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Film coating as a method to enhance the preparation of tablets from dimenhydrinate crystals

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Abstract

Crystals of dimenhydrinate as a model drug were used for crystal coating, a method that can be applied to increase the flowability of a material and facilitate the tablet making. An increase in particle size was observed during the film coating. The change in shape of the coated particles was also examined. Some physicochemical parameters changed during coating, e.g. the surface free energy parameters and the wetting of the samples. The amount of coating material (and therefore the coating time) influenced several parameters (the shape of the particles, the flow properties and surface free energy parameters, compressibility and compactibility). Several parameters of prepared tablet (porosity, breaking hardness) were examined. Accordingly, coating of the crystals can be performed in order to enhance the handling of a material with insufficient properties for tablet making.

Keywords: Crystal coating; Dimenhydrinate; Flowability; HPMC; Surface free energy; Tablet making

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1. Introduction

Various methods are applied to increase the flow properties and compressibility of drugs. This procedure can be the spherical crystallization (Szabó-Révész et al., 2001; Morishima et al., 1994; Di Martino et al., 2000) or prepare an intermediate product (pellets and granules (Ghebre-Sellassie, 1989)) from material. It is less known, that the film coating (Ghebre-Sellassie et al., 1987; Ichikawa and Fukumori, 1999) also can increases these parameters. Film coating is a very widespread method for protection, retardation and identification. Gastric-soluble polymers are used to protect ingredients from light, moisture and oxygen, for taste masking and for identification if a colored film is used. Intestine-soluble polymers and permeable polymers which provide drug diffusion are utilized for retardation or local effects, etc. (Cole, 1995).

It is important to know how the morphology (particle size and shape) altered after the coating of particles. The sticking of fine particles during coating is well-known from the literature and this phenomena disturb the determination of film thickness and efficiency of coating (Yuasa et al., 1999; Heng et al.,

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1996). Therefore, electro-microscopical study of surface of coated samples can used for checking the uniformity of film.

The surface free energy is an important physicochemical parameter of solid materials. Several calculation methods have been used to determine the surface free energy from wettability measurements (Buckton, 1990, 1995a). Various important parameters can be assessed from this, e.g. the spreading coefficient (Planinšek et al., 2000), the adhesion and cohesion forces between the dry particles (Barra et al., 1998) or between wet particles (Israelachvili, 1992), etc. It is well-known from the literature, that a decrease in the surface free energy cause an decline in the adhesion force (Li et al., 1992; Christenson, 1993). The adhesion of particles can influence and disturb the powder handling, because of sticking of the particles to other particles and to the surface of machines or container (Podczeck, 1998).

The other effect, which occur during the particle–particle interaction is the friction. This phenomenon can cause problems during the tablet making, e.g. increase the temperature of material, which can destroys the heat sensitive agents (Ketolainen et al., 1993). Several material (lubricants) used for eliminating this difficulty. The disadvantages of these mainly hydrophobic materials are disturbing the dissolution of active ingredient and decreasing the hardness of tablets (Sjökvist and Nyström, 1991; Desai et al., 1993).

The aims of our work were increase the flowability and compressibility of dimenhydrinate to promote the tablet making, protect from several harmful factors and prepare and tasteless solid dosage form. The possible least additives and technological step were used. The crystals were coated in a fluidized bed apparatus with top spray method. A gastric-soluble polymer was used for reach our aim. The protective effects of film (against of heat transition, water uptake) and the effect in dissolution of dimenhydrinate were examined our previous studies (Bajdik et al., 2000, 2002a,b).

In this study, three different samples were made with different amounts of the same coating fluid. The shape and the size of samples, flow properties, the surface free energy, compressibility, compactibility were measured and compared with uncoated sample.

