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EFFECTS OF FILM COATING ON PROCESSIBILITY OF DIMENHYDRINATE CRYSTALS

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1. INTRODUCTION

The main aim of pharmaceutical technological research is the preparation of a stable dosage form with optimum efficacy without serious side-effects. Solid oral dosage forms (especially tablets and capsules) play a predominant role in medication practice [1]. Research on the factors influencing the manufacturing of these forms is therefore of great importance. Tablets have long been used, but the technology relating to preparation and properties of tablets is constantly developing [2]. This is promoted by changes of the methods and equipment and the application of specific substances. The auxiliary materials and their amounts and the procedures applied must be chosen in accordance with the nature of the active component so that the latter does not undergo any unwanted alterations during the manufacturing. The preparation of modern solid dosage forms demands a well-planned process. The different preliminary steps (micronization, granulation, coating, compression, etc.) and their sequence are important because they can influence the appearance and bioavailibility of the final medicament [3]. Recognition of the effects of each technological stage and their combination on the properties of the ultimate form of the medication is therefore necessary for the development of the exact technology of a new solid dosage form.

2. LITERATURE SURVEY

2.1. Tableting

Compression during tableting is a complex and irreversible dynamic process [4]. The tablets can be produced by direct compression or pressurized from granules. Direct compression is the most efficient tablet manufacturing process because it is the fastest, simplest and least expensive tablet-compression procedure. It requires that different properties of the materials (crystal shape and size, compressibility, compactibility, free flow, plastic behaviour, etc.) should be favourable. Tableting demands the use of excipients (active and additives) with appropriate technological properties, and accordingly such vehicles have been developed and examined [5-13]. Mainly this method is applied for wet-sensitive agents (e.g. effervescent or chewable tablet-making) [14].

A preliminary step is generally necessary for tablet-making, most often involving enlargement processes such as granulation and pelletizing [15]. These methods can also enhance the shape of particles, thereby decreasing the specific surface and the surface roughness. In this way the poor properties of powders (flowability, space filling, compressibility, compactibility,

etc.) can be changed, and the tendency of particles to undergo adhesion, which also influences tablet-making can be decreased.

During compression, the particles can rearrange, break and deform. Various contacts between are formed the particles during this procedure. These contacts determine the mechanical properties of the tablets. Hence, knowledge of the compression process is very important in the technology of tablet-making. The behaviour of powders during such processes may be followed well with instrumented tablet machines or other, indirect methods. Modern instrumented tablet machines measure the precompression and main compression forces on the upper and lower punches, the punches displacement, the ejection force, the die wall hoop stress, the die and punch temperatures, etc. [16]. The temperature is an important parameter, because the energy expenditure of compression is the sum of the useful energy, the energy of reversible elastic strain and the energy dissipated as heat [17]. The main causes of the heat produced are the friction between the particles and the die wall or between the crystals, and the high pressure, which induces deformations in the crystals and alters their energy content. The heat originating and the changes occurring are influenced by crystal parameters such as their size, shape, surface area and thermal conductivity. The crystal rearrangement in the die can influence the heat genesis. It is well known that, if crystals are arranged side to side with a high thermal conductivity edge, this promotes the attainment of a higher temperature in a very small volume. This increased temperature can be higher than the melting point of the material and the crystals melt. Since melted materials recrystallize after compression, the particles lose their individuality. Such sites in the texture are called hot spots [18-20].

Direct measurement of the heat originating in the texture of tablets during compression is very difficult. Methods such as calorimetry [21], indirect measurements and calculations [22] are used to learn the behaviour of materials exposed to compression and heat. The energy distribution and therefore the heat produced in the texture are not uniform, as demonstrated by indirect experiments. For example, a light-yellow ring was observed in the edge of the texture of an Avicel PH 101 comprimate [23]. The reason for this was the uneven force distribution and therefore the uneven heat genesis. This light-yellow colour of Avicel PH 101 can be seen at 140 °C, which means that this temperature can be reached during loading.

The melting points of many organic materials are low, and are readily reached during the process of compression, e.g. busulfan 115-118 °C, hyoscyamine 106-109 °C, phenylbutazone 104-107 °C, or dimenhydrinate 102-105 °C [24]. If a material decomposes at the melting point, hot spots must be avoided because the biological effect may be influenced. This problem can

arise with hormones (e.g. betamethazone or spironolactone), carbohydrates, enzymes (pancreatin [25, 26]), and etc. Reduction of the heat that arises is therefore important with these materials.

This heat can be reduced via the decrease of friction (between the particles or between the particles and the wall of the apparatus) and pressure force and via cooling of the tablet machine. An increase of flowability can reduce the friction. This can be achieved by the use of other ingredients (glidants, lubricants) or technological procedures (spherical crystallization [27-29], granulation [30], film coating [31, 32]). The amounts of other additives that may be used are restricted because of various unpleasant effects. Talc is a well-known glidant, but it has a mucous membrane-irritating effect [33]. Magnesium stearate is a widely-used lubricant, which forms a thin film on the wall of the die and the surface of tablets. This film promotes the ejection of the tablets [9]. Too much lubricant can produce a hydrophobic surface on the tablets and can decrease their breaking hardness tablets [34]. The use of different technological methods is therefore more practical for tablet-making because of several other potential advantageous effects (restriction of heat transition, alteration of dissolution, protection of ingredients, etc.).

2.2. Granulation

The production of granules has two aims. Granulation is primarily a preparatory step prior to tableting or capsule filling. Another less common aim is to produce an independent dosage form. There are several methods for the preparation of granules (dry, wet, melting etc.) [35]. The most important process is wet granulation [36]. A powder or more generally powder mixture is wetted by a liquid, which fluid can be a solvent for any component of the powder mixture or can contain a binding agent. During the procedure, fluid bridges are formed between the particles [37]. In the course of the subsequent drying, the solvent evaporates and solid bridges are formed, which causes the agglomerates to stick together. This film can be the recrystallized material or the macromolecular film or both. The shape, porosity and structure of the granules formed can be determined by the movement of the powder, via the energy of rotation (a conventional coating pan, rotating drum or pelletizing disk), the energy of fluidization or a combination of these (centrifugal granulator).

Various specific ingredients can be applied, e.g. different fillers in powder for the preparation of granules or pellets with ideal properties (shape, texture, flowability, etc.). However, the application of such ingredients for the preparation of tablets with a high active agent content is restricted because of the size of the tablet [38]. Thus, one of the aims of pharmaceutical technological investigations is to determine a good technology which will enhance the processibility through the addition of a very small amount of some other substance.

2.3. Coating

Coatings were already used in Middle Ages. A number of Arab doctors (such as Al Razil and Avicenna) utilized the surface treatment of medicaments. This technological step became very popular because of its advantageous effects.

The following modes of coating are known:

- conventional sugar coating,
- melting coating [39],
- dry or compression coating [40],
- film coating [41].

2.3.1. Film coating

A film coating is a thin polymer-based coat applied to a solid dosage form (tablets, capsules or granules). This polymer film exhibits good properties of adhesion to the solid surface [42]. The first reference to tablet film coating appeared in 1930, but Abbott Laboratories produced the first film-coated tablet in 1954 [41]. Major progress in the preparation of film coatings was made with the introduction of semi-synthetic cellulose derivatives such as methyl- and ethylcellulose and, from 1955 onwards, fully synthetic polymethacrylates with their specific solubility properties adapted to the pH conditions of the digestive tract [43]. Organic solutions of polymers were initially used, which have a number of unpleasant properties, e.g. hazardous for health and the environment, a higher risk of explosion, and the need for use expensive solvents and apparatus. These fluids were therefore replaced by aqueous dispersions, which have been applied since 1972 [44].

Film formation from an aqueous polymeric dispersion is a complex matter. In the wet state, the polymer is present as a number of discrete particles and these have to come together in close contact, deform, coalesce and ultimately fuse together to form a smooth film. During this process, the surface of the solid is wetted by the dispersion solvent [41]. These procedures are accompanied by the loss of water as water vapour. The main factor which can influence the properties of the film and the efficacy of coating is the temperature [45, 46]. Bellow the minimum film-forming temperature, a glassy, cracked and uneven film is produced from the coating fluid [47].

Coating films can be divided into three groups: gastric-soluble, intestine-soluble and permeable films.

2.3.1.1. Gastric soluble films

Such conventional films can be used for the following purposes:

- for taste and odour masking,
- for protection against environmental factors (light, humidity or oxidation), thereby ensuring the physical and chemical stability of the active agent,
- for facilitation of the handling of the dosage form and the prevention of dusting,
- for improvement of the administration with the resulting enhancement of patient compliance,
- for colouring purposes, so as to allow easier identification.

Various polymers can be used for such film coatings. Different polyethylene glycols can be applied; as an example, Macrogol 6000 in ethanolic solution is a good and rapid film-former agent [48, 49]. Some cellulose derivatives (especially cellulose ethers, e.g. hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose or hydroxyethyl cellulose) are applicable for this purpose. Polyvidone and polyvinyl alcohol also form gastric-soluble films [50]. The methacrylate aminoester copolymers, which are insoluble in water, but dissolve in acidic media, are also of value, e.g. the copolymers of dimethylaminoethyl methacrylate and other methacrylate esters (Eudragit® E) [43]. The above-mentioned polymers can be combined with each other.

2.3.1.2. Enteric polymer films

These polymer films can be used with the following aims:

- for protection of the stomach against the irritating effect of the active agent,
- for protection of the active agent against the acidic medium of the stomach,
- for elimination of the disturbing effect of the active agent on digestion,
- for a local effect.

The following materials can be used as intestine-soluble coatings:

Shellac is a modified and purified resinous secretion of the insect *Laccifer lacca*, indigenous to India. It has been withdrawn because it suffers from quality variation and stability problems, but it is still used in the food industry [51].

Methacrylic acid copolymers are widely used because they possess free carboxylic groups: these form salts with alkalis and give rise to appreciable solubility at a pH in excess of 5.5. The best-known anionic copolymers are the Eudragit® L and S.

Different cellulose ethers can also be used, e.g. cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate or cellulose acetate trimellitate [41].

2.3.1.3. Permeable films

These films are insoluble over the entire pH range, but swell in digestive fluids. In the swollen state, they are permeable to water and dissolved actives. The hydrophilic groups within the polymer control the water absorption, the degree of swelling and the permeability of the films. The active ingredients thus enveloped are gradually dissolved by penetrating water and diffuse outwards through the intact polymer membrane. This group of films with different permeabilities can be used for similar aims of gastric or enteric coats. The chemical structures determine the permeability of the films and hence the speed of the release of the active agent. Combination of these neutral, permeable polymers with soluble types permits the attainment of the desired release mechanism [43].

The methacrylate copolymers and several cellulose ethers are the most important permeable film-forming agents. The carboxyl groups of methacrylate copolymers are fully esterized and these polymers are therefore neutral. Eudragit® NE contains poly(ethyl acrylate, methyl methacrylate 2:1) copolymers and the diffusion of the active ingredient through this film is slow. Eudragit® RL contains copolymers of acryl and methacryl esters and also quaternary ammonium salts. Ethylcellulose is widely applied because it forms a smooth coating film [52, 53].

3. AIMS

The primary aim of this study was to increase the processibility of dimenhydrinate, which is a heat-sensitive and hard compressible material. These properties are supported by industrial experience. Direct tablet-making, with quick and economical compression, can not be used. Some preliminary process is necessary. Two methods (the film coating of crystals with a gastric-soluble polymer and granulation) were used in this work. Three different polymers were applied for coating and the products were examined. The results are considered into two groups. In the first, the properties of the products coated with different polymers, the granules and the original untreated crystals were compared. In the other part of this study, different amounts of coating fluid, containing hydroxypropyl methylcellulose, were used and the effects were evaluated. The important parameters of the particles as concerns tablet-making were analysed: the size and shape of the particles, the flowability, the surface properties (wetting contact angle, surface free energy and lubrication), the compressibility, the compactibility, the dissolution of the active ingredient from the product and the behaviour of the drug under thermal stress, which was followed by thermomicroscopy and differential scanning calorymetry (DSC). The effects of different methods on these factors and properties of the tablets were compared.

