

INDIRECT METHODS FOR DETERMINATION OF THE PROTECTIVE EFFECTS OF COATING FILMS ON THE SURFACE OF CRYSTALS

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Abstract

The extents of the protective effects of coating films on the surface of crystals were determined. Three different samples were made with different quantities of coating fluid (Sepifilm LP 010 in 10% aqueous solution). Since the atomizing rate was constant, the coating time increased in parallel with the volume of coating fluid applied. The direct measurement of film thickness and smoothness is very difficult, and therefore indirect methods were used. Dimenhydrinate was chosen as model drug; this is a heat-sensitive antihistamine with a low melting point. This temperature can be reached during the tableting process. The behaviour of samples on exposure to heat was examined by differential scanning calorimetry. The water uptakes of the samples were determined with an Enslin apparatus. Plasticity was studied with an instrumented tablet machine. These indirect methods (thermal conductivity, water uptake and plasticity measurements) revealed connections between the results of the various experiments. An overlong coating time decreased the protective effect of the coating film.

Keywords: dimenhydrinate, DSC, film coating, HPMC, plasticity, thermal conductivity, water uptake

Introduction

Film coating is a method that is widely used for protection, retardation and identification. Gastric-soluble polymers are used to protect ingredients from light, moisture and oxygen, and for identification. Intestine-soluble polymers or permeable polymers which provide drug diffusion are utilized for retardation [1]. Several types of gastric-soluble films (cellulose derivatives, poly(methacrylates), poly(ethylene-glycols), etc.) have been used for protection. The film smoothness and thickness determine the protective effect of the coating film. These parameters are well measurable on the surface of tablets or pellets by means of image analysis [2]. The film coating of fine particles can be a useful procedure in tablet making but the sticking of these particles

disturbs the determination of film thickness. It is difficult to avoid this sticking effect [3]. It is important to know whether the protective effect is modified or not by the quantity of coating material applied. The film coating of fine crystals could possibly be more widely used if the film smoothness and thickness can be determined.

Knowledge of the process of compression is very important in the technology of tablet making. Compression during tableting is a complex and irreversible dynamic process [4]. 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 pre-compression and main compression forces on the upper and lower punches, the punch displacements, the ejection force, etc. [5]. A number of methods can be used to study compressibility from different determined data [6–8].

The determination of temperature is very important because the melting points of many organic materials are low, and are readily reached during the process of compression, e.g. busulfan 115–118, hyoscyamine 106–109, phenylbutazone 104–107 or dimenhydrinate 102–105°C [9]. It is well known that, if crystals are arranged side by side with a high thermal conductivity axis, 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 accordingly the crystals melt. Since melted materials recrystallize after compression, the particles lose their individuality. Such sites in the texture are called hot spots [10–12]. If a material decomposes at the melting point, hot spots must be avoided. This problem can arise with hormones (betamethazone or spironolactone), carbohydrates, enzymes (pancreatin [13, 14]), etc.

Direct measurement of the heat originating in the texture of tablets during compression is very difficult. Indirect methods such as ‘compaction calorimetry’ [15], or differential scanning calorimetry (DSC) [16] (temperature modulated or conventional) are used to learn the behaviour of materials exposed to compression and heat. Indirect experiments demonstrated that the energy distribution and therefore the heat produced in the texture are not even [17]. A thermoanalytical method (DSC) has been used as an indirect method to establish the changes in material properties at elevated temperature.

The water uptake (wetting) is also an important characteristic because it can influence the disintegration of tablets [18]. The bioavailability of a tablet therefore can be influenced by methods which modify the water uptake.

The aim of this study was to determine the protective effect of films on the surface of crystals. It was examined how the protective effect of a coating film is modified when the quantity of coating fluid is increased. The above-mentioned parameters (thermal conductivity, water uptake and compressibility) were examined with regard to the prediction of the smoothness and thickness of films.

Experimental

Materials

The model drug used was dimenhydrinate (Ph. Eur. 3rd, B.No.:280-69-015), which is an ethanolamine derivative antihistamine used for the treatment of motion sickness, nausea and vomiting [19]. This material is sensitive to heat: it decomposes at the melting point, as indicated by industrial experience and a previous study [16]. The drug is well absorbed from the gastrointestinal tract. In the event of oral administration, the onset of the effect occurs after about 15 min [20]. A gastric-soluble polymer was therefore used. The film-forming agent was hydroxypropyl-methylcellulose (HPMC) (Sepifilm LP 010[®], B.No.: 80741) (Seppic, Paris, France). Sepifilm LP 010[®] was applied in a 10% aqueous dispersion, containing binder, pigment and plasticizer [21].