2. Materials and methods

2.1. Materials

The model drug was dimenhydrinate (Ph. Eur. 4th), an ethanolamine derivative, heat sensitive antihistamine used for the treatment of motion sickness, nausea and vomiting (Parfitt, 1999). The film-forming agent was hydroxypropyl–methylcellulose (HPMC) (SEPIFILM LP 010®) (SEPPIC, Paris, France). SEPIFILM LP 010® was applied in an aqueous dispersion which containing a binder, a pigment and a plasticizer. Double distilled water and diiodomethane (Sigma, Germany) were used for contact angle determination.

2.2. Coating

A Strea-1 apparatus (Niro-Aeromatic AG, Switzerland) was applied with the top spray method. The coating material was a 10% aqueous dispersion of SEPIFILM LP 010®.

Parameters:

Nozzle diameter: 0.8 mm
Inlet temperature: 45 °C
Outlet temperature: 30 °C
Blow-out pressure: 5.6 bar
Atomizing pressure: 2 bar
Peripump: 2 ml/min

Sample 1: A 40 g aqueous dispersion was used for 100 g dimenhydrinate.

Sample 2: A 55 g aqueous dispersion was used for 100 g dimenhydrinate.

Sample 3: A 70 g aqueous dispersion was used for 100 g dimenhydrinate.

Since the parameters were constant, increase of the amount of coating fluid caused an increase in the process time (35, 42 or 50 min). The process time includes the coating and drying times.

2.3. Morphological study

A Hitachi S2400 (Hitachi Scientific Instruments Ltd., Tokyo, Japan) scanning electron microscope was utilized. A sputter coating apparatus (Bio-Rad SC 502®, VG Microtech, UK) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3–13 mPa.

2.4. Particle size distribution

A Laborlux S light microscope and a Quantimet 500 (Q500MC) image processing and analysis system (Leica Cambridge Ltd., Cambridge, UK) were used. Five hundred particles were measured. Before the tests, the dimenhydrinate crystals were dispersed in paraffin because of their tendency to aggregate. The coated crystals were measured without this treatment. The software calculates the roundness of the particles. This is a shape parameter. The value for a circle is 1. The larger this value, the worse the shape of the particles.

The equation used was (Ar Rashid et al., 1999):

$$\text{roundness} = \frac{(\text{perimeter})^2}{(4\pi \times \text{area} \times 1.064)} \tag{1}$$

2.5. Flow properties

A Powder Testing System PTG-1 (Pharma Test Apparatebau GmbH, Germany) was applied to determine the mass of a heap, the flow time of 100 ml of sample and the angle of repose.

2.6. Compressibility study

A STAV 2003 Stampfvolumeter was applied for the determination of densities (tapped and loose). Carr's index (Carr, 1965) and the Hausner ratio (Hausner, 1967) are parameters that are widely used to describe the compressibility:

$$\text{Carr's index} = \frac{\rho_\infty - \rho_0}{\rho_\infty} \times 100 \tag{2}$$

$$\text{Hausner ratio} = \frac{\rho_\infty}{\rho_0} \tag{3}$$

where ρ_∞ is the tapped density, and ρ_0 is the loose density.

2.7. Determination of porosity

A Quantachrome SPY-2 (Quantachrome Corp., Syosset, NY) stereopycnometer was used for the determination of the true volume of samples. This is accomplished by employing the Archimedes principle of fluid displacement to determine the volume. The displaced fluid was helium gas ($8\,\text{h}^{-1}$) which can penetrate the finest pores to ensure maximum accuracy. The true volume of the samples (V_P) can be calculated via the following equation:

$$V_\text{P} = V_\text{C} + \frac{V_\text{A}}{1 - P_2/P_3} \tag{4}$$

where V_C is volume of sample cell holder (48.8891 cm^3); V_A is additional volume (27.9403 cm^3); P_2 is pressure reading after pressurizing cell; P_3 is pressure reading after adding V_A.

The true density of samples can be calculated from their mass and true volume.