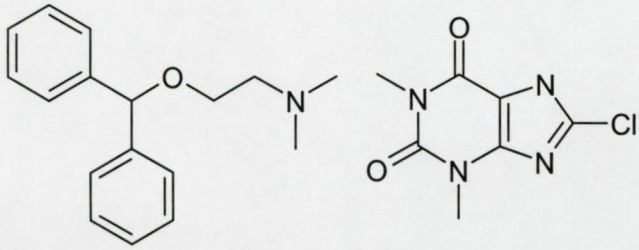
The film smoothness and thickness determine the protective effect of the coating film. These parameters are usually well measurable on the surface of tablets or pellets by direct methods (image analysis and screw micrometry) [54], but in present case this was impossible for several reasons. Indirect methods can also be used for film-coated crystals, and establishment of such methods was a further aim of the study.

Crystal coating is not widely used to promote compression, but rather to achieve several additional favourable effects (taste masking, protection against environmental factors, etc.) [41]. It may be beneficial to apply this technique because only small amounts of additives are involved (a lower possibility of interactions) and, with only one technological step, two aims can be reached (increase of processibility and protection). Moreover, these methods can be more economical than other preliminary processes. The main aim of this study was to investigate this.

4. MATERIALS AND METHODS

4.1. Materials

The model active agent applied was the dimenhydrinate (dramamnine) (Richter Gedeon Rt. Hungary).



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This material is a salt of diphenhydramine and 8-chlorotheophylline. The chlorine increases the acidity of theophylline to such an extent that this is real salt. Dimenhydrinate contains a minimum of 53-55% diphenhydramine (2-benzhydryloxy-N,N-dimethylamine) and 45-47% 8-chlorotheophylline (8-chloro-1,3-dimethyl-2,6(1H,3H)-purinedione). It forms colourless or white crystals or a powder which is odourless and bitter. It is well soluble in ethanol and other organic solvents, but only slightly soluble in water [55]. It is official in the European [56], the British [57] and the United States Pharmacopoeia [24]. It is heat-sensitive, but the sterilization of this material is possible at 100 °C during 30 min.

Dimenhydrinate is an ethanolamine derivative antihistamine (H1 antagonist) [58, 59]. The drug is well absorbed from the gastrointestinal tract and metabolized by the liver. Its clinical effect lasts for 4-6 h. It is applicable orally, intramuscularly or rectal [33]. It is therefore in circulation in several forms, e.g. injections, suppositories, syrups and tablets. Other forms are

under development, e.g. chewing gum [60], transdermal patch [61] and retard tablets [62]. The main fields of utilization are for the reduction of vomiting and nausea, especially in motion sickness, postoperative vomiting (in combination with other components) and labyrinthic disease [63, 64]. Its effective doses are 50-100 mg (not more than 400 mg) for adults and 25-50 mg (not more than 150 mg) for children. Its therapeutic blood level is 25-50 ng/ml. In the event of oral administration, the onset of the effect occurs after about 15 min [65]. The side-effects of H1-antagonists (sedation and fatigue) can occur [66]. The abuse of dimenhydrinate as a narcotic drug is known among adolescents [67, 68]. It is used in Hungary as the active agent of Daedelon and Daedelonetta [69].

Kollidon® 30 (BASF Aktiengesellschaft, Germany) is a synthetic, well water-soluble, light-yellow polymer (polyvinylpyrrolidone). It is official in the Hungarian Pharmacopoeia (Ph. Hg. VII). It is widely used in pharmaceutical technology e.g. as a binder for tablets and granules, or as a stabiliser for emulsion or suspensions, it increases the viscosity of eye-drops and it can be applied as a film coating (this film is well soluble throughout the gastrointestinal tract [70].

Sepifilm® LP 010 (SEPPIC Inc., France) is a powder mixture containing hydroxypropyl methylcellusose as a film-forming agent, a very often applied as an additive in pharmaceutical technology [71-73]. The other components of Sepifilm® LP 010 are microcrystalline cellulose as binder, stearic acid as hydrophobic plasticizer, and pigments [74]. Films prepared from it are well soluble in the gastric juice, and can therefore be used for protective purposes.

Eudragit® RD 100 (Rhöm GmbH Chemische Fabrik, Germany) is a fine white powder mixture which contains 100 parts of Eudragit® RL 100 and 10 parts of carboxymethylcellulose sodium. The films prepared from it quickly disintegrate and are well permeable, independently of the pH. It is therefore used in an aqueous dispersion for purposes of protective coating.

Eudragit® E PO (Rhöm GmbH Chemische Fabrik, Germany), fine white powder is a cationic copolymer of dimethylamino ethylmethacrylate and neutral methacryl esters. The film formed is soluble at pH<5 and permeable at pH>5. It is used as gastric-soluble protective coatings.

Sodium lauryl sulphate (Ph. Hg. VII.) a loose white powder, is a mixture of sodium alkyl sulphates, and especially sodium lauryl sulphate. It is mainly used as an emulsifier agent (o/w emulsion).

Magnesium stearate (Ph. Hg. VII.) is a sticky, fine, tasteless and odourless, white powder. It is insoluble in water. It is used as a glidant, lubricant and antiadhesive agent.

Polysorbate 80 (Ph. Hg. VII.) is a yellow oil-like fluid with a maximum water content of 3%. It is mainly used as an emulsifier agent, but it can be applied as a plasticizer in coating fluids.

Dibutyl sebacate is a colourless oil-like fluid, which is often used as a plasticizer in coating fluids [75].

4.2. Granulation

Dimenhydrinate crystals were aggregated in an open conventional coating pan (Dragex-1, Jørgen Jørgensen, Denmark). The rotation of the pan and the stirrers ensured the movement and the uniform wetting of the powder. A pneumatic atomizer was used to spray in the granulating solution, a 5% aqueous solution of Kollidon® 30. This fluid was carried by a peristaltic pump. Heated air was used for drying. The resulting powder was siphoned off with a tube situated at the hole in the pan. The granules contained only the active ingredient and the binder.

Parameters:

Pan speed: 40 rpm

Atomizing pressure: 0.5 bar

Peripump rate: 20 rpm

Nozzle diameter: 1 mm

Drying temperature: 35 °C

The larger particles were eliminated by a sieve with a mesh size of 1.2 mm at the end of the process.

The quantity of starting powder was 300 g, and 200 g of granulating fluid was utilized (with 10 g solid content). This sample was designated *Sample 1.*

4.3. Coating

4.3.1. Preparation of coating fluid

The fluid prepared from Eudragit® E PO was stirred for 2 h.

The composition of coating fluid was:

Eudragit® E PO..... 57.0 g

Sodium lauryl sulphate..... 4.0 g

Dibutyl sebacate..... 8.6 g

Magnesium stearate..... 14.5 g

Distilled water..... 278.0 g

Solid content of fluid: 23.23%

The fluid prepared from Eudragit® E PO was stirred for 30 min.

Eudragit® RD ..... 130.0 g

Polysorbate 80 ..... 26.0 g

Distilled water ..... 844.0 g

Solid content of fluid: 15.60%

The fluid prepared from Sepifilm® LP 010 was stirred for 30 min at high speed.

Sepifilm® LP 010 ..... 100.0 g

Distilled water ..... 900.0 g

Solid content of fluid: 10%

4.3.2. Coating process

The crystals were coated in a Strea-1 fluidized bed apparatus (Niro-Aeromatic AG., Switzerland). The top-spray method was applied. The suitably heated fluidizing air stream ensured the mixing and the drying. A peristaltic pump was used to convey the coating fluid, and a pneumatic atomizer was used to spray into the powder bed. The filters on top of the plastic column inhibit powder elimination from the tube. The resistance of these filters was controlled so as to eliminate the risk of a powder explosion. The coating and drying proceeded in one step, but drying for 15 min was applied at the end of coating for every sample.

The constant coating parameters:

Nozzle diameter: 0.8 mm

Inlet temperature: 45 °C

Blow-out pressure: 5 bar

Atomizing pressure: 2 bar

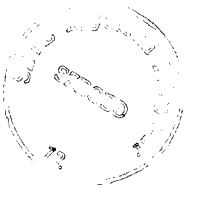
Peripump rate: 2 rpm

In the first part of the work, the properties of the products coated with different polymers, the granules and the original untreated crystals were compared. The applied solid content was constant for every coated sample (5.5 g/100 g dimenhydrinate). Accordingly, the quantities of applied coating fluids were:

24 g for Eudragit® E PO (*Sample 2*)

35 g for Eudragit® RD (*Sample 3*)

55 g for Sepifilm® LP 010 (*Sample 4*)



In the second section of the study the properties of products with different quantities of the same coating material (Sepifilm® LP 010) and of uncoated dimenhydrinate crystals were examined. The following products were prepared.

Sample 5 4 g of applied solid material/100 g dimenhydrinate
processing time 35 min

Sample 6 5.5 g of applied solid material/100 g dimenhydrinate
processing time 42 min
(corresponding to *Sample 4*)

Sample 7 7 g applied solid material/100 g dimenhydrinate
processing time 50 min

The processing time includes the coating and drying times.

4.4. Methods of investigation

4.4.1. Particle size and shape study

Study of the dimensions of particles is very important in several fields of pharmaceutical technology. These parameters influence the flowability of materials (and hence the processibility), the dissolution of the active ingredient from the samples (small particles dissolve out better than large ones) and thus the biological response to the preparation, etc.

Microscopy, and especially scanning electron microscopy (SEM), has been widely used to test the shape and surface of particles. A Hitachi S 2400 (Hitachi Scientific Instruments Ltd, Japan) scanning electron microscope was used. A sputter coating apparatus (Bio-rad 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.

A Laborlux S light microscope and a Quantimet 500 (Q500 MC) image processing and analysis system (Leica Cambridge Ltd., UK) were used to determine the shape and size of particles. 500 particles were measured. Before the tests, the dimenhydrinate crystals were dispersed in paraffin because of their tendency to aggregate. The treated 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 [76]:

$$\text{roundness} = (\text{perimeter})^2/(4*\pi*\text{area}*1.064) \quad (1)$$

4.4.2. Flow properties

A Powder Testing System PTG-1 (Pharma Test Apparatebau GmbH, Germany) was used for the determination of flow properties. This apparatus is controlled by software. The powder is contained in a barrel with 100 ml capacity. The powder can flow through a hole with a diameter of 10 mm to a plate which is connected to a balance (Sartorius BP 310 S, Sartorius A.G., Germany). The powder flow is controlled by sensors. This apparatus measures the flow time of 100 ml of material, and the mass and height of the heap and it calculates the angle of repose, the volume of the heap and the virtual densities of samples. The angle of repose is excellent if <25 ° and poor if >40 °. Values of 25 °-40 ° are acceptable [77].

A stirrer can be connected to the apparatus, its rotation rate also being regulated by the software. The stirrer can be used for materials with low flow properties. Five parallel experiments were performed.

4.4.3. Compressibility study

The powder rheological studies can be supplemented with compressibility studies. A STAV 2003 Stampfvolumeter (Engelsmann A.G. L. Germany) was applied for the determination of densities. This apparatus is in accordance with the DIN standards. Carr`s index [78] and the Hausner factor [79] were determined. These data relate the compressibility and the flowability of materials. Three parallel measurements were performed.

$$\text{Carr`s index} = \frac{\rho_\infty - \rho_0}{\rho_\infty} \times 100 \qquad (2)$$

$$\text{Hausner factor} = \frac{\rho_\infty}{\rho_0} \qquad (3)$$

where ρ_∞ is the tapped density,

and ρ_0 is the loose density.

Carr`s index is excellent if <15% and poor if >23%. Values between 15% and 23% are acceptable for tablet-making or capsule filling. A material is good for processing if the value of the Hausner factor is <1.25 [77].