Coating

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

Parameters: nozzle diameter: 0.8 mm, inlet temperature: 45°C, outlet temperature: 30°C, blow-out pressure: 5.6 bar, atomizing pressure: 2 bar, peripump: 10 ml min⁻¹, air volume: 30–40 m³ h⁻¹, yield of the coating experiment: 75–80%.

Sample 1 (Dim 1) – A 40 g aqueous dispersion was used for 100 g dimenhydrinate.

Sample 2 (Dim 2) – A 55 g aqueous dispersion was used for 100 g dimenhydrinate.

Sample 3 (Dim 3) – A 70 g aqueous dispersion was used for 100 g dimenhydrinate.

The experiments were made three times.

Morphological study

Microscopy, and especially scanning electron microscopy (SEM), has been widely used to test the shape and surface of particles. Modern SEM allows particles much smaller in size than a micrometre to be measured and the roughness of the surface to be observed. A Hitachi S 2400 (Hitachi Scientific Instruments Ltd., Tokyo, Japan) scanning electron microscope was utilized. A sputter coating apparatus (Bio-Rad SC 502, VG Microtech, UK) was applied to induce electric conductivity on the surface of the 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. 500 particles were measured. Before the tests, the dimenhydrinate crystals were dispersed in

paraffin because of their tendency to aggregate. The coated crystals were measured without this treatment.

Water uptake

The Enslin number (mL g^{-1}) was determined with a glass sieve and a pipette with 0.01 mL accuracy [18]. A monolayer of particles took up the maximum quantity of water possible through a filter paper under these conditions.

Compressibility test

The samples were compressed into tablets with a Korsch EK0 instrumented eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single flat punches 10 mm in diameter, furnished with strain gauges and a displacement transducer. The strain gauges allow the forces on the upper and lower punches to be followed with force measuring equipment, which was calibrated with a Wazau HM-HN-30 kN-D cell (Kaliber Ltd., Budapest, Hungary). The displacement transducer was fitted over the upper punch. The transducer distance accuracy was checked by using five measuring pieces (made of hardened steel) of different thickness (2.0, 5.0, 7.5, 10.0 and 15.0 mm) under a minimal measurable load (Mitutoyo, Tokyo, Japan). The compression was carried out electrically at 36 rpm at an air temperature of 24°C and a relative humidity of 45%. The compressed volume was 100 mm^3 for each sample. 10 tablets were compressed for each sample. The compression force on upper punch was 18 ± 1.8 kN. The deviation of pressing force was higher for uncoated crystals because of uneven filling.

DSC

A DSC 821° (Mettler-Toledo GmbH, Switzerland) apparatus was used to check the features of the material on exposure to heat. 7.3–7.6 mg dimenhydrinate was measured into the pans. Two heating methods were applied, each involving an isothermal segment and a dynamic segment (Table 1).

Table 1 Heating segments of DSC experiments

	Isothermal segment		Dynamic segment	
	Temperature/°C	Time/min	End-temperature/°C	Heating rate/ °C min^{-1}
Program 1	25	3	250	5
Program 2	25	3	107	5

The heating methods were combined with each other, the methods being separated by slow cooling (5°C min^{-1}). If possible the melting point was determined after the first heating. Three parallel examinations were made in every case. The mathe-

matical evaluation was carried out with the Anova test, with the SPSS 9.0 package; the confidence limit was 95%.

Results and discussion

The habit of the crystals is shown in the SEM photo. The dimenhydrinate consisted of crystals with mainly a columnar form and a broad size distribution (Fig. 1; Table 2). Many particles were broken. An increase in the size of the crystals was detected during coating, but this was different from that generally observed during granulation or pelletization (Figs 2–4; Table 2). The shape of the coated crystals was not similar to that of granules or pellets. Thus, this method does not involve granulation. An increase in particle size occurs during the coating of the fine particles and is difficult to avoid [3]. The cause of this significant increase is that the small and broken particles stick into the macromolecular film. Dim 2 exhibited the best shape. The thickness of the film can be determined for pellets by image analysis methods [2]. In this case, sticking disturbed such measurements. There was no relationship between the quantity of coating fluid (and therefore the coating time) and the particle size, which can be explained by the simultaneous breaking of the crystals and of the breaking film



