Surface Treatment of Acetylsalicylic Acid with Lubricants by the Wurster Method

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Surface treatment of acetylsalicylic acid (ASA) crystals was examined in a Wurster fluid bed system with water-soluble and water-insoluble lubricants. The influence of the coating process on the flowability, the compressibility and the dissolution rate of the crystals was studied, and the results were compared with the corresponding parameters of ASA crystals processed by a conventional (mixing) method. The coating materials were Carbowax® 6000 as water-soluble and stearin as water-insoluble lubricant. The control sample was unprocessed (commercial) ASA crystals. The Strea-1 fluid bed coater with the Wurster column could be used for the production of a lubricant coating on crystal surfaces. The coated crystals, in comparison with mixed samples, had very good compactibility, cohesivity and compressibility values. Their lubrication coefficient was higher and the friction work was less than those of mixed crystals. The dissolution of the active agent could be regulated by the lubricant coat. The rate of dissolution of ASA was primarily promoted by a film coat of Carbowax® 6000 from a capsule.

Key words acetylsalicylic acid; lubricant; coating; Carbowax® 6000; stearin; mixing

The surface treatment of particles usually means a coating process in the case of solid dosage forms.[1] The aim of the coating may be the protection of an active agent and/or the stomach, the masking of a drug taste or smell, the separation of incompatible ingredients, prolongation of drug action, *etc*.[2] However, coating with lubricants is not a customary pharmaceutical technology process. The use of lubricants is necessary in the formulations to reduce the friction between the tablet and the die wall and to prevent adhesion of the tablet material to the punches and the die wall. Lubricants are also used in capsule filling. They can promote the flowability of materials and hence the uniform space filling of capsules. Lubricants are used in mixture and in solution form. The surface properties of the lubricant, the time and mode of addition and the duration of mixing can influence the hardness, the disintegration and the dissolution characteristics of the final product.[3]

A fluid bed system is generally used for the coating process. Typical types of commercially available coating machines include the top-spray spouted bed, the rotary fluidized bed and the bottom-spray spouted bed with a draft tube (the Wurster method).[4]

The Wurster principle has been known since 1954.[5] This method is very important in the coating of small particles and crystals because of their agitated motion due to the collision of particles against the partition.[6] In consequence of this agitated motion, brittle crystals like phenacetin are easily fractured, and even harder crystals such as those of lactose become roundish.[7] Most studies of the Wurster process have been made by Japanese authors.[8—13]

In this work, the surface treatment of acetylsalicylic acid (ASA) crystals was examined in a Wurster fluid bed system with water-soluble and water-insoluble lubricants. The influence of the coating process on the flowability, the compressibility and the rate of dissolution of the crystals was studied, and the results were compared with the corresponding parameters of ASA crystals processed by a conventional (mixing) method.

The question was considered whether the coating process can be used for the surface treatment of ASA crystals with lubricants.

Experimental

Materials ASA (7th Hungarian Pharmacopoeia) was used as model material. Vivapur® 101 (microcrystalline cellulose) (Rettenmaier and Sohns Co., Ellwangen-Holzmühle, Germany) as dry binder, and sodium starch glycolate (Agrochemia Co., Sellye, Hungary) as disintegrant agent were used in tablet making. The two types of lubricants applied as coating material were Carbowax® 6000 (Fluka AG, Buchs, Switzerland) as water-soluble lubricant, and stearin (7th Hungarian Pharmacopoeia) as water-insoluble lubricant.

Surface Treatment of Crystals Coating Method (Wurster): Two hundred grams of ASA crystals was coated with up to 1% of lubricant in a Wurster fluid bed coater (Strea-1 Aeromatic, NIRO-Aeromatic AG, Bubendorf, Switzerland) equipped with a bottom spray head with an 0.8 mm nozzle. Two grams of Carbowax® 6000 was dissolved in 48 g of 30% ethanol (ASA coated 1); the inlet and outlet temperatures were set at 40 °C and 30 °C. The coating time was 11 min. Stearin (2 g) was used in a warm alcoholic solution (48 g of 40% ethanol) (ASA coated 2); the inlet and outlet temperatures were 50 °C and 42 °C. The coating time was 6 min. In both cases, the atomization pressure was 120 kPa and the spray rates were 5 and 10 ml/min.