4.4.4. Wetting and surface free energy determination

Particle-particle adhesion is a disturbing interaction in powder handling. The direction of the force between interlocking particles is horizontal. The adhesion between solid particles is essentially determined by the structure (e.g. shape, size and roughness) and the properties (elasticity and surface free energy) of the surface [80].

The most important parameter to consider in solid-solid contacts is the work of adhesion. This factor can be defined as the free energy change required to separate unit areas of two surfaces from contact to infinity in vacuum. If the surfaces are different, the energy is called the work of adhesion. If the surfaces are the same, the term work of cohesion can be used. The surface free energy of a material is the change in free energy during increase of the surface area by one unit. The commonly used symbol for the surface free energy of a solid is γ. The work of adhesion can be calculated from the surface free energy [81]. In the work of cohesion, two identical new surfaces are formed from originally homogeneous particles. The work of cohesion must compensate the surface free energy of both new surfaces. Since both parameters (the work of cohesion and the surface free energy) relate to unit area, the following equation can be used to determine the work of adhesion.

$$\Delta\gamma_k = 2\gamma_s \tag{4}$$

Under ideal conditions (no energy dissipation) the work of adhesion required separate two identical solid surfaces is numerically equal to the energy released if the two surfaces come into contact.

In general, the value of the surface free energy of a solid can be assayed by indirect methods. Assay of the contact angle, isothermal microcalorimetry and inverse gas chromatography are widely used methods for the determination of surface free energies [82], which can be divided into a dispersion part and a polar part [83].

$$\gamma=\gamma_p+\gamma_d \tag{5}$$

The Wu equation [84], which took into consideration the Young equation, is a widely-used mathematical approach to surface free energy. It can be calculated from the contact angle of a material in two different fluids.

$$(1+\cos\Theta)\gamma_1 = \frac{4(\gamma_s^d\gamma_l^d)}{\gamma_s^d+\gamma_l^d} + \frac{4(\gamma_s^p\gamma_l^p)}{\gamma_s^p+\gamma_l^p} \tag{6}$$

The polarities and surface tensions of the liquids are known, and thus the two unknown factors (the polar and dispersion components of the solid surface free energy) can be calculated from by two equations containing the results of two experiments. It is important to know the surface free energy parameters, which can be relevant in several fields of pharmaceutical technology (e.g. powder inhalations, suspensions, granules, etc.) [85, 86].

In this study, the contact angles were determined and the Wu equation was used for the determination of surface free energy. Measurements on the wetting of fine particles (powder) are very difficult, and therefore several preliminary methods are used for its determination [87, 88].

Compacts of the powder (200 mg) were prepared in a highly-polished stainless steel punch and die assembly (5x10 mm) in a Specac (Specac Graseby, England) hydraulic press with a 10 s dwell time, at a pressure of $2x10^8$ 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 [89], using a Krüss Tensiometer K12 (Krüss GmbH, 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. 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 [90]. From the force measurement, the contact angle was obtained by using Krüss tensiometer software (Krüss GmbH, Germany, 1996). Three parallel experiments were performed.

4.4.5. Thermoanalytical studies

4.4.5.1. Thermomicroscopy

A Boetius thermomicroscope (VEB Analytik Germany) was applied to visible alterations (sublimation, melting and recrystallization) in the crystals during the heating process. This apparatus contain a microscope with a heatable plate. The heating rate applied was 5 °C/min.

4.4.5.2. Differential scanning calorimetry (DSC)

Important effects (interactions) and properties in pharmaceutical technology can be investigated by DSC methods [91, 92]. A differential scanning calorimeter measures the difference between the heat flows to the sample and reference pans, which are subjected to the same temperature program. Heat flow corresponds to transmitted power and is measured in watts (W). If the heat flow is integrated with respect to time, a quantity of energy is obtained which is expressed in units of mJ [93]. If the sample absorbs energy, the enthalpy change is said to be endothermal, e.g. melting, desolvation, dehydration, decomposition, etc. If the sample liberates energy, the enthalpy change is said to be exothermal, e.g. crystallization and recrystallization [94].

The changes in energy and enthalpy of different thermal processes can be detected. The calorigram can be used for qualitative (crystallization, melting behaviour, polymorphism and chemical interactions) and quantitative (crystallinity) analyses. The temperatures and shapes of peaks are characteristic of the materials, and the sizes of the peaks are determined by the quantities of the materials.

This method can be used to evaluate the behaviour of material exposed to elevated temperatures [95, 96].

A DSC 821^e (Mettler-Toledo GmbH, Switzerland) apparatus was used in this study. 7.3-7.6 mg dimenhydrinate was measured into the pans (40 µl, aluminium) and an air atmosphere was applied. The DSC curves were studied with STAR^e software. The glass transition was evaluated according to DIN. Three parallel examinations were made in every case.

Three different heating programs were used. Each program included two heating methods, involving an isothermal segment and a dynamic segment (*Table 1*). The heating methods were combined with each other, the methods being separated by cooling.

Table 1 *Composition of heating methods*

Heating method	Isotherm segment		Dynamic segment	
	Temperature (°C)	Time (min)	End temperature (°C)	Heating rate (°C/min)
1	25	3	250	5
2	25	3	130	5
3	25	3	107	5

The different heating programs contained the following heating methods:

Heating program 1= heating method 1 - cooling - heating method 1

Heating program 2= heating method 2 - cooling - heating method 1

Heating program 3= heating method 3 - cooling - heating method 1

Other programs were also used, the details being provided in the Results section of the thesis.

4.4.6. Dissolution tests

The dissolution of dimenhydrinate was studied with a paddle method.

Test parameters:

- Apparatus: Pharma Test PTWII (Pharma Test GmbH, Germany)
- Paddle speed: 100 rpm
- Dissolution medium: 900 ml of artificial gastric juice (pH = 1.2±0.1)
- Temperature: 37±1 °C
- Samples taken at 1, 3, 5, 10, 20, 30 and 45 min
- Number of samples: 6
- Mass of sample: 0.50 g

- Measurement: with a UV spectrophotometer at 275 nm (Unicam Heλios Alpha, Spectronic Unicam, UK).

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

Kinetic evaluations were also performed. A plot of the logarithm of the quantity of undissolved material against time yielded a straight line, as confirmed by linear regression ($p<0.05$). The slope of this line is the drug-release rate constant (k). The following equation was used [97, 98]:

$$M_t/M_\infty = 1-exp(-kt) \tag{7}$$

where M_t is the amount of drug not released at time t, and M_∞ is the maximum amount of drug.

4.4.7. Water uptake

An Enslin apparatus with a glass filter and a pipette with 0.01 ml accuracy were used for these experiments. A monolayer of particles took up the maximum quantity of water possible through a filter paper under these conditions. The quantity of fluid was controlled every 10 s. Three parallel experiments were performed.

The characteristic water uptake time ($t_{63.2\%}$) is the time necessary for the uptake of 63.2% of the maximum quantity of water. The RRSBW equation was used. This equation can especially be used for determination of the characteristic time of dissolution of the active ingredient from solid dosage forms [99, 100]. Since the mechanism of water uptake is similar to dissolution, the equation can be used in this case.

$$M = M_0 \left\{ 1 - exp\left[-\frac{(t-T)^\beta}{a} \right] \right\} \tag{8}$$

where:

M = amount of water taken up after time t

M_0 = maximum amount of water taken up

T = delay time

β = shape parameter

a = time parameter

Linearized regression from parameters β and a without T gives

$$ln\,ln\frac{M_0}{M_0 - M} = \beta ln\,t - ln\,a \tag{9}$$

where β is the slope and $ln\ a$ is the intercept.

This equation was linearized by Langenbuchen [101]:

$$ln\ a = \beta * ln\ t_{63.2\,\%} \quad (10)$$

A plot of the double logarithm of $M_0/M_0\text{-}M$ versus the logarithm of time yielded a straight line. Linear regression ($p<0.05$) was carried out. The slope (β) and intercept ($ln\ a$) of this line can be used for the determination of $t_{63.2\%}$.

4.4.8. Compactibility tests

Compactibility tests are very important preformulation studies for establishment of the optimum parameters of tablet-making. Several parameters (upper and lower force, ejection force, displacement of upper punch, etc.) can be followed with instrumented tablet machines, which are equipped with strain gauges, a displacement transducer and a computer interface. Other data can be scored from the measured parameters.

The lubrication coefficient (R) can be calculated from the upper (F_{upper}) and lower forces (F_{lower}) [50]. This coefficient refers to the friction.

$$R = F_{lower}/F_{upper} \quad (11)$$

If the value of this parameter is close to 1, then the force is lost because of friction, and little rearrangement occurs since a high proportion of the upper force can be detected on the lower punch. Thus, a higher proportion of invested force is useful, yielding better mechanical properties of tablets. Consequently, a high lubrication coefficient is needed for economical tablet-making.

The force-displacement curve can be determined, and the plasticity calculated from it. The measured curve is a right-angled triangle for an ideal case, but it differs from such a triangle for real cases. This curve distinguishes three areas in the right-angled triangle. E_1 is the energy lost by the rearrangement of the particles, E_2 is the useful energy and E_3 is the energy lost by elastic recoil. The plasticity was calculated according to Stamm and Mathis ($PL_{S\text{-}M}$) [102]:

$$Pl_{S\,-\,M} = \frac{E_2}{E_2 + E_3} \times 100 \quad (11)$$

This parameter relates to the behaviour of the material under a load. If $PL_{S\text{-}M}$ is close to 100%, the material deforms well under the load.

The samples were compressed into tablets with a Korsch EK0 instrumented eccentric tablet machine (Emil Korsch Maschinenfabrik, Germany). The compression tools were single flat punches 10 mm in diameter. 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., Hungary). The displacement transducer was fitted over the upper punch. The transducer distance accuracy was checked by using five measuring pieces of different thicknesses (2.0, 5.0, 7.5, 10.0 and 15.0 mm) under zero load (Mitutoyo, Japan). The compression was carried out electrically at 36 rpm at an air temperature of 25 °C and a relative humidity of 25-35%. The compressed volume was 100 mm^3 for each sample. 20 tablets were compressed for each sample and the data on 10 tablets were analysed.

The breaking hardness of the prepared tablets was measured on the Heberlein apparatus (Heberlein & Co. AG., Switzerland). 10 tablets were measured.

4.4.9. Free film study

The deformation processes of films can also be examined in preformulation studies. The coating film must be suitably elastic, so that no injury occurs during the subsequent processes. Tensile testing instruments are used in the plastics, rubber and (in the past decade) pharmaceutical industries. These properties can be examined by different methods [103-105]. A strength tester (Chinoin Pharmaceutical and Chemical Works, Department of Instrumentation Technology, Hungary) was used in this study. This device contains a special specimen holder and a stamp and is connected to a computer via an interface; thus, not only can the ultimate deformation force be measured, but the process can be followed. The round specimen is located horizontally and the stamp moves vertically. If the measured plot is parallel to the x -axis the deformation is viscoelastic; if the plot rises linearly the deformation is elastic. 10 parallel experiments were performed.

Several technologies are known for the preparation of free films [106-108]. In this study, the coating fluid was sprayed onto a teflon surface and these films were examined. Film thickness was measured with a screw micrometer with an accuracy of 0.001 mm (Mitutoyo, Japan) at the middle of the specimen.

4.4.10. Statistical evaluation

The mathematical evaluation was carried out with the SPSS for Windows 9.0 package. The two-sample *T-test* was applied for the comparison of two groups of results. The one-way ANOVA test was performed for comparison of several groups of results. Regression analysis was applied for demonstration of a correlation between two variables. The confidence limit was 95% in every case. Accordingly, the difference was significant if $p<0.05$.