Fig. 1 Dimenhydrinate crystals (SEM)

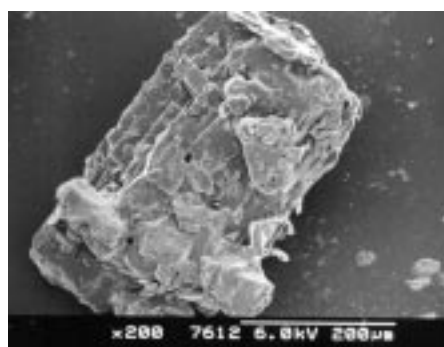


Fig. 2 Dim 1 sample (SEM)



Fig. 3 Dim 2 sample (SEM)

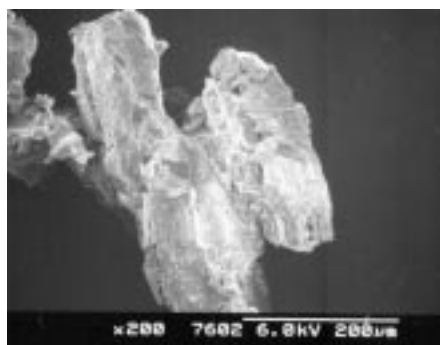


Fig. 4 Dim 3 sample (SEM)

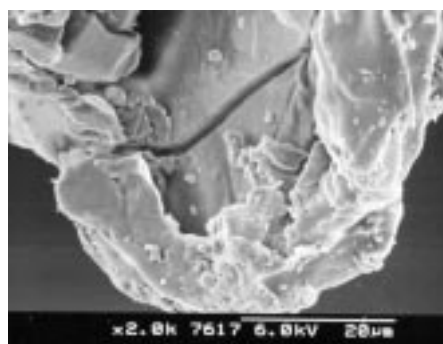


Fig. 5 Crack in coated crystals (Dim 3) (SEM)

during the film coating. Increase of the coating time led to a higher possibility of breaking of the coated crystals (Fig. 5), and therefore a decreased quality of the protecting film.

SEM photos indicated that Dim 2 exhibited the best of coating film quality. Since many parameters disturbed the exact determination of film thickness and

smoothness by means of image analysis, other indirect methods were used in the remaining part of the work reported here, and these support the assumption that the best product was Dim 2.

Table 2 Particle sizes of samples

Sample	Length/ μm	Breadth/ μm
Dimenhydrinate	83.84 (<i>SD</i> =54.50)	49.40 (<i>SD</i> =29.28)
Dim 1	201.95 (<i>SD</i> =114.47)	133.68 (<i>SD</i> =73.63)
Dim 2	239.49 (<i>SD</i> =129.69)	155.09 (<i>SD</i> =80.75)
Dim 3	229.90 (<i>SD</i> =159.57)	149.93 (<i>SD</i> =102.24)

Water uptake

The extent of water uptake of crystals is very important for the bioavailability of a tablet, because a large amount of water can promote tablet disintegration. The untreated crystals exhibited a good ability and a rapid water uptake (Table 3; Fig. 6). The coating film decreased the water uptake because it meant a restriction for the water. The coating film and the crystals did not dissolve in this quantity of water. In this case, therefore, there is a connection between the water uptake and the uniformity of the film. As the film uniformity and the thickness increased, the water uptake decreased. For Dim 3, the amount of the coating material was higher, but the coating time was therefore also increased which enhanced, the possibility of crystal breaks. The resultant of the two parallel features was the somewhat surprising result that Dim 2 displayed the smallest Enslin number. This was in accordance with the result of the morphological study: the smoothest film was observed for Dim 2.

Table 3 Enslin numbers of samples

	Dimenhydrinate	Dim 1	Dim 2	Dim 3
Enslin number/mL g^{-1}	0.80	0.68	0.56	0.65
<i>SD</i>	0.04	0.04	0.03	0.02

Compressibility test

The force-displacement curve was determined and the plasticity was calculated.

The force-displacement curve of the uncoated crystals may be seen in Fig. 7. The coating did not influence the shape of the force-displacement curve significantly. The smooth line is the measured curve, while the dotted lines are lines facilitating the calculation. There are three areas in the triangle. E_1 is the energy lost by rearrangement of the particles, E_2 is the useful energy and E_3 is the energy lost by elastic recovery [5].

