SURFACE TREATMENT OF DIMENHYDRINATE CRYSTALS

J. Bajdik[1], *K. Pintye-Hódi*[1], *Cs. Novák*[2], *P. Szabó-Révész*[1],
G. Regdon Jr.[1], *I. Erős*[1]* *and G. Pokol*[2]

[1]Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, H-6720 Szeged
[2]Institute of General and Analytical Chemistry, Budapest University of Technology and
Economics and Research Group for Technical Analytical Chemistry of the Hungarian Academy of
Sciences, Szent Gellért tér 4, H-1111 Budapest, Hungary

Abstract

Dimenhydrinate is a heat-sensitive antihistamine with a low melting point. The heat-sensitive feature is of importance if direct compression is used. Direct measurement of the heat originating in the texture of tablets during compression is very difficult. Thermoanalytical methods were used as indirect methods to describe the changes in material properties at high temperature: differential scanning calorimetry, thermomicroscopy and thermogravimetric analysis. Film coating method is widely used in pharmaceutical technology. A fluidized bed apparatus was applied to coat the crystals. The coating film forming agent was hydroxy-propyl-methylcellulose (HPMC), which is a gastric-soluble polymer. Thermoanalytical measurements reveal that dimenhydrinate crystals are sensitive to heat. Film coating method does not alter the shape of the DSC curve of dimenhydrinate, but increases the melting point. The presence of a macromolecular film reduces the thermal conductivity, because it separates the particles.

Introduction

Knowledge of the process of compression 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 pre-compression 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. [1]. 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 [2].

---

* Author to whom all correspondence should be addressed.

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 average rate of heat transfer can be determined by dividing the energy of compression by the duration of compression [3]. 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, then this promotes the attainment of a higher temperature in a very small volume. This increased temperature can be higher than the melting point of material and the crystals melt. Since melted materials recrystallize after compression, the particles lose individuality. Such sites in the texture are called hot spots [4–6].

The melting points of many organic materials are low, and are readily reached during process of compression, e.g. busulfan 115–118, hyoscyamine 106–109, phenylbutazone 104–107, or dimenhydrinate 102–105°C [7]. If a material decomposes at the melting point, then hot spots must be avoided. This problem can arise with hormones (betamethazone, spironolactone) carbohydrates, enzymes (pancreatin [8, 9]) and others. In this case, several methods may be used, which separate the crystals, e.i. spherical crystallization, granulation, film coating, etc. The film coating of crystals is a well-known process applied for taste and smell masking, retardation of active ingredient, identification, etc. [10].

Dimenhydrinate was chosen for this work; it is a heat-sensitive antihistamine with a low melting point. The heat-sensitive feature is known from industrial experience: a crust of this material is formed on the high-speed tablet machine if direct compression is used. A study was made of the behaviour of dimenhydrinate, coated crystals and the influence of a macromolecular film in thermal conductivity from crystals to crystals.

Direct measurement of the heat originating in the texture of tablets during compression is very difficult. Indirect methods such as `compaction calorimetry` [11], or differential scanning calorimetry (DSC) (modulated temperature or conventional) 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 even, 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 [12]. The reason for this was the uneven distribution of force 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.

Thermoanalytical methods were used as indirect methods to describe the changes in material properties at high temperature: (DSC), thermomicroscopy and thermogravimetric analysis.

Experimental

Materials

The model drug was dimenhydrinate (USP 23), which is an ethanolamine derivative antihistamine used for the treatment of motion sickness, nausea and vomiting [13]. The average crystals size was 50×85 µm. The film-forming agent was hydroxy-propyl-methylcellulose (HPMC) (SEPIFILM LP 010) (SEPPIC, Paris, France). SEPIFILM LP 010 was applied in an aqueous dispersion, which containing binder, pigment and plasticizer.

Morphological study

The particle size distribution was examined with a Laborlux S light microscope and a Quantimet 500 MC image processing and analysis system (Leica Cambridge Ltd. UK).

