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RESEARCH PAPER

Surface Treatment of Indomethacin Agglomerates with Eudragit

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ABSTRACT

Indomethacin is a widely used anti-inflammatory drug with serious side-effects. This drug was used as a model drug for the coating of agglomerates with a permeable film (Eudragit NE). The agglomeration of the crystals increased the flowability of the bulk crystals. The coating further improved the flowability, and also the uniformity of the mass of the filled capsules. The coating film also influenced the wetting of the samples. The coating decreased the surface free energy and therefore reduced the adhesion forces between both the dry and the wet particles. The modification of the flow properties and the even capsule filling can be explained by this phenomenon. Since coating film does not dissolve in the artificial gastric juice, the dissolution test was performed only in the artificial intestinal juice. The dissolution of indomethacin from the coated sample was changed significantly. Accordingly, coating of the crystals can be performed in order to protect the mucosa of the gastrointestinal tract or to promote the preparation of solid dosage form.

Key Words: Agglomerates; Coating; Eudragit NE; Indomethacin; Surface free energy.

INTRODUCTION

Indomethacin is a nonsteroidal anti-inflammatory drug, which causes irritation in the gastrointestinal tract, and especially in the stomach.[1–3] The crystals have disadvantageous properties (poor flow properties, a high tendency to adhesion, etc.), which decrease the possibility of processing. Several methods have been used to protect the stomach or to promote the preparation of solid dosage form. Prodrugs of indomethacin,[4]

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coprecipitates with mastic,[5] and Eudragits,[6,7] complexes,[8] a self-emulsifying system,[9] liposomes,[10] nanoparticles,[11] and coated pellets,[12,13] etc. have been prepared from indomethacin. The multiparticulate systems (fine particles) are recommended, because they can reduce the risk of preparation lodging in the diverticulum and reduce the possibility of intestinal perforation.[14,15]

Various methods are applied to increase the flow properties of drugs, e.g., spherical crystallization,[16–18] granulation,[19] film coating,[20] etc. 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, and for identification in the case of colored film. Intestine-soluble polymers or permeable polymers that provide drug diffusion are utilized for retardation.[21] A permeable polymer was used in this study.

The surface free energy is an important physicochemical parameter of solid materials. Several calculation methods have been used for determination of the surface free energy from wettability measurements.[22] Some important parameters can be assessed from this, e.g., the spreading coefficient,[23] and the adhesion and cohesion force between the dry particles[24] or between wet particles,[25] etc. These adhesion forces were determined in this work, because they can be important in the processing of agglomerates and for the safety of preparation.

The aim of this work was to study the effects of agglomeration of the crystals and coating of these agglomerates. Several parameters of the agglomerates—the flow properties, the disintegration of the agglomerates, the dissolution of the active ingredients, and the surface characteristics (roundness, wetting, and surface free energy)—were measured and compared.

EXPERIMENTAL

Materials

Indomethacin (BP 88) (Hemijapharm, Federal Republic Yugoslavia) was used as a model drug. Kollidon® 30 (BASF Aktiensgesellschaft, Germany) was applied as a binder in the agglomeration. Eudragit NE, which is not soluble, but is a permeable polymer in the gastrointestinal fluid, was used in the form of an aqueous dispersion (Rhöm Pharma GmbH Chemische Fabrik, Darmstadt, Germany) as coating material in the coating of the agglomerates. Double distilled water and diiodomethane (Sigma, Germany) was used for contact angle determination.

Aggregation

Crystals were aggregated in a conventional coating pan (Dragex-1, Jorgen Jorgensen, Copenhagen, Denmark). The granulating solution was a 5% aqueous solution of Kollidon 30. A 250 g solution was used for 450 g of bulk substance (only indomethacin).

The parameters were: pan speed, 40 rpm; atomizing pressure, 0.5 bar; Peripump, 20 mL/min; nozzle diameter, 1 mm; and drying temperature, 35°C.

Coating

A Strea-1 apparatus (Niro-Aeromatic AG., Bubendorf, Switzerland) was applied with the bottom spray method in a Wurster column. The coating material was 150 g aqueous dispersion of Eudragit NE for 100 g of indomethacin granules.

The composition of the coating fluid: consisted of Eudragit NE 30 D, 167.0 g; talc, 40.0 g; silicone emulsion, 2.0 g; distilled water, 791 g.