The plasticity was calculated according to Stamm and Mathis equation (PL_{S-M}) [22]:

$$PL_{S-M} = \frac{E_2}{E_2 + E_3} 100$$

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

The uncoated dimenhydrinate crystals exhibited the highest plasticity (Table 4). The coating caused a decrease in plasticity. This can be explained by the film between the crystals. The interactions between the crystals were influenced by the film. The free coating film exhibited elastic properties, which was supported by other experiment. Not only the quantity of coating material influenced the plasticity: the 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. Dim 2 exhibited the poorest plasticity, which can be explained in terms of the best protective effect of the coating film.

Table 4 Plasticity of samples

	Dimenhydrinate	Dim 1	Dim 2	Dim 3
$PL_{S-M}/\%$	69.66	59.61	43.77	52.93
SD	6.61	2.32	2.91	3.07

Despite the decreased plasticity, the tablettability of dimenhydrinate was not appreciably decreased by the coating because the tableting process is influenced by many parameters (flow rate of material, rearrangement of particles, lubrication, etc. [23]). Some parameters even improved (uniform filling, better lubrication, a smaller proportion of friction, etc.).

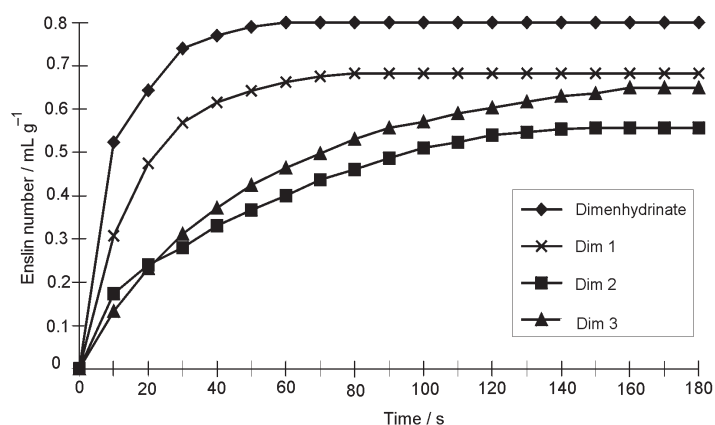


Fig. 6 Water uptake of samples

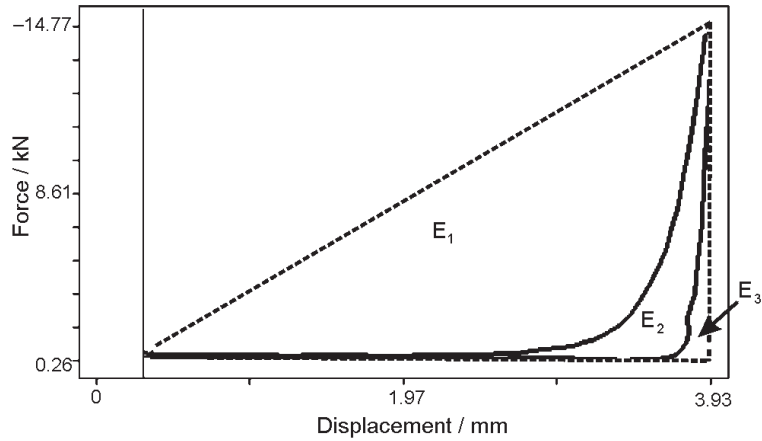


Fig. 7 Force-displacement curve of uncoated crystals

DSC measurements

Samples were heated, cooled and re-heated according to program 1 (Table 1) at first, however, the curve had a quite different shape during reheating (Figs 8 and 9). The