Conventional Method (Mixing): Two hundred grams of ASA crystals was mixed with up to 1% of Carbowax® 6000 (ASA conv. 1) and stearin (ASA conv. 2) in a Turbula mixer (W. A. Bachofen Maschinenfabrik, Basel, Switzerland). The mixing time was 5 min. The particle size of Carbowax® 6000 was 2—9 μm and that of stearin was 8—15 μm.

The control sample was unprocessed crystals (ASA unprocessed).

Particle Size Distribution The particle sizes of the unprocessed and processed crystals were measured by sieve analysis (DIN sieve, German Standard).

Morphological Study The ASA surface was observed with a scanning electron microscope (SEM) (Hitachi 2400S Hitachi Scientific Instrument Ltd., Tokyo, Japan). A Polaron sputter coating apparatus (Polaron Equipment, Ltd., Greenhill, UK) was applied to induce electric conductivity on the surface of the sample. The air pressure was 1.3—13 mPa.

Compactibility and Cohesivity The values were characterized by the modified Kawakita equation[14,15]:

$$\frac{N}{C}=\frac{1}{a}\cdot N+\frac{1}{ab} \quad (1)$$

where a and b are constants. C was calculated according to the following equation

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$$C=\frac{V_0-V}{V_0} \tag{2}$$

where V_0 is the poured volume (250 ml) of the powder column, and V is the volume of the powder column after different numbers of taps N. Regression analysis was performed. The relationship between the variables (N/C and N) could be described in terms of a linear model. The compactibility ($1/a$) and the cohesivity ($1/b$) were obtained from the slope ($1/a$) and the intercept ($1/ab$) of the straight line.

The poured and tapped volumes were measured with a Stampfvolumeter 2003 (J. Engelsman AG Apparatebau, Ludwigshafen, Germany).

Study of Plasticity and Compressibility A Korsch EKO instrumented eccentric tablet machine connected with a computer (E. Korsch Machinenfabrik, Berlin, Germany) was applied. The average tablet weight was 500 mg (250 mg ASA+250 mg Vivapur® 101). The compression tools were single, flat punches 10 mm in diameter, furnished with strain gauges and a displacement transducer. The rate of compression (force–displacement and force–time curves) was then constructed, using the data provided by the determination of energy parameters produced by the compression of ten test tablets. The pressure force was 6 kN. It was then possible to determine the effective work (E_2), the degree of elastic recovery (E_3), and the friction work (W_f). The lubrication (R) was calculated according to Higuchi (R=lower punch force/upper punch force).[16] The plasticity was described in terms of the methods of Stamm–Mathis ($Pl_{S\text{-}M}$)[17]:

$$Pl_{S\text{-}M}=\frac{E_2}{E_2+E_3}\cdot 100\ (\%) \tag{3}$$

where E_2 and E_3 can be calculated from the force–displacement curve. If the plasticity value is near 100, the material has a plasticity property. The compressibility (Pr_{mass}) was calculated *via* the following equation[18]:

$$Pr_{mass}=\frac{\sigma_x}{W_{spec}}=\frac{\sigma_x}{E_2/m}\left(\frac{\mathrm{Pa}}{\mathrm{J\cdot kg^{-1}}}\right) \tag{4}$$

where σ_x is the tensile strength and W_{spec} is the specific work. W_{spec} expresses the effective work (E_2) used in the compression of unit mass of substance (m) at a given compression force. The tensile strength σ_x includes the breaking hardness (H), the diameter (d) and the height (h) of the compact[19]:

$$\sigma_x=\frac{2H}{\pi\cdot d\cdot h} \tag{5}$$

The breaking hardness was investigated using the Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical parameters of the tablets were measured with a screw micrometer (Mitutoyo Corp., Tokyo, Japan).