The porosity of samples (ε) was calculated from the true (ρ_t) and tapped (ρ_v) densities (Kumar et al., 2002).

$$\varepsilon = \left(1 - \frac{\rho_\text{tapped}}{\rho_\text{true}}\right) \times 100 \tag{5}$$

The tapped density (or apparent density) of tablets can be calculated from the geometrical data on the tablets, measured with a screw micrometer (Mitutoyo Corp., Kawasaki, Japan).

The tap density of crystals can be calculated from the volume of samples after 300 taps, measured with a STAV 2003 Stampfvolumeter (Engelsmann A.G. Luwigshafen, Germany).

2.8. Wetting and surface free energy determination

Compacts of the powder (200 mg) were prepared in a highly polished stainless steel punch and die assembly (5 mm × 10 mm) in a Specac (Specac Graseby, England) hydraulic press with a dwell time of 10 s, at a pressure of 2×10^8 Pa. The exact size of the plates was measured with a micrometer. The contact angle of the liquids was determined by means of the Wilhelmy plate technique (Buckton, 1995b), using a Krüss Tensiometer K12 (Krüss GmbH, Hamburg, Germany). Temperature was controlled at $20 \pm 0.5\,^\circ\text{C}$ by means of water flowing from a circulator (Haake, Germany). The test liquid (bidistilled water or diiodomethane) was placed in a clean glass dish and raised by means of a motorized platform at a speed of 1.2 mm/min. From the force measurement, the contact angle was obtained by using the Krüss tensiometer software (Krüss GmbH). Three parallel experiments were performed.

The solid-surface free energy was calculated according to the method of Wu (1971). This is the sum of the polar (γ_s^p) and dispersion (γ_s^d) components of the solid. The solid-surface free energy can be assessed by contact angle measurements with two liquids of known polarity and can be assessed by solving two equations with two unknowns:

$$(1+\cos\Theta)\gamma_l = \frac{4(\gamma_s^d\gamma_l^d)}{\gamma_s^d+\gamma_l^d} + \frac{4(\gamma_s^p\gamma_l^p)}{\gamma_s^p+\gamma_l^p} \tag{6}$$

where γ_l is the liquid surface tension and γ_s is the solid-surface free energy. The dispersion part of the surface tension was 21.8 mN/m for water and 50.8 mN/m for diiodomethane. The polar part of the surface tension was 51 mN/m for water and 0 mN/m for diiodomethane (Oh and Luner, 1999).

2.9. Compactibility study

Compression during tableting is a complex and irreversible dynamic process (Rippie and Danielson, 1981). The behavior of powders during such processes may be followed well with instrumented tablet machines or other indirect methods (Ridgway Watt, 1988).

The samples were compressed into tablets with a Korsch EK0 instrumented eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single flat punches 10 mm in diameter, furnished with strain gauges. The strain gauges allow the pressure forces on the upper and lower punches to be followed with force measuring equipment, which was calibrated with a Wazau HM-HN-30 kN-D cell (Kaliber Ltd., Budapest, Hungary). The compression was carried out electrically at 36 rpm at an air temperature of 24 ± 2 °C and a relative humidity of 45 ± 5%. The same parameters of the tablet machine were applied in every case. The compressed volume was 100 mm^3 for each sample and the setting of upper punch was same. Ten tablets were compressed for each sample. The tablets were stored 1 day in a closed plastic tube from preparation to measurement.

The lubrication coefficient (R) was calculated from the data of forces.

$$R = \frac{F_{\text{lower}}}{F_{\text{upper}}} \tag{7}$$

If the value of this parameter is close to 1, then the force losing because of friction and rearrangement is little. The higher proportion of invested force is useful, the better mechanical properties of tablets.

The breaking hardness of prepared tablets was measured on the Heberlein apparatus (Heberlein & Co. AG, Switzerland).