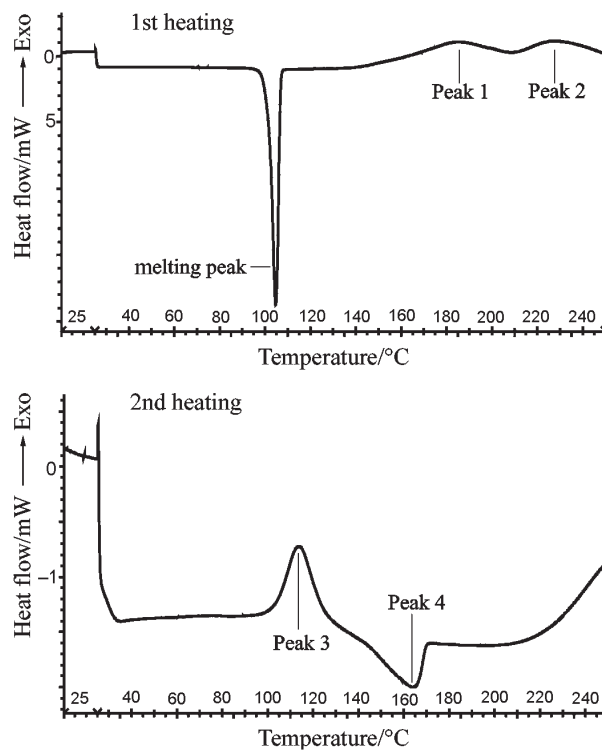


Fig. 8 DSC curves of uncoated crystals, applying program 1

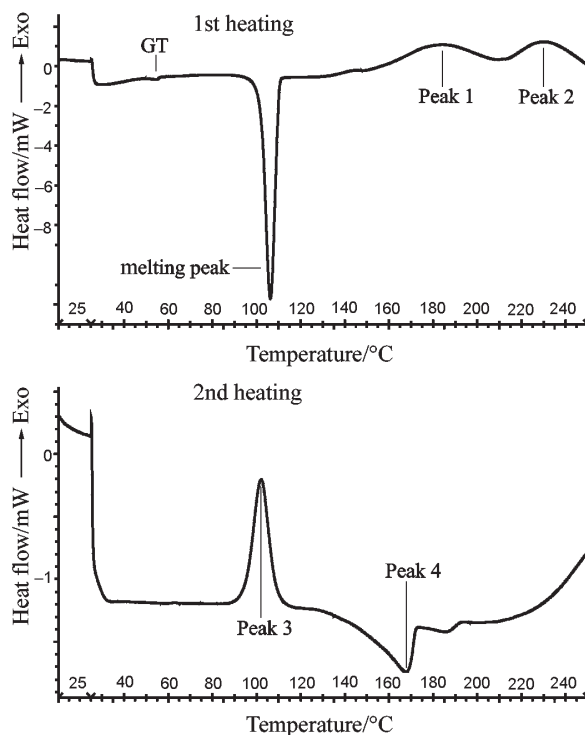


Fig. 9 DSC curves of Dim 2, applying program 1

coated and uncoated samples exhibited similar behaviour. The slight change at about 55°C in the curve of the coated crystals was explained by the presence of Sepifilm LP. This alteration was caused by the glass transition (*GT*) of HPMC and the congealing temperature of the plasticizer stearic acid [9] (Fig. 9). During the reheating the *GT* disappeared. The cause of this phenomenon can be the change of structure of macromolecular film. This phenomena can depend on heating, cooling and re-heating time. The structure of the substance needs enough time to be re-built. During re-heating the endotherm melting peak and the two exotherm peaks disappeared, while another exotherm peak and an endothermal peak appeared at other temperatures. These alterations in the shape of the curve were 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 heating was stopped after the first peak, only an exotherm peak (peak 2) was detected at about 230°C, which accorded with the second exotherm peak in the first heating of the uncoated crystals. Therefore, the material was not decomposed after the first exotherm peak, but was not transformed to the crystalline state after cooling, and the process continued as during the first heating. This problem also arose if heating was stopped after the melting peak. The virtual melting point of the coated crystals was

higher; this could be caused by reduction of the thermal conductivity of the crystals by a macromolecular film (Table 5).

Table 5 Virtual melting points of samples, applying program 1

	Dimenhydrinate	Dim 1	Dim 2	Dim 3
Melting point/°C	103.35	105.24	105.98	105.44
<i>SD</i>	0.65	0.50	0.66	0.56

Applying program 2, heating was interrupted during the rising part of the endotherm melting peak (Table 1) and, after cooling, the effect of heating to 250°C was examined (Figs 10 and 11). The melting peak in the first period was not evaluated statistically, because the peak was not complete. There was no significant difference in the melting point in the second heating period (Table 6). There was a difference in the shapes of the curves on re-heating. A lower melting enthalpy value has been obtained during the second heating for the melting of uncoated crystals than for the coated samples. The change was significant ($p < 0.05$) (Table 7). This alteration was explained by the differing thermal conductivities of the crystals. Since a thin macromolecular film separates the coated crystals, this can impede the transport of the heat from crystals to crystals. As the time of heat transport above the melting point was short (about 20 s) and the heat transport was restricted, a smaller fraction of the dimenhydrinate decomposed than in the case of the uncoated crystals. This difference was observed if exactly the same mass of crystals was measured. The more the active ingredient remaining in the given volume, higher melting enthalpies have been calculated. In the remainder of this paper the values of heat of fusion will be compared with regarded to the result of water uptake and the plasticity of the material.