Dissolution Test The investigations were performed by the USP dissolution method (paddle). The medium was artificial gastric juice (pH=1.2) and its temperature was 37±0.5 °C. The paddle speed was 50 rpm. The samples were analyzed spectrophotometrically (Spectromom, MOM, Budapest, Hungary) at 276 nm. The dissolution rate of ASA was determined from the capsules and the normal tablets. The hard gelatine capsules ($N^0.0$) were filled with 250 mg of unprocessed or processed ASA crystals. The normal tablets contained 3% of sodium starch glycolate as disintegrant agent besides 50% of ASA and 47% of Vivapur® 101. The tablets were also made with a Korsch EKO instrumented eccentric tablet machine. The compression tools were single, flat punches 10 mm in diameter. The tableting force was 10 kN. The results of the dissolution rate of ASA were evaluated by Rosin–Rammler–Sperling–Bennett–Weibull (RRSBW) distribution, and the characterized dissolution time ($t_{63.2\%}$) was determined after linearized regression and transformation by Langenbucher according to the following equation[20]:

$$M=M_0\left\{1-\exp\left[-\frac{(t-T)^{\beta}}{a}\right]\right\} \tag{6}$$

where M is the amount of material dissolved after time t, M_0 is the amount of initial material (maximum), T is the delay time, β is a shape parameter and a is a time parameter. Linearized regression from parameters β and a without T gives:

$$\ln\ln\frac{M_0}{M_0-M}=\beta\cdot\ln t-\ln a \tag{7}$$

where β is the slope and $\ln a$ is the intercept of the straight line. After the transformation according to Langenbucher:

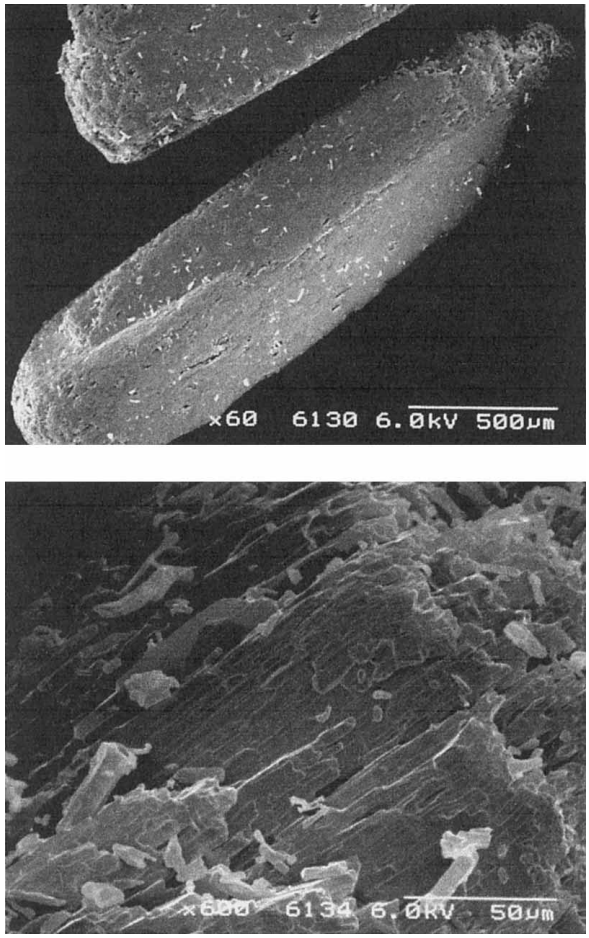

Fig. 1. Unprocessed (Commercial) ASA Crystals
(a) Surface of crystal; (b) edge of crystal.

$$\ln a=\beta\cdot\ln t_{63.2\%} \tag{8}$$

where $t_{63.2\%}$ is the characterized dissolution.

The regression analysis was carried out with the Statgraphics package (Copyright STSC, Inc. and Statistical Graphics Co., U.S.A.); the confidence limit was 95%.

Results and Discussion

The unprocessed, commercial ASA crystals were tetragonal prism-shaped (Fig. 1). Small crystal-debris could be observed on the surface of the larger crystals (Fig. 1a), and the crystal edges were uneven and fragmented (Fig. 1b). About 85% of the particles were between 0.63 and 1 mm in size.