Parameters were: core, indomethacin agglomerates (320–800 μm); nozzle diameter, 0.8 mm; inlet temperature, 45°C; outlet temperature, 30°C; coating time, 15 min; drying time, 5 min; blow-out pressure, 5.6 bar; atomizing pressure, 2 bar; and peripump, 2 mL/min.

Morphological Study

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

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 indomethacin crystals were dispersed in paraffin because of their tendency to aggregate. The treated crystals were measured without this procedure. 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:[26,27]

$$Roundness = (Perimeter)^2(4 \cdot \pi \cdot Area \cdot 1.064)$$

Flow Properties

A Powder Testing System PTG-1 (Pharma Test Apparatebau GmbH, Hamburg, Germany) was used for the determination of flow time of 100 mL of material and angle of repose. Five parallel experiments were performed.

Capsule Filling

The granules (320–800 μm) were filled into the capsules (size 0). A Zuma semiautomatic capsule filling machine (150 A/4 with 150/B-3, Zuma s.r.l., Italy) was used. One hundred and fifty capsules were filled. The material was poured into the machine-opened empty capsules. After this the machine tapped and closed the capsules. The uniformity of the mass of the capsules was determined. Twenty capsules were measured on an analytical balance (Sartorius H110, Sartorius AG, Goettingen, Germany).

Wetting and Surface Free Energy Determination

Compacts of the powder (200 mg) were prepared in a highly polished stainless steel punch and die assembly (5×10 mm) in a Specac (Specac Graseby, Orpington, England) hydraulic press with a 10 s dwell time, 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,[22] using a Krüss Tensiometer K12 (Krüss GmbH, Hamburg, Germany). Temperature was controlled at 20 ± 0.5°C, with water flowing from a circulator (Haake, Germany). The test liquid (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 using Krüss tensiometer software (Krüss GmbH, Hamburg, Germany, 1996). Three parallel experiments were performed.

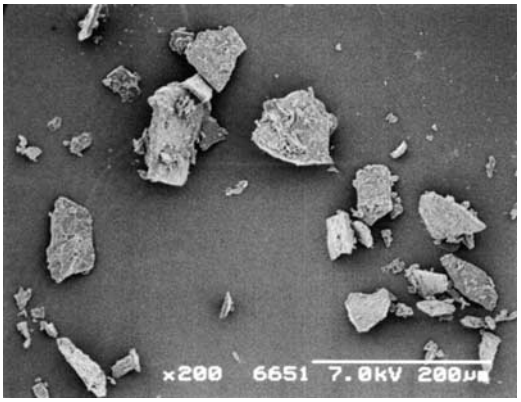

Figure 1. Indomethacin crystals (SEM).

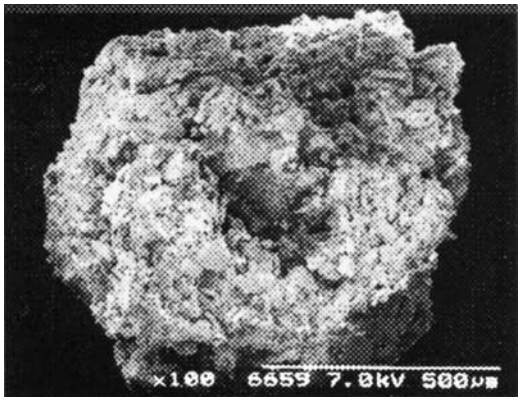

Figure 2. Indomethacin crystal aggregate (SEM).

The solid surface free energy was calculated according to the method of Wu.[28] It 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 of two liquids of known polarity and can be assessed by solving two equations with two unknowns:

$$(1 + \cos\ \Theta)\gamma_1 = \frac{4(\gamma_s^d \gamma_1^d)}{\gamma_s^d + \gamma_1^d} + \frac{4(\gamma_s^P \gamma_1^P)}{\gamma_s^P + \gamma_1^P} \quad (1)$$

where γ_l=the liquid surface tension and γ_s=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.[29]

Cohesion occurs between two identical particles, and adhesion occurs between two different particles. The adhesion force between the particles was calculated according to the Derjaguin approximation.[24] The use of this model is valid for two rigid nonporous macroscopic spheres. In this case, when the force can be determined between two identical particles in the same sample, the force called ''adhesion force'' in a previous publication,[25] is therefore also used in our publication. The determination of adhesion force is valid for spheres. Since the present agglomerates were nearly spherical, this equation can be used for the estimation. Since these particles were not exactly spheres and other parameters too can be considered, e.g., capillary condensation, deformation, etc., the force calculation does not furnish exact data, but can be used to predict how the material behaves.