Table 6 Virtual melting points of samples in re-heating part, applying program 2

	Dimenhydrinate	Dim 1	Dim 2	Dim 3
Melting peak/°C	104.20	104.50	104.89	104.84
<i>SD</i>	0.37	0.11	0.09	0.41

Table 7 Comparison of heat of fusion of melting peaks in re-heating parts, applying program 2

	Dimenhydrinate	Dim 1	Dim 2	Dim 3
Heat of fusion/J g ⁻¹	3.51	9.78	25.45	9.76
<i>SD</i>	4.72	3.83	10.62	1.77

Comparative studies

The different indirect methods of determining the protective effect of the film were compared mathematically by linear regression (the *t*-test was significant ($p < 0.05$)).

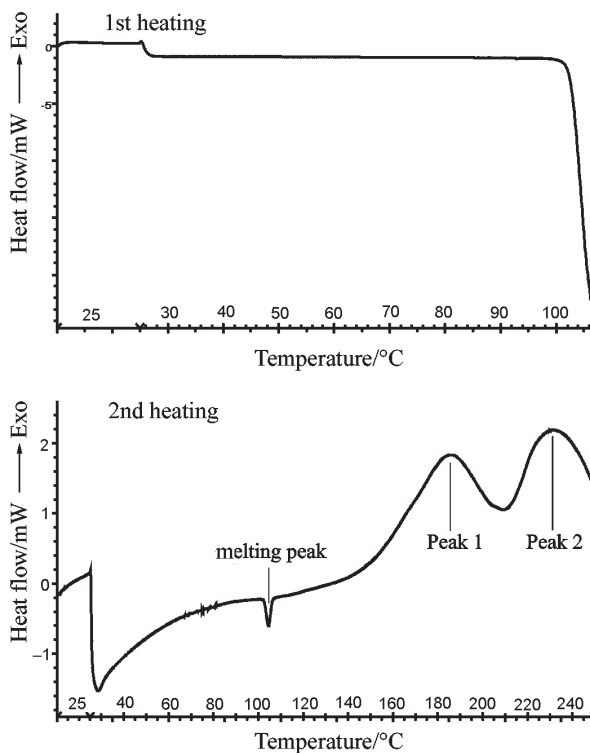


Fig. 10 DSC curves of uncoated crystals, applying program 2

The first comparison was that of the Enslin number and the heat of fusion value of the DSC curve. The relationship is shown in Fig. 12. DSC measurement in this study can be used to predict the impedance of water uptake.

Comparison of the plasticity of the investigated materials and the melting enthalpies, a linear correlation was observed between these two parameters (Fig. 13).

It can be stated that for the investigated materials the three parameters can be used to predict the protective effect of the film. DSC is therefore a good method with which the control of the film coated fine particles production can be done.

Conclusions

Thermoanalytical studies reveal that dimenhydrinate crystals are sensitive against heating. Different DSC heating methods demonstrated that this change is caused by decomposition at a temperature of 250°C. At temperatures below the temperature of the second exotherm peak during of the first heating of dimenhydrinate, but above the melting point, the material does not decompose, but the dimenhydrinate loses its crystalline state. If this occurs during compression, it disturbs the possibility of uniform, exact and rapid tablet making. Film coating, a method widely used in pharmaceutical technology, does not alter