The film formation was first studied with 1% Carbowax® 6000 and 1% stearin in the fluid bed coater. The Strea-1 Aerocoater with the Wurster method facilitated the agitated motion of the crystals in the product column. The electrostatic charge of the crystals was eliminated by the dosage of the lubricants after the first minute of the coating process. Particle size of about 10% of the crystals was decreased by breaking and friability during the coating process (Fig. 2). Increase in particle size because of the sticking effect was negligible. An even Carbowax® 6000 film coat could be seen on the surface of the crystals (coated 1) (Fig. 3a), and the edges were covered and rounded by this film formation (Fig. 3b). One percent of stearin, in contrast, did not produce an even film coat on the surface of the crystals (Fig. 4a), and the edges were partly-covered and rounded (coated 2) (Fig. 4b). This could

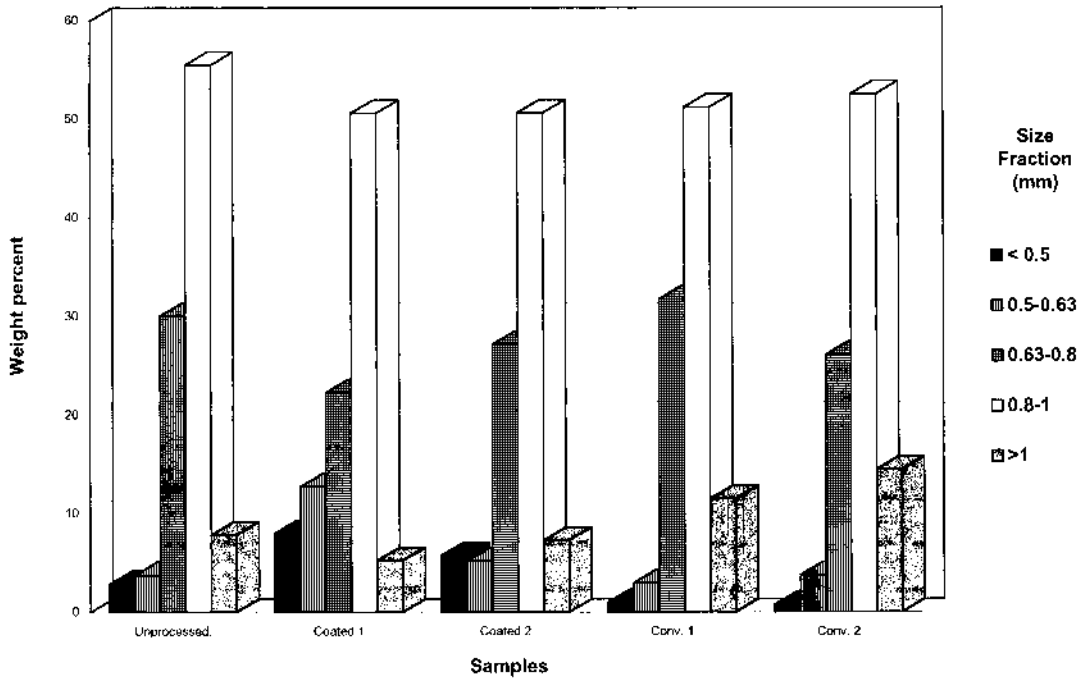

Fig. 2. Particle Size Analysis of Unprocessed and Processed ASA Crystals

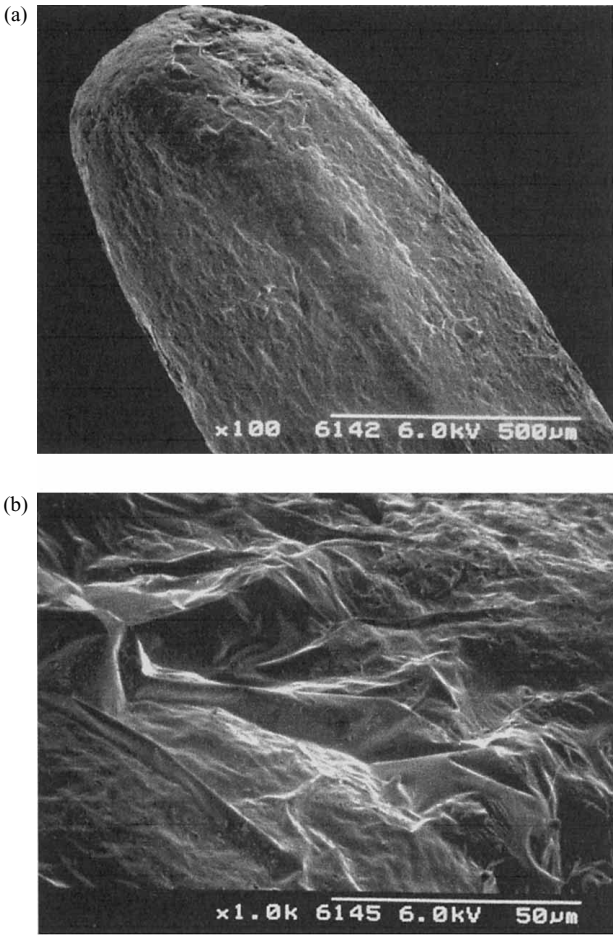

Fig. 3. ASA Crystals with Carbowax® 6000 Film Coat (coated 1)
(a) Surface of coated crystal; (b) edge of coated crystal.

