of ibuprofen in the presence of surfactant. According to results the particle size and the standard deviation of the agglomerates could be well controlled by surfactant concentration. Moreover, an appreciable improvement in tabletability of the raw material following the recrystallization by ESD techniques, owing to smaller size of constituent crystals of the agglomerates was seen. More importantly, the dissolution of the agglomerates obtained in presence of SLS was markedly improved when compared to the untreated powder. DSC and XPD experiments showed that obtained particles, did not undergo structural modifications. In conclusion, the crystallization technique developed in this study can be considered as a suitable alternative to untreated granulation process to obtain agglomerates of ibuprofen with improved tableting properties and enhanced dissolution rate.

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