3. Results

The habit of the crystals is shown in the SEM photo. The dimenhydrinate is columnar small crystals with a wide size distribution (Fig. 1) (Table 1). Many particles were broken. An increase in the size of the crystals was detected during coating (Figs. 2–4) (Table 1). The 2.5–3.0 times increase in dimensions corresponds to the aggregation of 15–27 (2.5^3–3.0^3) crystals in a

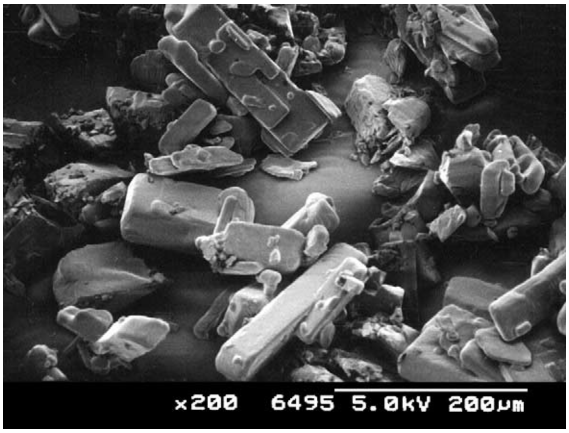

Fig. 1. Dimenhydrinate crystals (SEM).

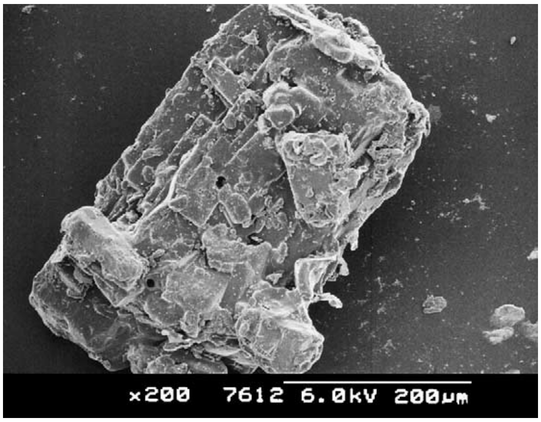

Fig. 2. Dim 1 sample (SEM).

Table 1
Average particle sizes of samples

Sample	Length (μm)	Breadth (μm)	Roundness
Dimenhydrinate	83.84 (S.D. = 54.50)	49.40 (S.D. = 29.28)	1.40 (S.D. = 0.28)
Sample 1	201.95 (S.D. = 114.47)	133.68 (S.D. = 73.63)	1.64 (S.D. = 0.49)
Sample 2	239.49 (S.D. = 129.69)	155.09 (S.D. = 80.75)	1.72 (S.D. = 0.45)
Sample 3	229.90 (S.D. = 159.57)	149.93 (S.D. = 102.24)	1.85 (S.D. = 0.65)

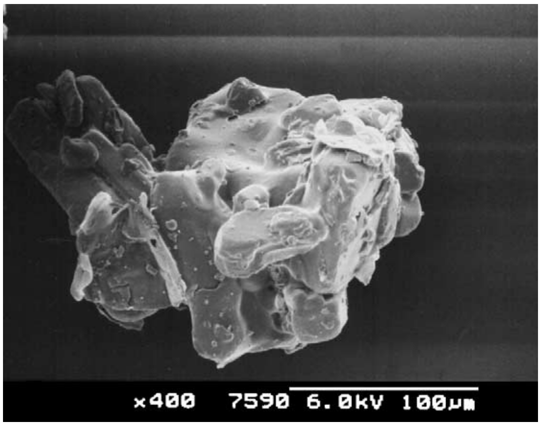

Fig. 3. Dim 2 sample (SEM).

coated particle. It can be seen in the SEM pictures, that the polymer film caused increase in the particle size and covered the surface of these small agglomerates. There was obviously no relationship between the solid content of the coating film and the particle size. Between the shape parameters (roundness values) of the different coated samples exhibited a difference. There was higher value of shape parameter if more the used amount of coating material.