5. RESULTS

5.1. Effects of coating and granulation

5.1.1. Shape and size of particles

The habit of the crystals is shown in the SEM photo. The dimenhydrinate consisted of small crystals, mainly with a columnar form and with a wide size distribution (*Table 2, Fig. 1*). Many particles were broken. The measurements with the image analysis system supported these results. The roundness value was the lowest for the untreated crystals, but this value differed significantly from 1.0. The better roundness value can be explained by the smooth surface rather than by the ideal shape (the columnar shape can be seen in the SEM pictures). The standard deviation was high for every sample; this can be explained by the wide size distribution.

Fig. 1 Untreated dimenhydrinate crystals

Table 2 *The analysis of shape and size of samples*

Sample	Length (µm)	Breadth (µm)	Roundness
Dimenhydrinate	83.84 (SD=54.50)	49.40 (SD=29.28)	1.40 (SD=0.28)
Sample 1	541.41 (SD=268.62)	376.75 (SD=187.88)	1.79 (SD=0.44)
Sample 2	165.89 (SD=104.23)	104.11 (SD=67.56)	1.89 (SD=0.59)
Sample 3	231.75 (SD=134.96)	144.86 (SD=81.39)	1.97 (SD=0.67)
Sample 4	239.49 (SD=129.69)	155.09 (SD=80.75)	1.72 (SD=0.45)

The SEM pictures of the crystal granules revealed that the connection between the crystals and the shape of the particles differed from that for these parameters of pellets (*Fig. 2*). The cause of this difference is the lack of additive, which promotes the building of pellets. The uneven surface of the particles is supported by the high roundness value. The size of the particles

(length and width) was significantly higher than that of the original crystals. The binder macromolecular film can also be seen.

A significant increase in the size of the crystals was detected during coating (*Table 2*) (*Figs 3-5*), but this was significantly less than during agglomeration. The cause of this increase is that the smaller and broken particles stick into the macromolecular coating film. This alteration occurs during the coating of the fine particles and is difficult to avoid [109, 110]. The coated dimenhydrinate gave a larger roundness value because the sticking of the particles modifies the surface. The sticking of the particles can be reduced by the appropriate set-up of the drying air volume and the air temperature.

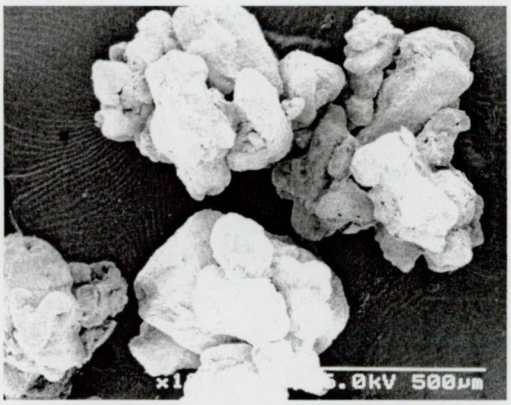


Fig. 2 Sample 1 (SEM)

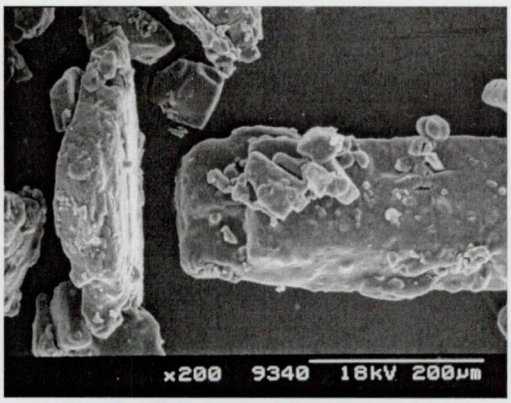


Fig. 3 Sample 2 (SEM)

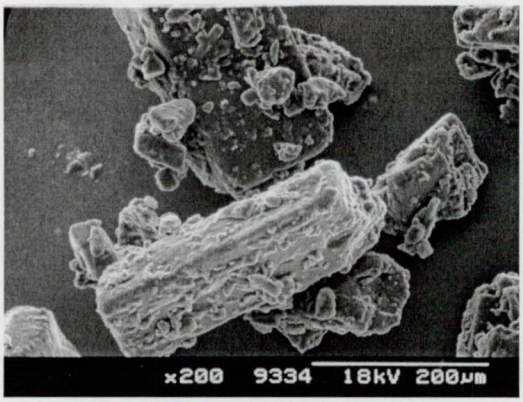


Fig. 4 Sample 3 (SEM)

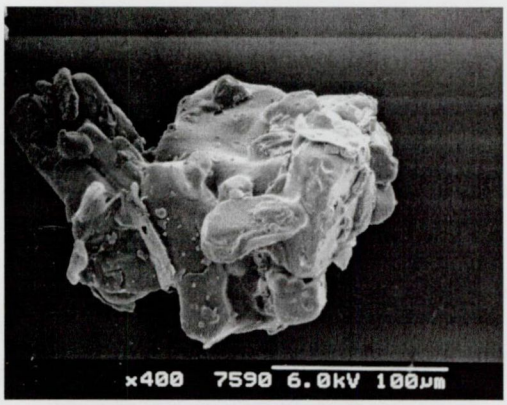


Fig. 5 Sample 4 (SEM)

5.1.2. Flow properties

A material flows if the gravitational force exceeds the forces between the particles (friction, electrostatic and adhesion forces) and the forces between the particles and the wall of the container.

The flow properties of the crystals were inappropriate (*Table 3*), and these crystals were unsuitable for the tableting process. The flow time was not measurable because the material did not flow constantly when the higher speed of the stirrer of the Pharma Test apparatus was

applied (25 rpm). There was a high standard deviation in the mass of the heap because the filling of the space of these samples was not even. This was indicated by the small crystals with a wide size distribution and the high surface area.

Table 3 *The flowing parameters of samples*

Sample	Flow time (s)	Angle of repose (°)	Mass of heap (g)
Dimenhydrinate	no flow	52.53 (SD=1.13)	41.73 (SD=0.31)
Sample 1	6.70 (SD=0.05)	31.90 (SD=0.37)	46.00 (SD=0.66)
Sample 2	8.60 (SD=0.2)	33.80 (SD=0.60)	48.10 (SD=0.50)
Sample 3	7.90 (SD=0.15)	34.90 (SD=0.33)	44.80 (SD=0.61)
Sample 4	7.10 (SD=0.05)	33.40 (SD=1.19)	41.50 (SD=0.83)

Every treatment (coating and granulation) of the crystals significantly increased the powder flow. The parameters for the treated crystals were appropriate for processing.

5.1.3. Compressibility studies

According to the estimation of Wells, the compressibility (the Hausner ratio and Carr`s index) of dimenhydrinate crystals was not ideal for tablet-making (*Table 4*) [77]. The rearrangement of the crystals was not adequate. The processing of these crystals enhanced these factors and these parameters became excellent.

Table 4 *The compressibility of the samples*

Sample	Carr`s index (%)	Hausner ratio
Dimenhydrinate	25.57 (SD=0.51)	1.3434 (SD=0.0092)
Sample 1	7.15 (SD=0.73)	1.0770 (SD=0.0085)
Sample 2	6.89 (SD=0.56)	1.0740 (SD=0.0064)
Sample 3	14.74 (SD=0.15)	1.1728 (SD=0.0021)
Sample 4	10.38 (SD=0.11)	1.1158 (SD=0.0013)

5.1.4. Surface free energy

The wetting contact angle of a powder can be applied for the indirect determination of the solid surface free energy. It can be seen from the data, that the smallest angles in water and diiodomethane were measured for the untreated dimenhydrinate crystals (Table 5). The surface treatment decreased these parameters. This was found on the application of polymer film and different components e.g. hydrophobic stearic acid and magnesium stearate.

Table 5 *Wetting and surface free energy of the samples*

Sample	Θ_{water} (°)	$\Theta_{diiodomethane}$ (°)	γ_p (mN/m)	γ_d (mN/m)	γ_{total} (mN/m)
Dimenhydrinate	37.65 (SD=2.17)	30.27 (SD=0.21)	26.14	44.32	70.46
Sample 1	48.33 (SD=0.50)	42.20 (SD=0.40)	22.49	39.15	61.63
Sample 2	74.43 (SD=1.58)	52.97 (SD=0.40)	11.11	33.95	45.06
Sample 3	55.83 (SD=0.48)	45.00 (SD=0.98)	19.11	37.82	56.93
Sample 4	64.77 (SD=0.85)	54.03 (SD=0.62)	15.87	33.43	49.29

The solid surface free energy components were calculated via the Wu equation. The treatment decreased these parameters. The smallest reduction was observed for *Sample 1*. This can be explained by the small amounts of other ingredients. Progressively decreased surface free energies were observed for *Samples 2*, *3* and *4*.

It is known that a decline in surface free energy can cause a reduction in adhesion [111, 112]. Consequently, these results accord with those from the flowability and compressibility studies.

5.1.5. Thermoanalytical studies

5.1.5.1. Thermomicroscopy

The melting point was determined to be 102-104 °C. After cooling, a brown glass-like spot remained without recrystallization. The results were not influenced by the presence of a film coat.

5.1.5.2. DSC studies

5.1.5.2.1. Analysis of shape of curves

The shapes of the DSC curves of the original crystals and the crystal agglomerates were similar, and the shapes of the curves of the different coated samples did not differ significantly either. Therefore, two curves (a coated and an uncoated sample) were presented for every heating program. The upper curve is the curve of the first heating and the other is the curve of reheating.

In heating program 1, the samples were heated according to heating method 1 (to 250 °C), cooled and reheated. The bulk crystals and the treated crystals exhibited very similar DSC curves. A quite different shape of the curve was observed during reheating (*Figs 6 and 7*). The endothermal melting peak and the two exothermal peaks disappeared, while another endothermal peak and an exothermal peak developed at other temperatures. Two small differences can be seen in the DSC curve for the coated crystals. The slight change at about 50 °C can be explained by the glass transition (*Tg*) of the coating polymer for the coated crystals (it could not be detected for the granules). The second difference is the wider peak.

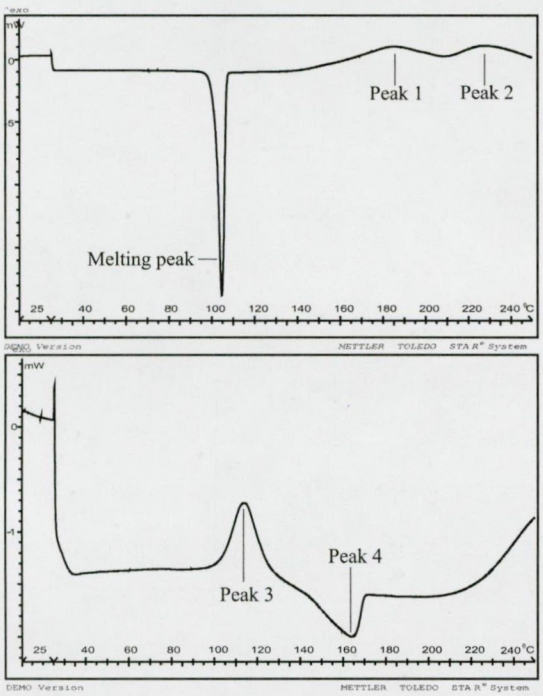


Fig. 6 DSC curve of uncoated crystals (heating program 1)

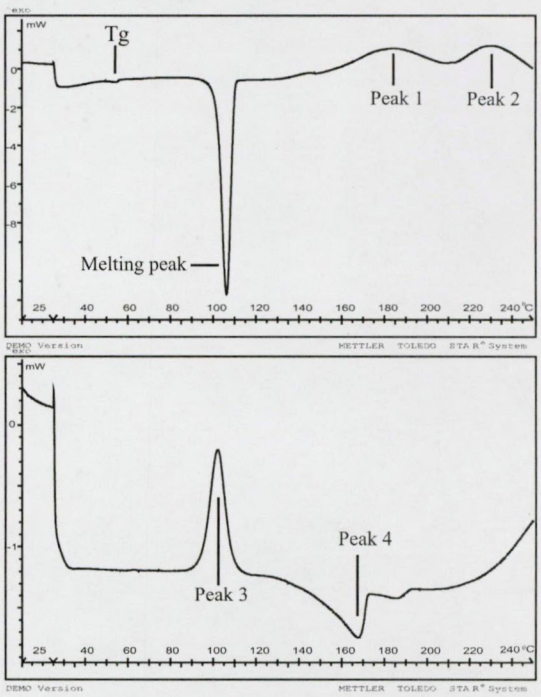


Fig. 7 DSC curve of coated crystals (heating program 1)

In the next experiment, the maximum first heating temperature was only 130 °C. An endothermal peak can be detected after the first heating. During the reheating (to 250 °C), the two exothermal peaks remained at the same temperatures as for heating program 1, but the

endothermal melting peaks disappeared (*Figs 8 and 9*). The cause of this phenomenon may be that the material did not decompose after the first endothermal peak, but it did not transform to the crystalline state after cooling, and therefore the melting peak was not involved in the second heating. This was supported by thermomicroscopy, where recrystallisation could not be detected during cooling. The duration of cooling between the two heatings did not influence this behaviour. The samples were stored at room temperature for 1 day, 2 days or 1 week before the reheating. The melting peak could not be detected after 1 week. The mixture of another component with a great surface area (silica colloidal hydrated, talc) likewise caused no crystallization. Change of the rate of heating of the dynamic segment from 5 °C/min to 1 °C/min similarly did not indicate crystal formation and thus the melting peak could not detected. The presence of a coating on the surface of the crystals did not influence this property.