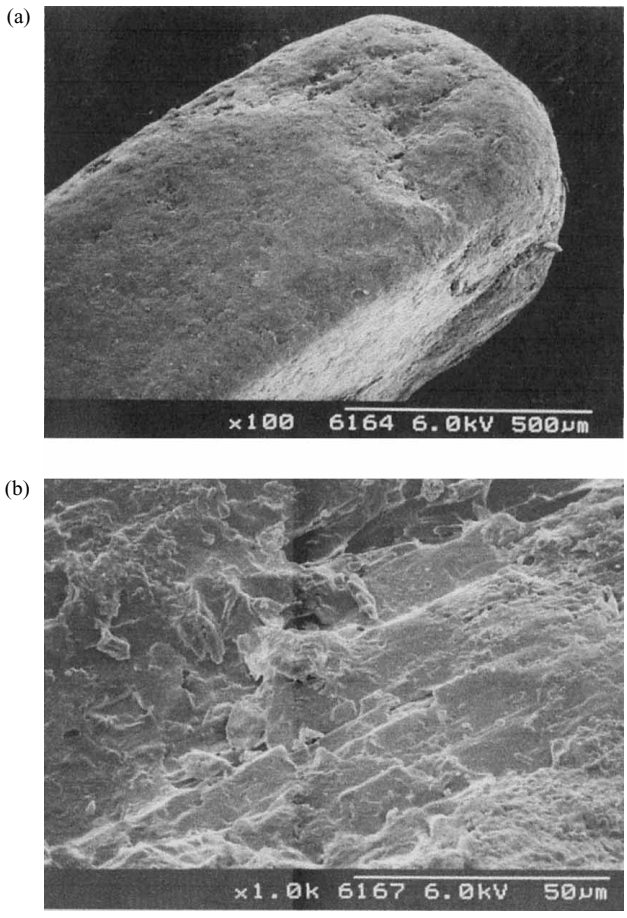

Fig. 4. ASA Crystals with Stearin Coat (coated 2)
(a) Surface of coated crystal: (b) edge of coated crystal.

be explained by the fast solidification and non-film-forming property of the stearin.

The second step in the use of lubricants was the mixing method. During the mixing process, a proportion of the ASA crystals agglomerated. The interparticulate forces between the crystals were strong because the agglomerates were left together during the sieving analysis, and this was confirmed by SEM (Fig. 5a). The amount of small particles decreased and the percentage of long crystals (1 mm) increased (Fig. 2). After the mixing process the surface of the ASA crystals was also studied, and small particles of Carbowax® 6000 could be observed (conv. 1) (Fig. 5b). The stearin was unevenly spread in certain spots on the surface of the crystals, especially on the edges (conv. 2).