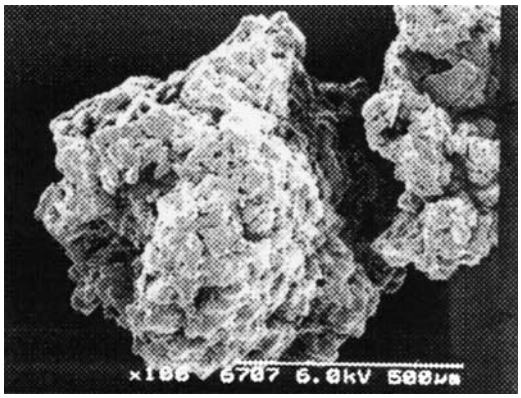

Figure 3. Coated indomethacine crystal aggregate (SEM).

In this case, when the force can be determined between two identical particles in the same samples, the equation can be simplified.[25] The force between two dry particles is

$$F = 2\pi R\gamma_S \quad (2)$$

where γ_S = the surface energy of the particles.

The force between two wet particles is

$$F = 2\pi R\gamma_{SL} \quad (3)$$

where γ_{SL}=the interfacial tension between the solid and the liquid, which is calculated from the polar and dispersion parts of the solid and the liquid:

$$\gamma_{SL} = \gamma_S + \gamma_L - \frac{4(\gamma_S^d\gamma_L^d)}{\gamma_S^d + \gamma_L^d} - \frac{4(\gamma_S^P\gamma_L^P)}{\gamma_S^P + \gamma_L^P} \quad (4)$$

where γ_S=the solid-surface free energy and γ_L=the surface tension of the liquid. Water was used as the test liquid for this calculation because the gastric juice mainly consists of water. Of course, the exact composition of the gastric juice is individual and depends on the composition of the food, i.e., it can contain surfactant-like materials, which may have altered the surface tension, but this parameter was not involved in the calculation.

Disintegration

The granules were exposed to acidic fluid to simulate the first compartment of gastrointestinal tract. The disintegration of crystal aggregates (1.00 g and 320–800 µm) was tested in 50 mL artificial gastric juice (pH=1.2±0.1) at 37±2°C. The uncoated agglomerates were tested in the fluid for 15 min and the coated agglomerates for 60 min. The agglomerates were stirred during the testing. After the testing the wet agglomerates were sieved through a sieve with a wire distance of 320 µm. After drying (105°C), the proportion of undisintegrated aggregates was measured. Three parallel experiments were performed.

Dissolution Tests

The dissolution of indomethacin from the granules (coated and uncoated) was studied with a paddle method.

Test parameters: apparatus, Pharma Test PTWII (equipped with a rotating paddle) (Pharma Test GmbH, Germany); paddle speed, 50 rpm; dissolution medium, 900 mL artificial intestinal juice (pH=7.5±0.1); temperature, 37±1°C; samples taken at 1, 3, 5, 10, 20, 30, 45, 60, 75, 90, and 120 min; number of samples, 6; mass of sample, 30 mg; measurement with a UV spectrophotometer (Unicam Heλios Alpha, Spectronic Unicam, UK) at 267 nm.

Preliminary examinations demonstrated that the coating material did not disturb the measurements.

The characteristic dissolution time ($t_{63.2\%}$) was determined. This is the time necessary for the dissolution of 63.2% of the maximum quantity of drug. The Rosin-Rammler-Sperling-Bennet-Weibull (RRSBW) equation was used:

$$M = M_0\left\{1 - \exp\left[-\frac{(t - T)^\beta}{a}\right]\right\} \quad (5)$$

where M=amount of dissolved drug after time t, M_0=maximum amount of drug, T=delay time, β=shape parameter, and a=time parameter.

Table 1. Particle size of samples.

Sample	Breadth (µm)	Length (µm)	Roundness (shape parameter)
Indomethacin	24.48 SD=14.78	40.37 SD=22.43	1.42 SD=0.25
Uncoated agglomerates	484.72 SD=216.88	657.82 SD=281.06	1.48 SD=0.22
Coated agglomerates	498.92 SD=195.50	693.31 SD=294.86	1.42 SD=0.18

Table 2. Flow properties of samples.