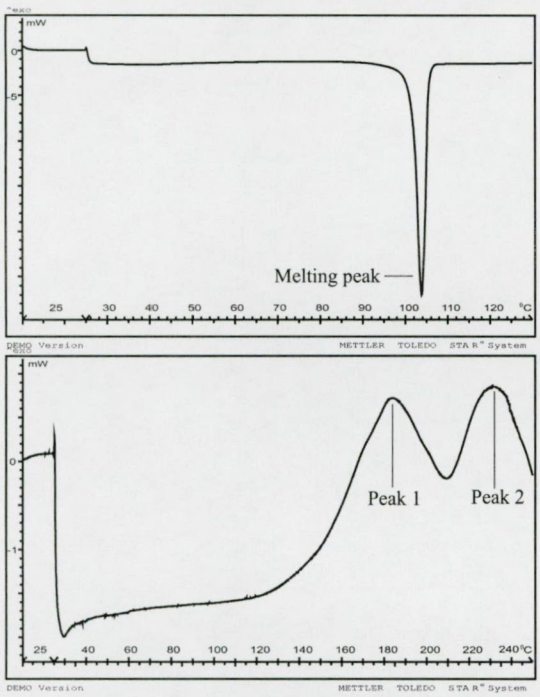


Fig. 8 DSC curve of uncoated crystals (heating program 2)

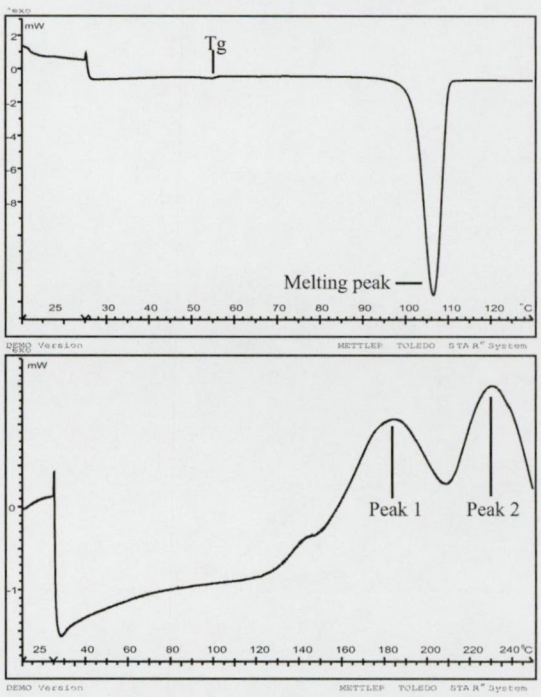


Fig. 9 DSC curve of coated crystals (heating program 2)

The alterations in the shape of the curve of reheating of the sample, measured according to heating program 1, can be explained by the decomposition of the material at these high temperatures. The second exothermal peak in the first heating related to the material involved in the decomposition: when the first heating was stopped after the first peak (210 °C), only an exothermal peak (Peak 2) was detected during reheating, at about 230 °C, which accorded with the second exothermal peak in the first heating (to 250 °C) of the uncoated crystals. Consequently, the change at the temperature of second peak can cause the decomposition.

According to heating program 3, the first heating was interrupted during the increasing part of the endothermal melting peak and, after cooling, the effect of heating to 250 °C was examined (*Figs 10 and 11*). The melting point in the first period was not evaluated statistically, because the peak was not full. A significant difference was detected in the melting peak in the second heating period for certain coated samples. The melting peak was smaller than the peak in the first heating method (to 250 °C). This peak was significantly higher for *Sample 4* and could not be evaluated for *Sample 1*. The other peaks were similar to the peaks in the first heating method (to 250 °C).

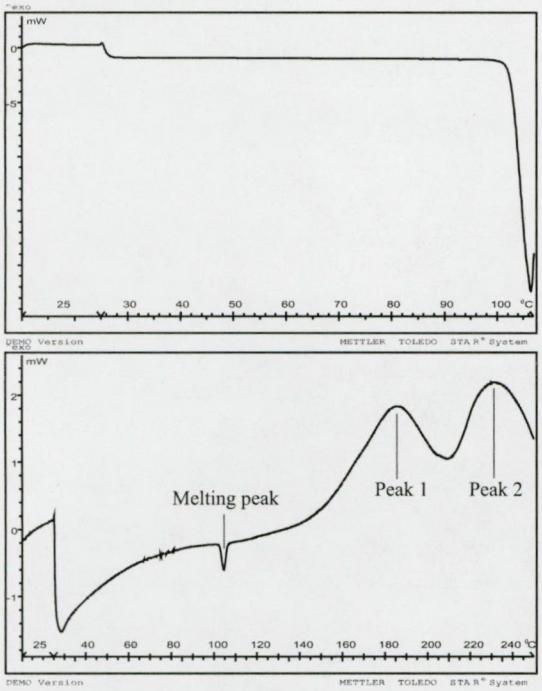


Fig. 10 DSC curve of uncoated crystals (heating program 3)

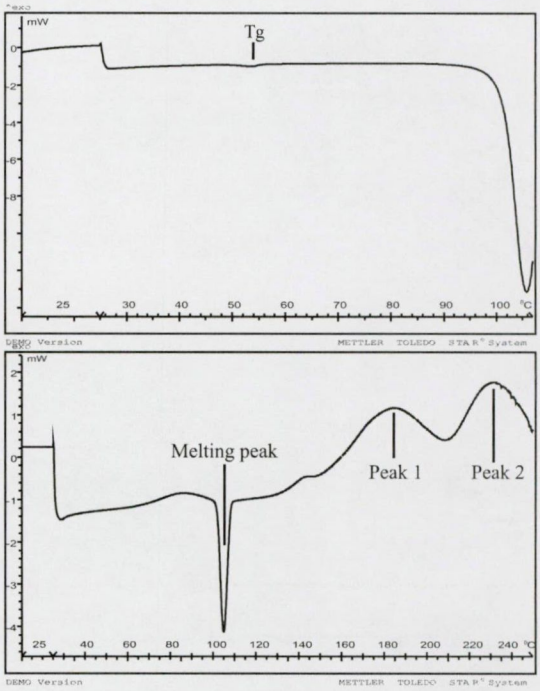


Fig. 11 DSC curve of coated crystals (heating program 3)

Heating of the material up to 300 °C did not cause any other change during the reheating.

5.1.5.2.2. Mathematical analysis of curves

5.1.5.2.2.1. Heating program 1

It can be seen from the temperatures of the peaks that there was no significant difference between the data for the uncoated crystals and granules (*Table 6*). On the other hand, the temperature of the melting peak of the coated crystals was significantly higher than those for the other two samples. The temperature of Peak 3 shifted to lower temperatures and Peak 4 shifted to higher temperatures for the coated samples. This can be explained by the slightly different behaviour of the samples exposed to heat.

Table 6 *Data on DSC curves of samples (heating program 1)*

Sample	Melting peak (°C)	Peak 1 (°C)	Peak 2 (°C)	Peak 3 (°C)	Peak 4 (°C)
Dimenhydrinate	103.35 (SD=0.57)	183.94 (SD=1.02)	229.54 (SD=1.15)	114.56 (SD=1.03)	162.65 (SD=1.03)
Sample 1	103.30 (SD=0.72)	183.39 (SD=0.66)	230.13 (SD=1.05)	112.17 (SD=6.42)	163.91 (SD=0.91)
Sample 2	104.75 (SD=0.26)	183.78 (SD=0.75)	232.56 (SD=0.76)	96.67 (SD=1.15)	166.97 (SD=0.45)
Sample 3	104.93 (SD=0.22)	186.25 (SD=0.52)	230.46 (SD=0.34)	105.37 (SD=1.14)	163.38 (SD=0.44)
Sample 4	105.98 (SD=0.25)	183.67 (SD=0.75)	231.05 (SD=0.44)	101.64 (SD=0.64)	167.67 (SD=0.23)

The change in the temperature of the melting peak can be explained by the presence of an even macromolecular film on the surface of the particles. Such coating films (especially of Sepifilm® LP 010) can separate the crystals and can disturb the heat conductivity between the particles. Therefore, more time is necessary for the melting of the coated crystals, and thus the apparatus detects a higher value for the temperature of the melting peak. This is supported by the wider melting peaks for the coated samples. Hence, the melting point should preferably be called the virtual melting point because the bulk crystals and the inner structures of these crystals are the same, and thus the shifted detected melting point can only be explained by the fact that the surface treatment did not change.

The effect of the polymer film on the heat conductivity was supported in another experiment. A thin (55±10.2 μm) Sepifilm® LP 010 film was laid on the bottom of the pan (it covered it entirely) and the powder was then measured into the pan. The virtual melting point calculated by the software significantly increased, to 106.62±0.39 °C. If this film was laid on top of the powder, the detected melting point was 135.50±0.27 °C.

5.1.5.2.2.2. Heating program 3

The virtual melting point in the first period was not evaluated statistically, because the peak was not full. There was no significant difference between the different samples in the temperatures of the peak detected during reheating (*Table 7*). There was only a difference in the size of the melting peak after reheating. This peak could not be measured for the granules. The quantity of the material can be characterized by the areas under the curve (AUC) of the peaks.

The higher the AUC, the more the active ingredient remaining in a volume. A higher value was observed for the AUC of the endothermal melting peak of the second heating for Sepifilm® LP 010-coated crystals than for the other samples. This is explained by the restriction of heat transport; hence the melting is less complete for these coated crystals and so a smaller fraction of dimenhydrinate decayed. The melting peak of reheating was therefore higher.

Table 7 *Data of DSC curves of samples (Heating program 3)*

Sample	**Melting peak (°C)**	**Peak 1 (°C)**	**Peak 2 (°C)**	**AUC of melting peak (J/g)**
Dimenhydrinate	104.20 (SD=0.37)	184.00 (SD=0.48)	230.00 (SD=0.12)	0.57 (SD=0.84)
Sample 1	no measurable	183.54 (SD=0.05)	230.86 (SD=0.29)	no measurable
Sample 2	104.03 (SD=0.30)	183.45 (SD=0.12)	231.55 (SD=0.82)	1.30 (SD=0.53)
Sample 3	104.07 (SD=0.08)	185.19 (SD=0.71)	230.14 (SD=0.38)	0.25 (SD=0.14)
Sample 4	104.89 (SD=0.09)	183.74 (SD=0.34)	230.62 (SD=0.27)	25.45 (SD=10.62)

The better heat restriction effect of Sepfilm® LP 010 can be interpreted by the different structures of film and the whole sample.