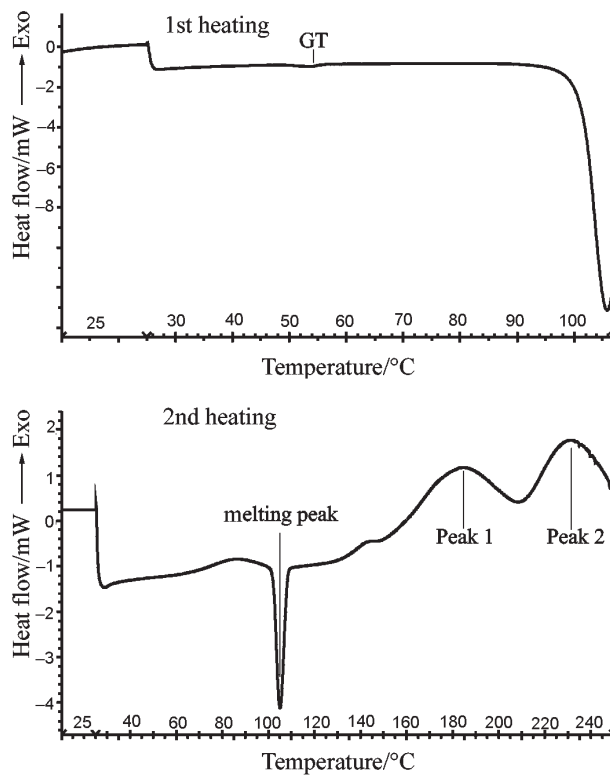


Fig. 11 DSC curves of Dim 2, applying program 2

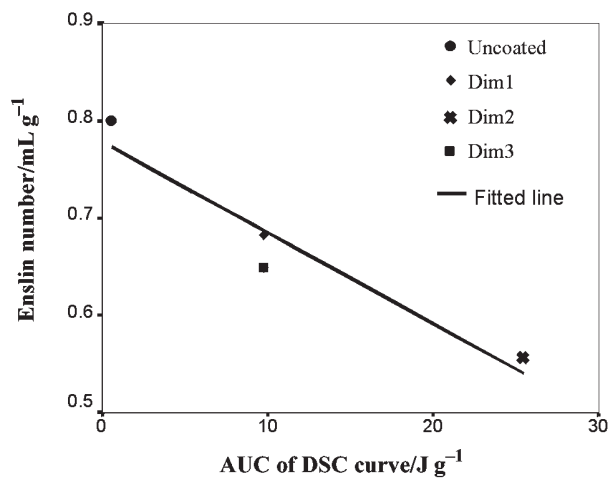


Fig. 12 Relationship between melting enthalpies of samples and Enslin number (R value: 0.9588, slope: 0.0093, intercept: 0.7782)

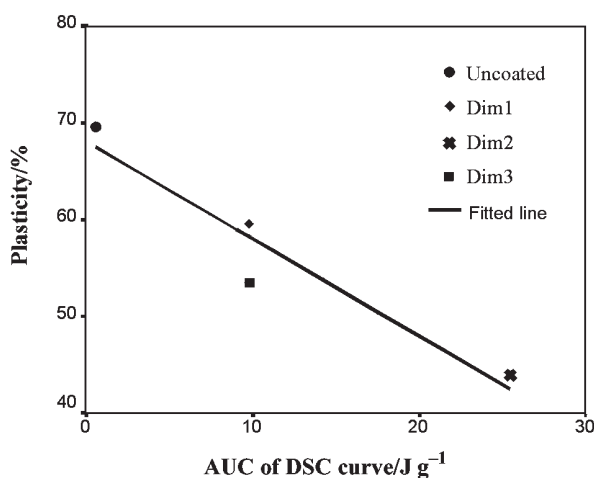


Fig. 13 Relationship between the melting enthalpies of samples and plasticity (R value was 0.9553, slope: 0.9084, intercept: 62.83)

the shape of the DSC curve of dimenhydrinate, but it increases the melting point of coated crystals compared with the uncoated crystals. This can be explained by the presence of a macromolecular film which reduces the thermal conductivity, because it separates the particles.

An increased time of film coating increases the possibility of the crystals breaking with accompanying decreases in the smoothness and uniformity of the film. The particle size of coated crystals does not vary linearly with the coating time.

Since the determination of film uniformity on the crystals by direct methods is very difficult, the indirect methods mentioned in this work can be used. There are linear relationships between the protective effect of the coating film and water uptake, plasticity of samples and thermal conductivity of the investigated materials. Determination of these parameters can therefore be useful for prediction of the protective effect of a coating film. The use of DSC can lead to direct information on the material and can be utilized to predict other information.

Finally, it may be stated that the film coating of crystals may facilitate the tablet making of materials that are heat-sensitive, exhibit low flow ability and are difficult to compress.

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This work was supported by grants from the Hungarian Scientific Research Fund (OTKA): T-026351, T-026459, T-026579 and T-033054.

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