The changes in the shape and size of the particles can be explained in terms of several simultaneous phenomena. The higher amount of polymer caused an increased possibility of particles sticking-together. Cracking and breaking of the crystals occurred frequently during coating (Fig. 5). Another cause of an alteration in shape was the breaking of the coating film; the surface of the particles was therefore uneven and the coating effect of the film was also decreased (Figs. 6 and 7). The broken film ‘tongue’ also influenced the shape of small agglomerates (Fig. 8). The possibility of these phenomena increased when the process time was increased, and the overall resultant of these events determined the shape and the size of the coated crystals.

The porosity is also very important parameter in the pharmaceutical technology. It was the smallest for the uncoated sample; the porosity of Sample 1 differed slightly from that of the untreated crystals, but this parameter was increased significantly ($P < 0.05$) for the other two samples (Table 2). These data also demon-

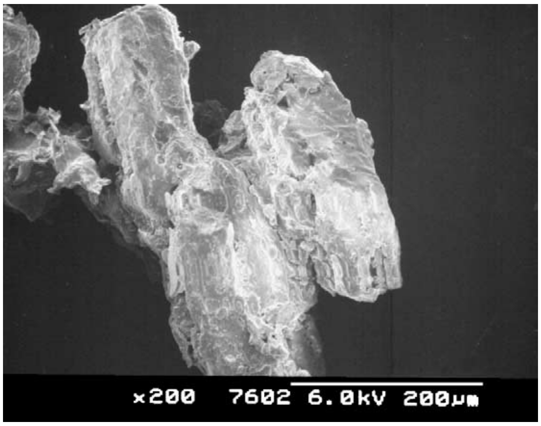

Fig. 4. Dim 3 sample (SEM).

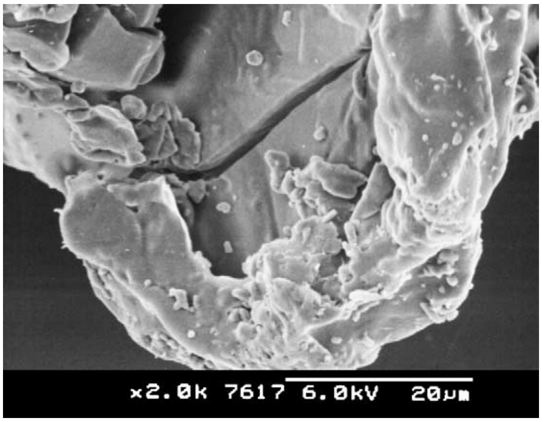

Fig. 5. Crack in coated crystals (Dim 3) (SEM).

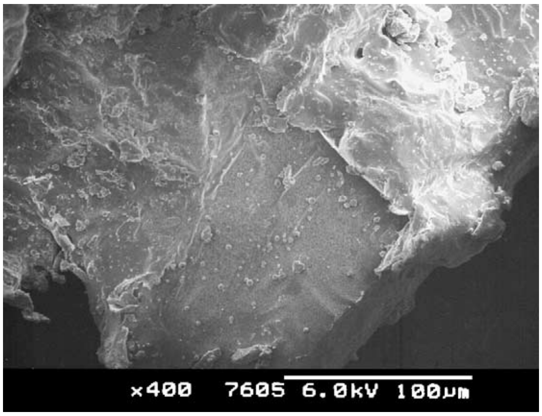

Fig. 6. Uneven coated surface (Dim 3) (SEM magnification: 400×).

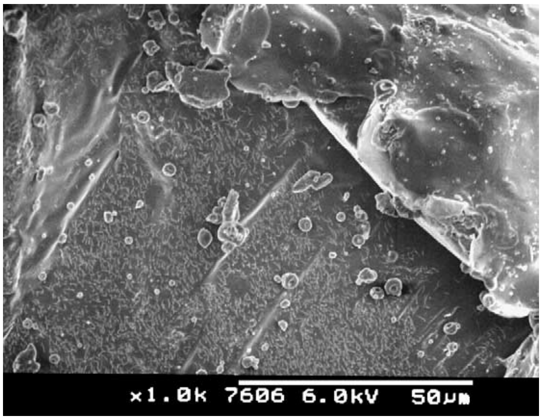

Fig. 7. Uneven coated surface (Dim 3) (SEM magnification: 1000×).

strate, that the too long process significantly changed the shape of the particles.