5.1.6. Dissolution tests

The characteristic dissolution time could not be determined because the dissolution was very rapid. It can be seen from the dissolution curve that the kinetics of dissolution was similar for the different samples (*Fig. 12*).

A plot of the logarithm of the quantity of material remaining undissolved versus time was linear for each sample, as confirmed by linear regression ($p<0.05$). This is typical of first-order kinetics. The uncoated crystals exhibited the slowest dissolution, as indicated by the rate constant of drug release (k) (*Table 8*). The coated crystals underwent rapid dissolution.

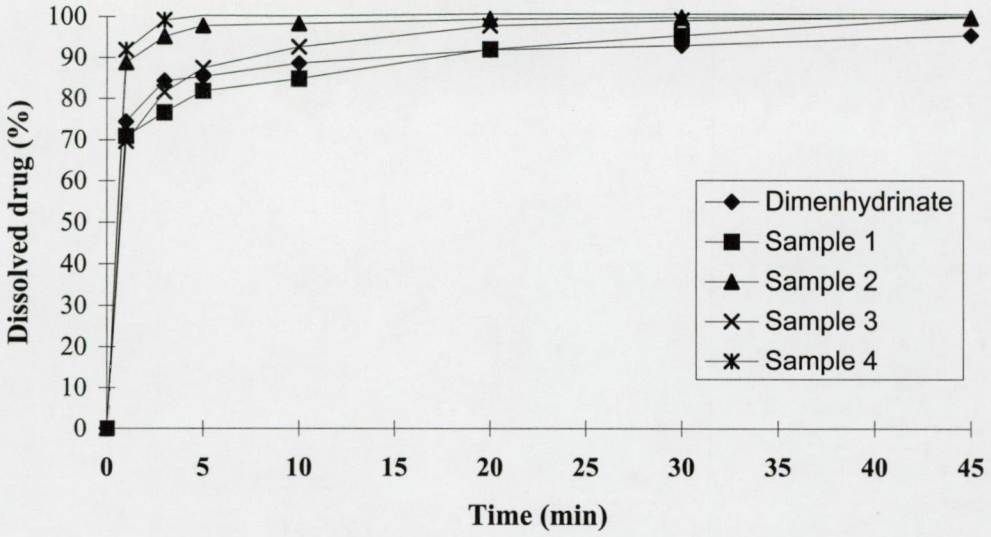


Fig. 12 Dissolution of active ingredient from different samples

Table 8 *Evaluation of kinetic of dissolution*

Sample	***k***	***R* value**
Dimenhydrinate	0.0325	0.9801
Sample 1	0.0568	0.9744
Sample 2	0.1569	0.9501
Sample 3	0.1142	0.9913
Sample 4	0.5000	0.9652

The visual observations confirmed these results. The uncoated crystals stuck to each other, disintegrated after a few minutes and subsequently dissolved. Clumps formed before the feed of the crystals into the dissolution medium because of the unfavourable flow properties. The untreated crystals wetted well, as can be seen from the wetting contact angle. Particle aggregation could not be observed for the granules and the coated samples. There was a well-soluble polymer film on the surface of the treated crystals, which influenced the eroding of the crystals. The coating film separates the crystals and so the specific surface area is higher; it is known that the surface and shape of particles can significantly modify the dissolution [113]. The tendency to adhesion of the coated particles was also reduced by the decreased surface free energy. Sample 4 displayed the most rapid dissolution. This is due to the HPMC film. The effect of HPMC in enhancing the dissolution of materials with low solubility is well known from the literature [114]. The disintegration of larger agglomerates prolonged the dissolution for *Sample 1*.

It can be concluded that crystal coating with these polymers did not worsen the release of the active ingredient, which is important, because the onset of the effect of dimenhydrinate must be quick.

5.2. Effects of quantity of coating fluid

5.2.1. Shape and size of particles

The increase of the polymer film on the surface of the different samples through the use of different quantities of coating fluid can be followed in the SEM pictures, but sticking of the crystals can be seen (*Figs. 13-15*); this can cause irregularities in the film. A significant increase in the size of the particles can be detected for the coated samples (*Table 9*). The 2.5-3.0-fold increase in the dimensions corresponds to the aggregation of 15-27 (2.5^3-3.0^3) crystals in a coated particle. There was no obvious relationship between the solid content of the coating film and the particle size. This can be explained by two simultaneous processes. The particles are built up and broken down at the same time.

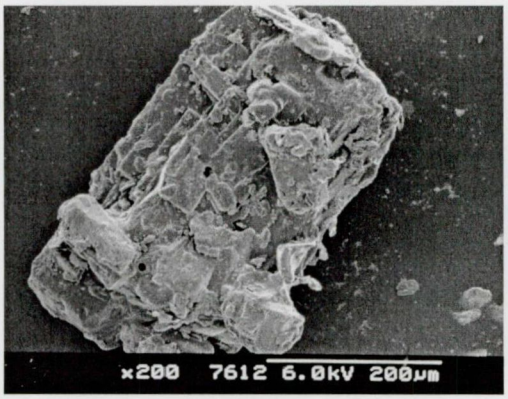


Fig. 13 Sample 5

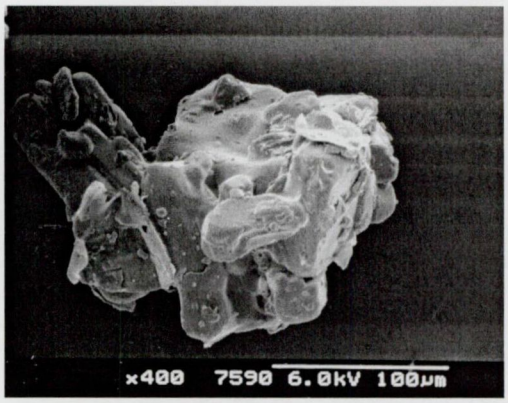


Fig. 14 Sample 6

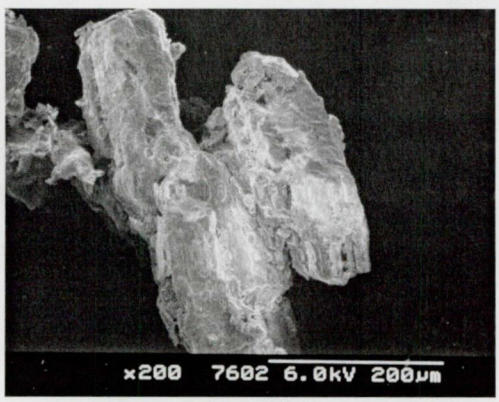


Fig. 15 Sample 7

Table 9 *The analysis of shape and size of samples*

Sample	Length (μm)	Breadth (μm)	Roundness
Dimenhydrinate	83.84 (SD=54.50)	49.40 (SD=29.28)	1.40 (SD=0.28)
Sample 5	201.95 (SD=114.47)	133.68 (SD=73.63)	1.64 (SD=0.49)
Sample 6	239.49 (SD=129.69)	155.09 (SD=80.75)	1.72 (SD=0.45)
Sample 7	229.90 (SD=159.57)	149.93 (SD=102.24)	1.85 (SD=0.65)

The changes in shape can be followed via the roundness value. It can be seen that this parameter decreased when the amount of coating fluid applied (and hence the coating time) was increased. This was also explained by the two processes mentioned above. More fluid caused an increase in the film thickness and the possibility of the particles sticking together was higher. Cracking and breaking of the crystals frequently occurred during coating (*Fig. 16*). Another cause of an alteration in shape was the breaking of the coating film between the stuck crystals; the surface of the particles was therefore uneven and the coating effect of the film was decreased (*Figs 17 and 18*). A broken film `tongue` likewise influenced the shape of small agglomerates (*Fig. 19*). 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.

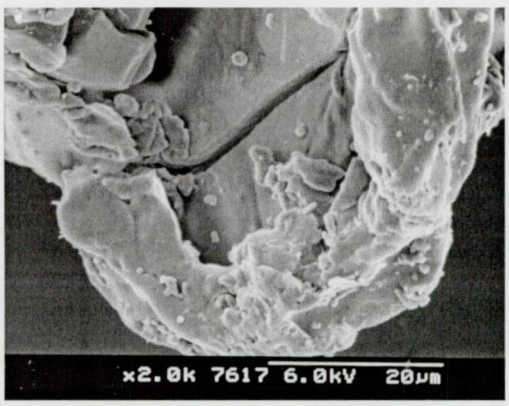


Fig. 16 Sample 7 (SEM)

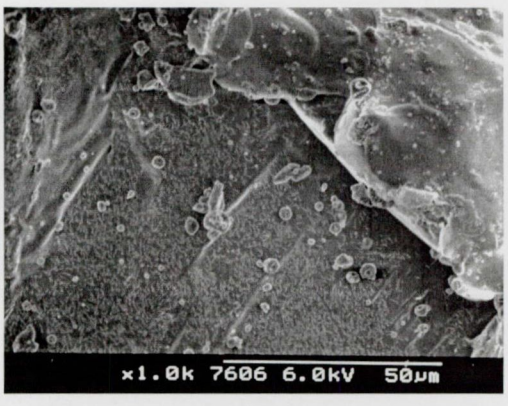


Fig. 17 Sample 7 (SEM)

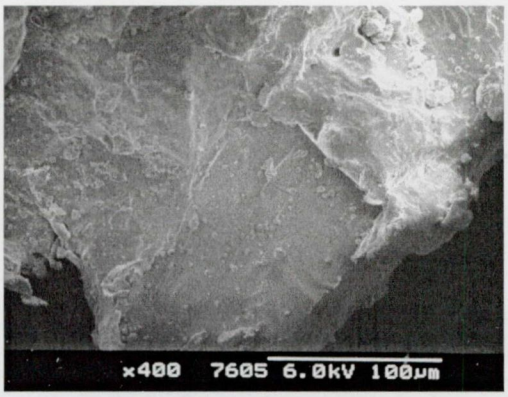


Fig. 18 Sample 7 (SEM)

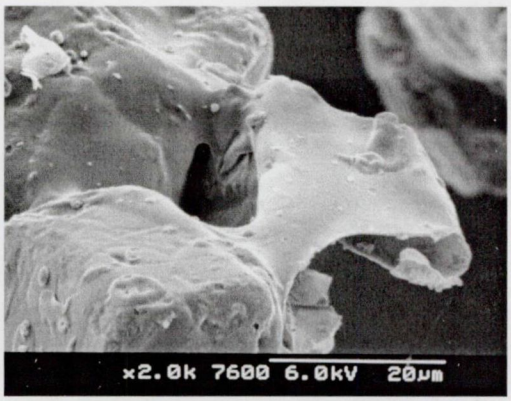


Fig. 19 Sample 7 (SEM)

5.2.2. Flow properties

It can be seen from the data in *Table 10* that the flow properties of each coated sample were significantly better than those for the untreated crystals. There was a slight decrease in every parameter for the samples prepared with a higher quantity of coating fluid.

Table 10 *Flow parameters of samples*

Sample	**Flow time (s)**	**Angle of repose (°)**	**Mass of heap (g)**
Dimenhydrinate	no flow	52.53 (SD=1.13)	41.73 (SD=0.31)
Sample 5	6.40 (SD=0.05)	32.40 (SD=0.60)	43.90 (SD=0.50)
Sample 6	7.10 (SD=0.05)	33.40 (SD=0.64)	41.50 (SD=0.83)
Sample 7	7.90 (SD=0.04)	34.8 (SD=1.19)	37.90 (SD=0.48)

The effect of a deterioration in the shape of the particles on the powder rheological characteristic was evaluated since the shape of the particles can influence the flowability [115]. The roundness values and every flow parameter were compared for all the coated samples. A higher value of the shape parameter decreased the all of the flowability factors. If the particles are of closely similar size, this can mainly be justified by an increased possibility of connection because of the more uneven surface of the particles. The movement and rolling of the particles were more restricted in this case. Therefore, the flow time can be longer and the angle of repose higher. The filling of the spaces of these particles was therefore poorer the loose density of the sample with a worse shape was lower, and thus the mass of the heap was also lower.