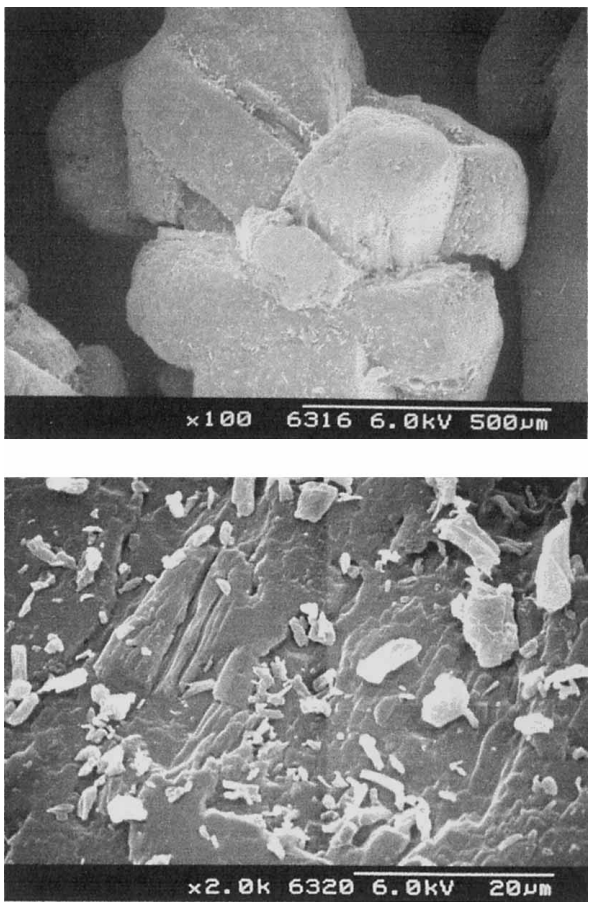

Fig. 5. ASA Crystals with Carbowax® 6000 after Mixing (Conv. 1)
(a) Crystal agglomerate; (b) crystal surface with small particles of Carbowax® 6000.

Table 1. Compactibility (1/*a*) and Cohesivity (1/*b*) Values of Unprocessed and Processed ASA Crystals by Kawakita Model

Sample	1/*ab* (intercept)	1/*a* (slope)	1/*b*	r^2
ASA unprocessed	125.72	25.84	4.88	0.97
ASA coated 1	53.79	32.40	1.66	0.97
ASA coated 2	33.31	28.02	1.17	0.99
ASA conv. 1	131.35	24.40	5.37	0.97
ASA conv. 2	234.60	25.60	9.14	0.98

The coating and the cohesivity of the unprocessed and processed ASA crystals were investigated. Both parameters were very important in capsule filling and tablet making. The coated products (coated 1, coated 2) exhibited better compactibility (Table 1). The very good compactibility value of ASA coated 1 crystals could be ascribed to the even film coat of Carbowax® 6000 on the crystal surface (Fig. 3). The mixing process did not influence the compactibility of the samples of ASA conv. 1 or conv. 2. The cohesivity values gave information on the flow properties of the crystals. It was interesting that the coating process influenced the flowability of the crystals favourably, but the mixing method affected it disadvantageously (Table 1). With the latter method, the lubricants increased the unevenness of the surface of the crystals (Fig. 5).

The compressibility parameters are shown in Table 2. The mass of tablets was 500 mg, which was the maximal space filling of the die cavity. The pressure force was 6 kN. The difference in the pressure force could be explained by the arrangement of the ASA crystals in the die cavity. On the basis of the lubrication coefficient (R) and the friction work (W_f), the coating process was better than the mixing method. The relatively large breaking hardness and the small compressibility (Pr_{mass}) of the unprocessed ASA crystals related to the large effective energy (E_2) and the large friction work (W_f) during the pressing. The compressibility (Pr_{mass}) of the processed samples was greater than that of the unprocessed crystals. As concerns the standard deviation (S.D.), the coated samples had better homogeneity and reproductibility than the mixed sample. For ASA conv. 1 and conv. 2, the standard deviations of the compressibility were very high because of the uneven space filling (arrangement) in the die cavity. The plasticity values ($Pl_{S\text{-}M}$) of the unprocessed and processed crystals showed the good plastic properties of the crystals. The values were the same, not being influenced by the coating or mixing processes.

Table 2. Compressibility Parameters of Unprocessed and Processed ASA Crystals

Sample	Upper punch force (kN)	Lubrication coefficient (R)	Friction work (W_f) (N.m)	Breaking hardness (N)	Plasticity ($Pl_{S\text{-}M}$) (%)	Compressibility (Pr_{mass}) (Pa/J·kg^{-1})
ASA unprocessed	6.09 (SD=0.54)	0.399 (SD=0.01)	4.36 (SD=0.30)	110.2 (SD=9.22)`	98.67 (SD=1.26)	76.94 (SD=6.56)
ASA coated 1	6.18 (SD=0.52)	0.682 (SD=0.01)	2.59 (SD=0.41)	149.8 (SD=10.0)	98.64 (SD=0.49)	122.36 (SD=7.80)
ASA coated 2	5.54 (SD=0.48)	0.690 (SD=0.01)	2.36 (SD=0.33)	123.8 (SD=10.3)	98.39 (SD=0.67)	113.69 (SD=4.44)
ASA conv. 1	5.76 (SD=0.43)	0.552 (SD=0.01)	2.70 (SD=0.19)	125.6 (SD=9.8)	98.48 (SD=0.84)	115.64 (SD=18.80)
ASA conv. 2	6.68 (SD=0.87)	0.573 (SD=0.01)	2.70 (SD=0.34)	148.6 (SD=13.7)	98.41 (SD=0.41)	124.53 (SD=19.92)