Sample	Time (s)	Angle of repose (°)
Indomethacin	Not measurable	52.08 SD=1.09
Uncoated agglomerates	9.10 SD=0.15	32.20 SD=0.31
Coated agglomerates	7.75 SD=0.57	32.00 SD=0.33

This equation was linearized by Langenbucher:[30]

$$\ln a = \beta^* \ln t_{63.2\%} \quad (6)$$

Linear regression ($p<0.05$) was carried out for the determination of $t_{63.2\%}$ (SPSS 9.0 package Copyright STSC, Inc. and Statistical Graphics Co., Chicago, IL).

RESULTS AND DISCUSSION

The habits of the crystals and agglomerates are shown in the SEM photos (Figs. 1, 2, and 3). The indomethacin consisted of very small, irregular crystals with a broad size distribution (Fig. 1) (Table 1). These crystals formed a compact of almost spherical agglomerates during conventional methods of granulation (Fig. 2). The coating resulted in a uniform film on the surface of the aggregates (Fig. 3). There was a slight, but nonsignificant increase in particle size during the coating (Table 1). This slight increase was explained by the presence of the coating film. Image analysis systems can be used for the determination of film thickness on the surface of pellets.[31] The detected difference was the film thickness and the simultaneous breaking and attrition of the crystal agglomerates.

The roundness value was not changed significantly ($p<0.05$) during the coating; therefore, the shape of the crystal agglomerates was not altered significantly (Table 1).

The flow properties of the crystals were unsatisfactory since they did not flow freely (Table 2). These crystals were unsuitable for further processing (coating, tabletting, and capsulating).[32] It can be seen from the data, however, that the agglomerates and the coated agglomerates displayed good flow properties (Table 2). The coated crystals exhibited a significantly shorter flow time than that of the uncoated crystals.

Table 3. Uniformity of mass of capsulated agglomerates.

Sample	Mass of capsules (g)	SD (g)	RSD (%)
Uncoated	0.3009	0.0088	2.91
Coated	0.3261	0.0058	1.76

Table 4. Wetting of agglomerates.

Sample	Contact angle of water (°)	Contact angle of diiodomethane (°)
Uncoated	72.87 SD=0.64	41.10 SD=1.13
Coated	71.23 SD=0.66	61.47 SD=0.67

Since the flow properties are important during the processing of granules, the products were examined during capsule filling. The relationship was investigated between the results of flow property experiments and capsule filling. The agglomerates were filled into capsules and the mass of the capsules was measured (Table 3). It can be seen that the uncoated agglomerates showed a higher relative standard deviation (RSD) than did the coated ones. This can be explained by the difference in flow properties. It can be stated that the coating increased the flow properties and facilitated even capsule filling.

What is the cause of this advantageous effect? This question is very complex. The slightly modified surface and roughness of the agglomerates may be the first cause of this effect, but other phenomena too play a part in this behaviour, e.g., it can be the surface free energy.

It is important to know the contact angles of different liquids for determination of the surface free energy of a solid (Table 4). The contact angle of water was not changed significantly after coating, but the contact angle of diiodomethane was increased by the coating film.

The surface free energy was derived from the contact angles. The polar part of the surface free energy was increased, but the calculated total surface free energy was decreased after the coating (Table 5). This can be explained by the thin polymer film on the surface of the agglomerates.

If the surface free energy is known, then the forces between the wet and dry particles can be calculated. The average size of the agglomerates was determined as the radius of the spheres (uncoated: 571.27 μm, coated: 591.62 μm) for the calculation.

Table 5. Surface energy of agglomerates.

Sample	γ^p (mN/m)	γ^d (mN/m)	γ_s (mN/m)
Uncoated	10.53	39.65	50.19
Coated	13.84	29.64	43.47

Table 6. Forces between agglomerates.

Sample	F_{dry} (mN)	F_{wet} (mN)
Uncoated	0.180	0.104
Coated	0.162	0.078

The force between the dry coated particles is smaller than that between the uncoated agglomerates (Table 6). The flow properties and the capsule filling findings are supported by this result. The increased adhesive effect between the dry particles can decrease the flow of material.