Flowability tests revealed that the flow properties of the original crystals were inappropriate (Table 3). There was no flow without stirring. These crystals were unsuitable for the tabletting process (Wells, 1988). It can be seen from the data, however, that the coated crystals displayed excellent flow properties.

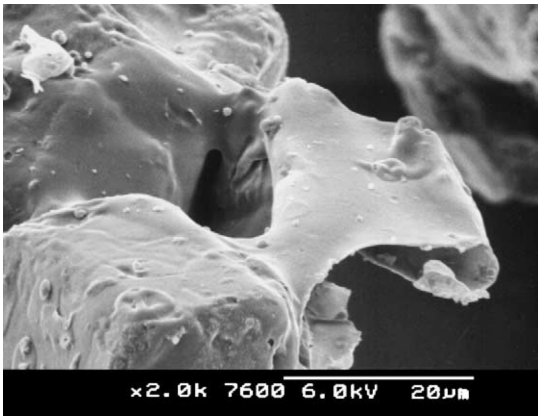

Fig. 8. ‘Film tongue’ (Dim 2) (SEM).

Table 2
Densities of crystals

Sample	Virtual density (g/cm^3)	True density (g/cm^3)	Porosity (%)
Dimenhydrinate	0.6214	4.0667	88.63
	0.0020	0.0091	0.03
Sample 1	0.5175	4.1341	88.70
	0.0013	0.0058	0.02
Sample 2	0.4392	4.1685	90.57
	0.0014	0.0099	0.02
Sample 3	0.4402	4.1443	90.81
	0.0024	0.0234	0.05

It can be seen that the higher amount of coating material caused worse flowing properties. The difference was significant ($P < 0.05$) for flowing time and mass of heap. The cause of this change was the deterioration of the shape of particles.

Similar data can be seen from the results of compressibility test. The coating significantly increased both parameter (Hausner ratio, Carr’s index) and the

Table 3
Flow properties of samples

Sample	Flow time (s)	Angle of repose (°)	Mass of heap (g)
Dimenhydrinate	No measurable	52.53 (S.D. = 1.13)	41.73 (S.D. = 0.31)
Sample 1	6.4 (S.D. = 0.05)	32.4 (S.D. = 0.63)	43.9 (S.D. = 0.29)
Sample 2	7.1 (S.D. = 0.09)	33.4 (S.D. = 0.64)	41.5 (S.D. = 0.83)
Sample 3	7.9 (S.D. = 0.04)	34.8 (S.D. = 1.19)	37.9 (S.D. = 0.48)

Table 4
Compressibility parameters of samples

Sample	Carr’s index (%)	Hausner ratio
Dimenhydrinate	25.57 (S.D. = 0.51)	1.3435 (S.D. = 0.0092)
Sample 1	9.69 (S.D. = 0.57)	1.1073 (S.D. = 0.0070)
Sample 2	10.38 (S.D. = 0.11)	1.1158 (S.D. = 0.0013)
Sample 3	13.46 (S.D. = 0.51)	1.1555 (S.D. = 0.0067)

raised coating time also caused a small decline in these factors (Table 4).

It can be seen that the presence of the film on the surface of crystals significantly ($P < 0.05$) changed the wetting of the sample with the used fluids (polar water and non-polar diiodomethane), and hence the surface free energy parameters decreased (Table 5). There is no significant difference between different coated samples. HPMC is polar but the coating film contained other components. The cause of decreased wetting of the coated samples with water can be the presence of hydrophobic ingredients of SEPIFILM LP 010, e.g. stearic acid as plasticizer.

There is no significantly difference between the surface free energy parameters of different coated samples. Therefore, the higher amount of coating materials did not reduce more surface free energy and therefore the tendency of particles for adhesion.