Table 3. Dissolution Rate of Unprocessed and Processed ASA Crystals from Capsules by RRSBW Distribution

Sample	$\ln a$ (intercept)	β (slope)	$t_{63.2\%}$ (min)	r^2
ASA unprocessed	−4.5010	1.0326	78.17	0.94
ASA coated 1	−4.4784	1.2282	38.33	0.98
ASA coated 2	−6.2537	1.4579	72.94	0.98
ASA conv. 1	−3.7473	0.9142	59.62	0.99
ASA conv. 2	−4.6479	1.1012	68.09	0.99

Table 4. Parameters of Dissolution Rate of Unprocessed and Processed ASA Crystals from Tablets with 10 kN Pressure Force by RRSBW Distribution

Sample	$\ln a$ (intercept)	β (slope)	$t_{63.2\%}$ (min)	r^2
ASA uncoated	−5.0248	1.6561	20.78	0.99
ASA coated 1	−4.8115	1.6073	19.96	0.96
ASA coated 2	−4.6366	1.3503	30.99	0.99
ASA conv. 1	−5.0764	1.5957	24.08	0.94
ASA conv. 2	−5.2541	1.6239	25.42	0.98

The rates of dissolution of the unprocessed and processed ASA crystals were determined on capsules and tablets compressed at 10 kN. The tablets contained sodium starch glycolate near the dry binder (Vivapur® 101) because of fast disintegration. The characterized dissolution time ($t_{63.2\%}$) indicated that Carbowax® 6000 promoted the rate of dissolution of crystals from capsules (Table 3). In particular, the coating process with Carbowax® 6000 was very advantageous for the dissolution rate of the crystals (coated 1). The stearin in the coating and mixing processes did not influence the dissolution rate of crystals (coated 2, conv. 2). The values of $t_{63.2\%}$, in comparison with the same values of ASA crystals from capsule, decreased substantially when the unprocessed and processed crystals were compressed into tablets (Table 4). This was connected with the breaking and deformation of the crystals under the pressure force. The other important fact was that the tablets contained a super-disintegrant agent (sodium starch glycolate); after the disintegration of the tablets, therefore, dissolution immediately began on the large surface at once. The different influence of the lubricants on the dissolution rate of ASA could also be observed in the case of the tablets.

Conclusion

Finally, it can be stated that the Strea-1 fluid bed coater with the Wurster column was suitable for the production of a lubricant coat on crystal surfaces. The coated crystals, in comparison with mixed samples, had very good compactibility, cohesivity and compressibility values (Table 5). Their lubrication coefficient was higher and the friction work was less than those of mixed crystals. Through use of the coating method with a lubricant (Carbowax® 6000 and stearin), improvements could be attained in the physicochemical process, *e.g.* mixing, filling and tabletting. The dissolution of the active agent could be regulated by the lubricant coat. Rapid dissolution of ASA was observed from capsules when the crystals were coated with Carbowax® 6000.

Table 5. Parameters of Processed ASA Crystals in Comparison with Unprocessed ASA Sample

	Coating process		Mixing process	
	Coated 1	Coated 2	Conv. 1	Conv. 2
Compactibility ($1/a$)	+	+	0	0
Cohesivity ($1/b$)	+	+	−	−
Lubrication (R)	+	+	±	±
Friction work (W_f)	+	+	±	±
Plasticity ($Pl_{S\text{-}M}$)	0	0	0	0
Compressibility (Pr_{mass})	+	+	±	±
Dissolution rate from capsules	+	−	±	−
Dissolution rate from tablets	0	−	−	−

0, Same as the result for unprocessed ASA; +, significantly better than the result for unprocessed ASA; −, significantly worse than the result for unprocessed ASA; ±, slightly, but not significantly different from the result for unprocessed ASA.

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