Smaller particles in the stomach involve a lower possibility of an adverse effect in the case of a mucosa-destroying drug.[15] The aim of formulation was therefore to attain a smaller adhesive effect between the particles in the gastrointestinal liquid. There was a decrease in the cohesion force between the wet agglomerates (Table 6). Hence, the safety of application of the preparation can be slightly improved, without side-effects.

It can be stated that the coating decreases the cohesive force between both the wet and the dry particles. Several properties of the agglomerates are explained by this effect.

It can be important to know the behavior of agglomerates in the gastric juice because serious local side-effects can develop in the stomach. This was proved by the disintegration test in artificial gastric juice. While the uncoated crystal aggregates disintegrated to an extent of almost 100% in 15 min (0.74±0.21% left on the sieve), the coated aggregates did not disintegrate in artificial gastric juice in 60 min (96.32±0.36% left on the sieve). Indomethacin may therefore have fewer side-effects in the stomach if the agglomerates are coated, as the contact effect of particles on the stomach wall cannot be decreased.

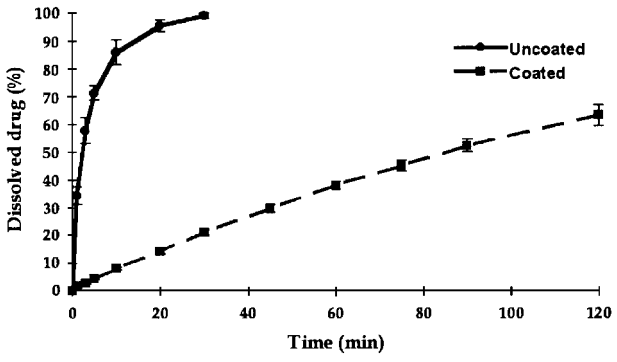

Figure 4. Dissolution of indomethacin from the agglomerate.

Table 7. Mathematical evaluation of dissolution of indomethacin from agglomerates.

Sample	ln a	β	$t_{63.2\%}$ (min)	R
Uncoated	−0.9029	0.7019	3.62	0.9761
Coated	−4.5244	0.9209	136.09	0.9893

Previous experiments showed that indomethacin cannot be measured in the gastric fluid. Since indomethacin is a weak acid and consequently at low pH it is less ionized and soluble.[33] The coated granules did not disintegrate in gastric fluid, therefore, the dissolution testing was performed in artificial intestinal fluid. The results of the dissolution test demonstrated the difference between the uncoated and the coated aggregates. There was a significant difference in shape between the dissolution profiles (Fig. 4). The dissolution was completed in 30 min for uncoated agglomerates, but was not quantitative in 120 min for coated agglomerates.

The dissolution was evaluated on the basis of the characteristic dissolution time ($t_{63.2\%}$). This was significantly longer for the coated crystal aggregates (Table 7).

The shape parameter of dissolution curve (β) exhibited a value close to 1 for the coated agglomerates, which supported the close to linear dissolution profile. The value for the uncoated agglomerates explains the rapid initial dissolution of indomethacin.

The coating film did not dissolve, but the permeability of the film allowed indomethacin liberation. The side-effect due to contact between the particles and the mucosal surface can therefore be avoided.

CONCLUSIONS

It can be stated that indomethacin consists of small particles with a broad size distribution. Aggregation in the coating pan resulted in crystal aggregates with a size and shape suitable for coating. A uniform film was formed on the agglomerate surface during coating. The untreated crystals exhibited the worst, and the coated agglomerates the best flow properties. The coating of the crystal agglomerates decreased the surface free energy and therefore the adhesive forces between both the wet particles and also the dry particles. The better flow properties and the even capsule filling can be explained by the smoother surface of agglomerates

reduction of the adhesion force between the dry particles. The decrease of the wet particles can reduce the possibility of production of large aggregates in the gastrointestinal fluid, which more easily causes deposition in the stomach, and therefore, the possibility of an adverse effect is smaller. The coated indomethacin agglomerates did not disintegrate in 60 min in gastric fluid. The coating altered the dissolution profile of the preparations. Since the coating film did not dissolve in the physiological pH range, application of this type of coating material can therefore decrease the chance of a side-effect of indomethacin.

Finally, it can be stated that the coating of agglomerates of drug with serious mucosa-destroying side effect with a nondissolving film can have a good potential effect on capsule filling, because it facilitates the processing and reduces the possibility of side-effects.

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