5.2.3. Compressibility studies

Both parameters (Carr`s index and the Hausner factor) were significantly better for every coated sample (*Table 11*).

The increased coating time caused a slight decrease in this behaviour of the coated samples. This was demonstrated by the alteration in the shape and thus the small change in the flow properties. There was also a connection between the roundness value and the compressibility of the samples. The uneven surface diminished the spontaneous insertion, and therefore the mechanical impression could cause a longer rearrangement and a higher change in the volume of the sample.

Table 11 *Compressibility of samples*

Sample	Carr`s index (%)	Hausner ratio
Dimenhydrinate	25.57 (SD=0.51)	1.3434 (SD=0.0092)
Sample 5	9.69 (SD=0.57)	1.1073 (SD=0.0070)
Sample 6	10.38 (SD=0.11)	1.1158 (SD=0.0013)
Sample 7	13.46 (SD=0.51)	1.1555 (SD=0.0067)

5.2.4. Surface free energy

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 by the fluids used (polar water and non-polar diiodomethane) (*Table 12*). There was no practically relevant difference between the different coated samples. HPMC is polar, but the coating film also contained other components. The cause of the decreased wetting of the coated samples with water may be the presence of hydrophobic ingredients in the Sepifilm® LP 010, e.g. stearic acid as plasticizer.

The surface free energies of the coated samples were significantly lower than those of the uncoated crystals. There was no significant difference between the surface free energy parameters of the differently coated samples. Accordingly, a higher amount of coating material did not further reduce the surface free energy and therefore the tendency of the particles to undergo adhesion.

Table 12 *Wetting and surface free energies of samples*

Sample	Θ_{water} (°)	$\Theta_{diiodomethane}$ (°)	γ^p (mN/m)	γ^d (mN/m)	γ_s (mN/m)
Dimenhydrinate	37.65 (SD=2.17)	30.27 (SD=0.21)	26.14	44.32	70.46
Sample 5	63.53 (SD=1.04)	50.68 (SD=1.01)	16.01	35.08	51.09
Sample 6	64.77 (SD=0.85)	54.03 (SD=0.62)	15.87	33.42	49.29
Sample 7	65.80 (SD=1.65)	57.37 (SD=0.68)	15.83	31.81	47.64

5.2.5. Water uptake study

It can be concluded that the uncoated crystals took up the greatest amount of water (*Table 13*). The coated crystals can take up a lower amount, but the difference was not significant, except for *Sample 6*. The characteristic water uptake time ($t_{63.2\%}$) of the bulk crystals was the shortest (*Table 14*). A higher amount of polymer causes a longer wetting time. The curve of water uptake also indicates this finding (*Fig. 20*).

Table 13 *Water uptakes of samples*

	Dimenhydrinate	*Sample 5*	*Sample 6*	*Sample 7*
Enslin number (ml/g)	0.80	0.68	0.56	0.65
SD	0.04	0.04	0.03	0.02

Table 14 *Characteristic water uptake times of samples*

Sample	Characteristic water uptake time (s)	*R* value	ln *a*	β
Dimenhydrinate	9.83	0.9910	-2.0340	0.8796
Sample 5	18.90	0.9977	-2.8617	1.0122
Sample 6	38.65	0.9690	-3.5414	0.9716
Sample 7	45.80	0.9970	-3.9039	1.0217

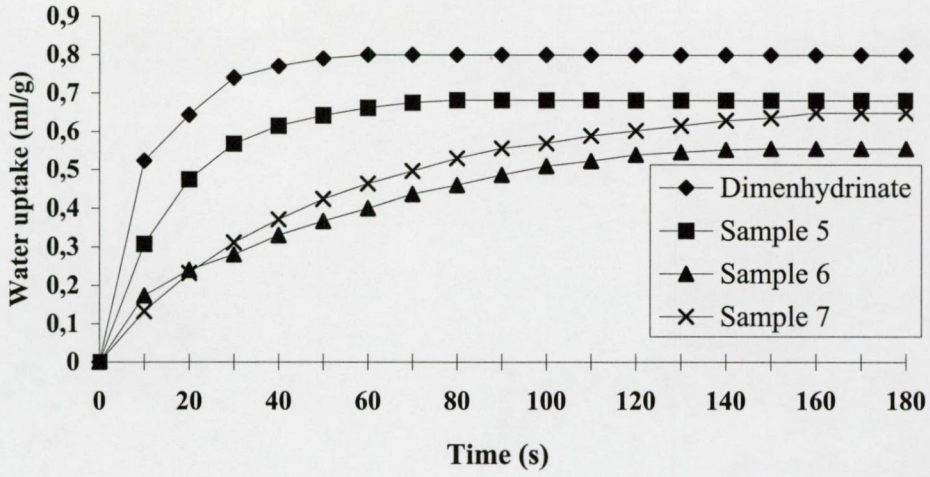


Fig. 20 Water uptake of samples

The explanation of this phenomenon can be that the uncoated crystals are smaller and thus the surface area of the crystals was higher; the uptake of fluid was not restricted, and therefore the quantity of fluid was high and this process was rapid. The presence of the coating film (because of the hydrophobic components) can disturb the contact of the crystals with the fluid and the particles are larger. These factors can prolong the water uptake time. There is no unequivocal relation between the quantity of coating fluid applied and the water uptake and characteristic water uptake time because several factors can influence these. An increased process time can increase the particle size and the thickness of the film, but the surface smoothness can decline and the frequency of breaking and cracking of the crystals can rise. The sum of these positive and negative effects can determine the water uptake.

5.2.6. Thermoanalytical studies

5.2.6.1. DSC studies

5.2.6.1.1. Analysis of shape of curves

The above-mentioned heating programs were used for thermal analysis. The shapes of the DSC curves of the samples were similar to those in the previous studies. These curves are therefore not presented again in here. The quantity of coating material did not change the characteristic features of the curves.

5.2.6.1.2. Mathematical analysis of curves

The slight change at about 55 °C in the curve for the coated crystals was explained by the presence of Sepifilm® LP 010. This change was caused by the glass transition of HPMC and the congealing temperature of the plasticizer stearic acid. The glass transition temperature is the

temperature at which a polymer changes from a brittle substance to a rubber solid [116]. The DSC technique is widely used for its determination [117, 118]. The action of a plasticizer is to lower the glass transition temperature of the pure polymer [41]. There were slight differences in the glass transition temperatures (*Tg*) of the coating films on the different samples (*Table 15*). The coating material was the same but the structure of the film formed can be different, and so can cause such a small change. The *Tg* values of different samples are similar for every heating program.

Table 15 Tg *values of coating films on different samples*

Sample	**Heating program 1 (°C)**	**Heating program 2 (°C)**	**Heating program 3 (°C)**
Sample 5	52.78 (SD=0.08)	52.51 (SD=0.05)	52.80 (SD=0.17)
Sample 6	55.63 (SD=0.22)	55.37 (SD=0.41)	55.58 (SD=0.69)
Sample 7	54.83 (SD=0.09)	55.17 (SD=0.66)	54.77 (SD=0.19)

5.2.6.1.2.1. Heating program 1

It can be seen that the melting peaks for coated samples shifted to higher temperatures (*Table 16*). The difference was significant for every coated sample. There is no obvious relationship between the amount of coating material and the virtual melting point. Changes in the temperatures of Peaks 3 and 4 can also be observed.

Table 16 *Data on DSC curves of samples (heating program 1)*

Sample	**Melting peak (°C)**	**Peak 1 (°C)**	**Peak 2 (°C)**	**Peak 3 (°C)**	**Peak 4 (°C)**
Dimenhydrinate	103.35 (SD=0.57)	183.94 (SD=1.02)	229.54 (SD=1.15)	114.56 (SD=1.03)	162.65 (SD=1.03)
Sample 5	105.30 (SD=0.34)	183.69 (SD=0.36)	231.81 (SD=0.51)	105.91 (SD=5.11)	167.79 (SD=0.60)
Sample 6	105.98 (SD=0.25)	183.67 (SD=0.75)	231.05 (SD=0.44)	101.64 (SD=0.64)	167.67 (SD=0.23)
Sample 7	104.97 (SD=0.09)	183.86 (SD=0.36)	232.54 (SD=1.88)	100.46 (SD=2.45)	168.71 (SD=0.56)

5.2.6.1.2.2. Heating program 3

The melting peaks could not be detected for any of the samples during the first heating because the peaks were not complete. A lower value was observed for the AUC of the endothermal melting peak during the second heating for the uncoated crystals than for the coated samples (*Table 17*). The change was significant. The highest peak was detected for *Sample 6*.

Table 17 Data on DSC curves of samples (heating program 3)

Sample	**Melting peak (°C)**	**Peak 1 (°C)**	**Peak 2 (°C)**	**AUC of melting peak (J/g)**
Dimenhydrinate	104.20 (SD=0.37)	184.00 (SD=0.48)	230.00 (SD=0.12)	0.57 (SD=0.84)
Sample 5	104.50 (0.11)	183.50 (SD=0.05)	231.17 (SD=0.76)	9.78 (SD=3.83)
Sample 6	104.89 (SD=0.09)	183.74 (SD=0.34)	230.62 (SD=0.27)	25.45 (SD=10.62)
Sample 7	104.84 (SD=0.41)	184.62 (SD=0.19)	230.48 (SD=1.09)	9.76 (SD=1.77)

There was a relationship between the AUC of the melting peak during reheating and the protective effect of the coating film. The latter effect is determined by the film smoothness and the thickness. Thus, not only the quantity of polymer applied can determine this protective effect. The sample prepared with a high coating time exhibited an uneven surface (because of the higher frequency of breaking of the crystals), which was not covered by smooth film. The smallest amount of coating material was not sufficient for an even coating of the surface of the crystals. Hence, the protective effect of the film was best for *Sample 6*.

5.2.7. Compactibility study

The untreated crystals were the most difficult to compress because the filling of the die and therefore the pressure force were the lowest and non-uniform (*Table 18*). Hence, the mass of the tablets was also uneven. The filling with the coated crystals was very good, and the mass of the tablets was uniform. The tablets of the coated crystals were very similar. The uniformity of filling can be characterized by the standard deviation (SD) of the pressing force measured on the upper punch.

Table 18 *Compactibility of the samples*

Sample	Upper punch force (kN)	Lubrication coefficient	Breaking force (N)
Dimenhydrinate	17.87 (SD=1.52)	0.49 (SD=0.01)	45.00 (SD=3.54)
Sample 5	18.83 (SD=0.22)	0.62 (SD=0.01)	129.8 (SD=3.42)
Sample 6	19.90 (SD=0.45)	0.69 (SD=0.02)	100.8 (SD=4.86)
Sample 7	19.46 (SD=0.66)	0.59 (SD=0.02)	98.0 (SD=2.65)

The lubrication coefficient was significantly reduced for the uncoated samples. Accordingly, the force, wasted because of friction was higher for the uncoated dimenhydrinate. The tablets prepared from the coated crystals exhibited a higher breaking hardness. Some tablets prepared from the uncoated crystals broke during packaging. *Sample 5* displayed the best breaking hardness.

The Stamm-Matis plasticity can be calculated from the force-displacement curve. A force-displacement curve of a tablet pressed from the uncoated crystals can be seen in *Fig. 21.* The characteristics of the curves obtained during tablet preparation from the coated samples were similar, but the areas (*E1, E2* and *E3*) were different.