The untreated crystals were the most difficult to compress, because the filling of the die and therefore the pressure force were uneven (Table 6). Hence, the properties of the tablets was also inconstant. Since every factor of tablet machine was the same, the behavior of the material during compression can be characterized by the relative standard deviation (RSD) of the pressing force measured on the upper punch. The RSD of the upper punch force was 8.51% for dimenhydrinate, 1.16% for Sample 1, 2.26% for Sample 2 and 3.39% for Sample 3. These results accord with those of the flowability and compressibility studies, because they point to the uneven flowing and uneven filling of the die. It can be also seen the slightly increase for samples coated with higher amount of polymer.

The tablets prepared from the coated crystals exhibited a smaller porosity than that of the uncoated ones (Table 6). This change was significant, but there was no significant difference between the various coated products, shown by the ANOVA test (Scheffe method, $P < 0.05$). The causes of the decrease were the better compressibility of the coated samples, the better die filling and therefore the higher force and the film filling the small pores in the texture of samples.

The lubrication coefficient was significantly reduced for uncoated samples. Therefore, the force which wasted because of friction was higher for the dimenhydrinate without coating. So the tablets prepared from the coated crystals exhibited a higher breaking hardness. Some tablets prepared from uncoated crystals broke during the package. The best breaking hardness can be detected for the Sample 1.

Table 5
Surface free energy parameters

Sample	Θ_{water} (°)	$\Theta_{\mathrm{diiodomethane}}$ (°)	γ^{p} (mN/m)	γ^{d} (mN/m)	γ_{s} (mN/m)
Dimenhydrinate	37.65 (S.D. = 2.17)	30.27 (S.D. = 0.21)	26.14	44.32	70.46
Sample 1	63.53 (S.D. = 1.04)	50.68 (S.D. = 1.01)	16.01	35.08	51.09
Sample 2	64.77 (S.D. = 0.85)	54.03 (S.D. = 0.62)	15.87	33.42	49.29
Sample 3	65.80 (S.D. = 1.65)	57.37 (S.D. = 0.68)	15.83	31.81	47.64

Table 6
Tablet making of samples

Sample	Upper punch force (kN)	R	Porosity (%)	Breaking hardness (N)
Dimenhydrinate	17.87 (S.D. = 1.52)	0.49 (S.D. = 0.012)	71.22 (S.D. = 0.20)	45.00 (S.D. = 3.54)
Sample 1	18.83 (S.D. = 0.22)	0.62 (S.D. = 0.005)	69.41 (S.D. = 0.32)	129.80 (S.D. = 3.42)
Sample 2	19.90 (S.D. = 0.45)	0.69 (S.D. = 0.021)	69.29 (S.D. = 0.17)	100.8 (S.D. = 4.86)
Sample 3	19.46 (S.D. = 0.66)	0.59 (S.D. = 0.022)	69.50 (S.D. = 0.35)	98.00 (S.D. = 2.65)

4. Conclusion

There was an increase in particle size after coating. The polymer film stuck together the small particles and covered these small agglomerates. Increase of the polymer content of the film did not alter the size significantly, but the shape of the particles did change. The shape was influenced by coating time. The coating of dimenhydrinate crystals improved the flowing, compressibility properties of the original particles. There is an worsen effect of decreased shape of different coated particle in these parameters. Therefore, the higher amount of coating material and coating time is not advisable to apply. The coating significantly changed the surface free energy, but the amount of coating material did not influenced this, because the surface of crystals coated for every samples. Better tablets can be produced from coated crystals with the same tablet machine inset because of better lubrication, better die filling and compressibility.

A crystal coating with less auxiliary (4 g for 100 g dimenhydrinate) can therefore be useful for preparation of tableting, because it in one step increases the flowability, compressibility of the particles, enhance the tablet making and the coating polymer film provides additional possibilities for change of the disadvantageous properties (unpleasant odor or taste) and protect of materials (light, moisture and heat transition).

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