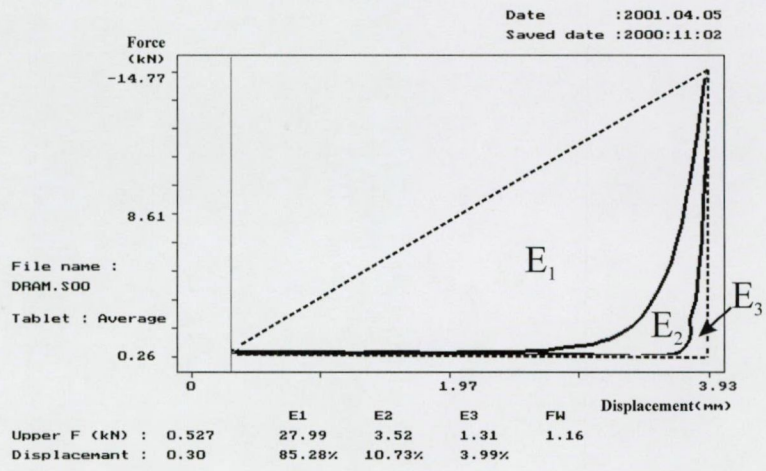


Fig. 21 Force-displacement curves recorded during tablet-making from uncoated samples

The uncoated dimenhydrinate crystals had the highest plasticity (*Table 19*). The coating caused a decrease in plasticity. This can be explained by the film between the crystals. The

coating film exhibited an elastic property and thus the elastic recovery of the samples (*E3*) was increased.

Table 19 *Plasticity of samples*

	Dimenhydrinate	*Sample 5*	*Sample 6*	*Sample 7*
$PL_{S\text{-}M}$ (%)	69.66 (SD=6.61)	59.61 (SD=2.32)	43.77 (SD=2.91)	52.93 (SD=3.07)

The elasticity of a film can be explained by the evaluation of process of film deformation. The deformation curve can be divided into three parts (*Fig. 22*): a short elastic period, a visco-elastic segment, and a long elastic segment, continuing on to the deformation point.

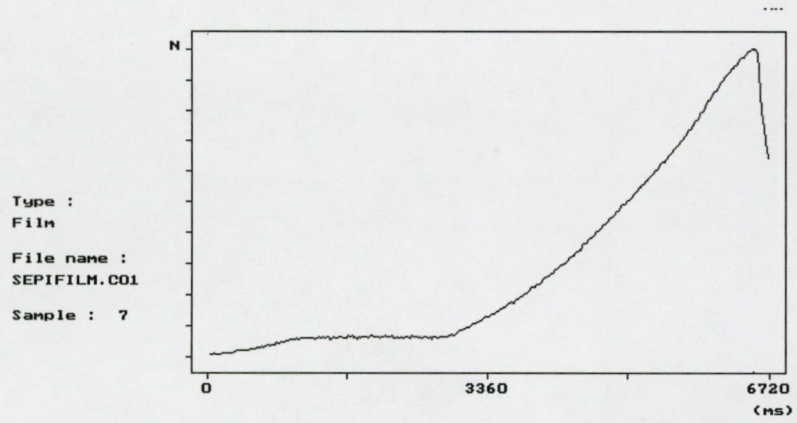


Fig. 22 Deformation curve of Sepifilm® LP 010 free film

Not only the quantity of coating material influenced the plasticity: its uniform distribution on the surface also plays an important part, for there is a relationship between the continuity and the elastic behaviour of the film, i.e. between the film uniformity and the plasticity. *Sample 6* exhibited the poorest plasticity, which can be explained in terms of the best protective effect of the coating film. This conclusion is supported by the results of SEM observations, water uptake studies and thermoanalytical studies.

Despite the reduced plasticity, the coating did not decrease the tabletability of dimenhydrinate appreciably because the tableting process is influenced by many parameters. Some parameters even improved (uniform filling, better lubrication, a smaller proportion of friction, etc.). Overall, it can be stated that coating is a good method of tablet preparation.

5.2.8. Dissolution tests

It can be seen from the dissolution curve that the dissolution of the active ingredient was rapid (*Fig. 23*).

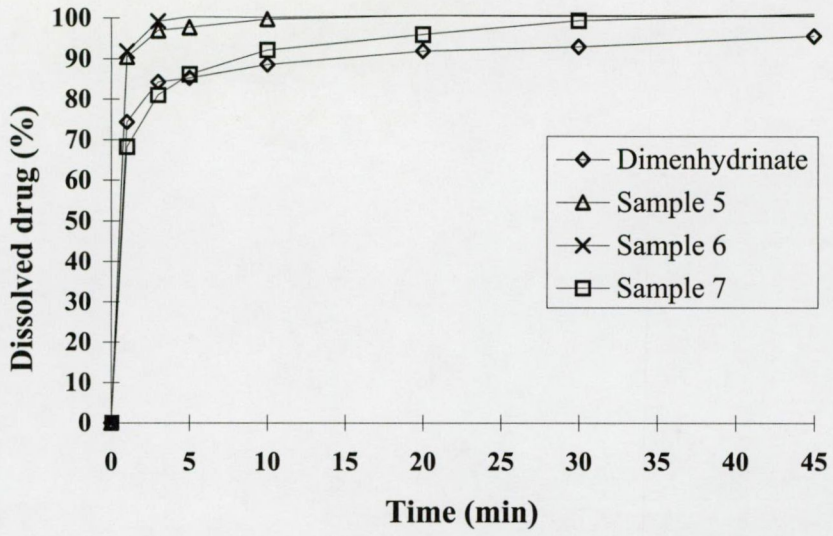


Fig. 23 Dissolution of dimenhydrinate from the samples

The uncoated crystals exhibited the slowest dissolution, which was confirmed by the drug release rate constant (*k*) (*Table 20*). All of the coated crystals underwent rapid dissolution. The non-sticking of the particles and the effect of HPMC in enhancing the dissolution may be responsible for this phenomenon. The dissolution displayed a first-order kinetics for each of the samples. This was confirmed by statistical analysis.

Table 20 *Evaluation of kinetic of dissolution*

Sample	***K***	***R* value**
Dimenhydrinate	0.0325	0.9801
Sample 5	0.2832	0.9918
Sample 6	0.5000	0.9652
Sample 7	0.0926	0.9849

6. SUMMARY

The main aims of this study were to protect dimenhydrinate crystals against environment parameters and to promote the processibility of its crystals (with poor properties) for tablet-making. The goal was to use the least possible additives and technological steps. Crystal coating was chosen. The crystals were coated in a fluidized bed apparatus by a top-spray method. Three different gastric-soluble polymers were used for coating and the products were compared with the original crystals and the granules. Another aim of this study was to establish indirect methods which can be used to determine the thickness and smoothness of films on the surface of crystals because direct methods cannot be used for coated crystals.

It can be stated from the results that:

- Dimenhydrinate consists of small columnar crystals with low flow properties. The space filling, compressibility and compactibility of these crystals are not appropriate for direct compressing. Coating and granulation improved these parameters.
- The particle size increased during crystal coating, but remained significantly lower than that for granules.
- The surface treatment of the crystals significantly decreased the surface free energy; hence, the adhesion force between the particles can also be decreased.
- Heated dimenhydrinate crystals (above the melting point of 104-105 °C) leave a brown glass-like spot without recrystallization. This temperature can be detected on a high-speed rotation tablet machine during tablet-making. Thus, a method can be applied which can protect the crystals against generated heat. The coating can influence the heat conductivity between the crystals as the virtual melting point of the coated crystals was significantly increased. There was no effect on the granulation thermal behaviour of the crystals.
- The treatment of crystals enhanced the dissolution of the active ingredient. The coating with Sepifilm® LP 010 particularly promoted the dissolution because of the HPMC content.
- Further increase of the amount of coating material did not further change the particle size because two simultaneous processes are involved which both increase (sticking, and thicker film) and decrease (breaking of crystals and film) the particle size, so that the shape of the product prepared with a longer coating time was worse.
- Coating with different quantities of coating fluid prepared from Sepifilm® LP 010 improved the powder rheological parameters, the compressibility, the dissolution of the active ingredient and the lubrication during tablet-making and lowered the surface free energy. The virtual melting points of these coated samples were higher since the heat conductivity

between the crystals was restricted. This phenomenon can be beneficial for the preparation of tablets from heat-sensitive material.

- The coating with Sepifilm® LP 010 worsened the wetting and plasticity of the samples. This can be explained by the presence of coating film.
- The measurement of water uptake and compactibility and thermoanalytical studies can be used as indirect methods for determination of the protective effects of films.
- Too long a coating time is not practical because the frequency of the breaking of the crystals rises, which can reduce the efficacy of protection by the film coating.

The effects of the amount of coating fluid prepared from Sepifilm® LP 010 on the tablet-making are presented in *Fig. 24.*

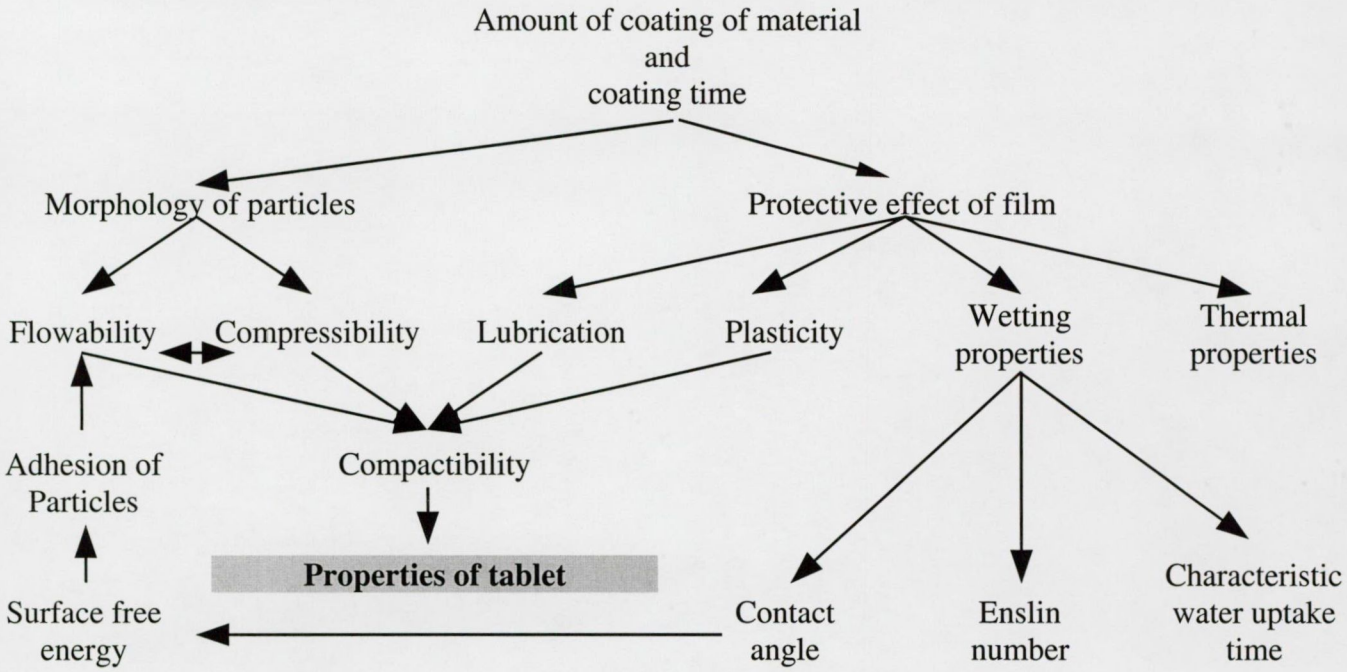


Fig. 24. Effect of amount of coating fluid on tablet-making

It can be concluded that near granulation, the coating of the crystals with a gastric-soluble polymer is a good method for improving the tablet-making of material with low flow and compactibility properties. There are other favourable effects of crystal coating, e.g. it is able to prevent the decomposition of heat-sensitive material because it reduces the generation of the heat of friction and disturbs the heat conductivity. The intermediate product prepared with Sepifilm® LP 010 has the best properties. Consequently, the coating of crystals without any other technological step can be a useful method facilitating the economical preparation of tablets that dissolve rapidly, and the active ingredient is also protected against harmful factors.

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ANNEX

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