Coating

A Strea-1 (Niro-Aeromatic AG, Switzerland) fluidized bed apparatus was applied with the top-spray method. The coating dispersion was transported by peristaltic pump, and the spray rate was 10 ml min^{-1}. The atomizing was performed with compressed air through a nozzle 0.8 mm in diameter. The drying temperature was 40°C. The average size of the coated crystals was 180×275 µm. The enhancement in size can be explained by the presence of a macromolecular HPMC film and a slight aggregation of the crystals during coating.

NMR study

Untreated dimenhydrinate crystals and two preheated samples (130 and 250°C) were examined. The sample heated to 130°C exhibited minor changes relative to the NMR curve of the untreated crystals. However the higher temperature of preheating caused more appreciable alteration in the curve. The difference can be explained by the decomposition of the material.

Thermal analysis

Thermomicroscopy

A Boetius thermomicroscope (VEB Analytik Germany) was applied to visible alterations in the crystals during the heating process. The heating rate applied was 5°C min^{-1}.

Thermogravimetric analysis

A Derivatograph-C (MOM, Hungary) was used to check the water content of uncoated dimenhydrinate crystals.

DSC

A DSC 821^e (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. Three 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}
1	25	3	250	5
2	25	3	130	5
3	25	3	107	5

The heating methods were combined with each other, the methods being separated by cooling.

The sample numbers to be seen in Table 2 will be used below to denote the experiments. The melting point was determined after the first heating if possible. The glass transition of the coating polymer can also be determined with this DSC method [14,15]. The evaluation was made according to DIN. DSC curves were studied with STAR^e Software.

Table 2 DSC experiments

	Uncoated crystals	Coated crystals
1 – cooling – 1	I	II
2 – cooling – 1	III	IV
3 – cooling – 1	V	VI

Three parallel examinations were made in every case. The mathematical evaluation was carried out with the two-sample T-test, with SPSS 9.0 package; the confidence limit was 95%.

Results and discussion

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.

Thermogravimetric analysis

No water was detected in the uncoated crystals.

DSC measurements

Glass transition

The slight change at about 55°C in the curve of the coated crystals was explained by the presence of SEPIFILM LP. The glass transition of HPMC and the congealing temperature of plasticizer stearic acid [7] caused this alteration. The action of a plasticizer is to lower the glass transition temperature of the pure polymer [10]. There was no significant difference in glass transition temperature (GT) in the different experiments (Table 3).

Table 3 Glass transition temperatures

	II	IV	VI
GT/°C	55.63	55.37	55.58
SD	0.22	0.41	0.69

DSC experiments

In experiments I and II, a quite different shape of the curve was observed during reheating (Figs 1 and 2). The two samples exhibited similar behaviour. The endothermal melting peak and the two exothermal peaks disappeared, while another endothermal peak and an exothermal peak develops at other temperatures. These
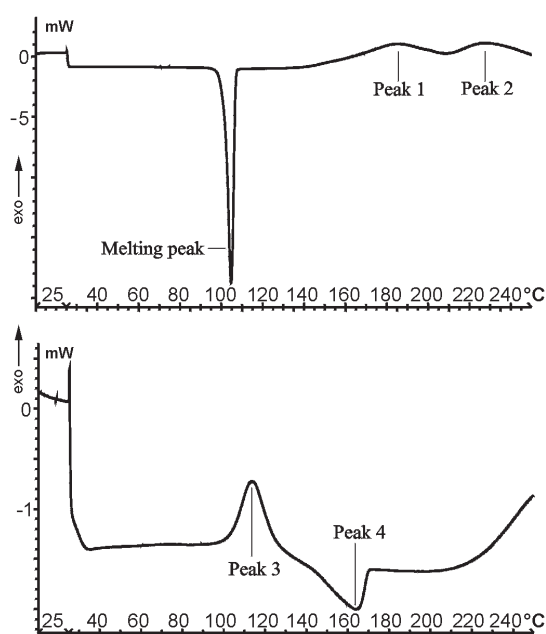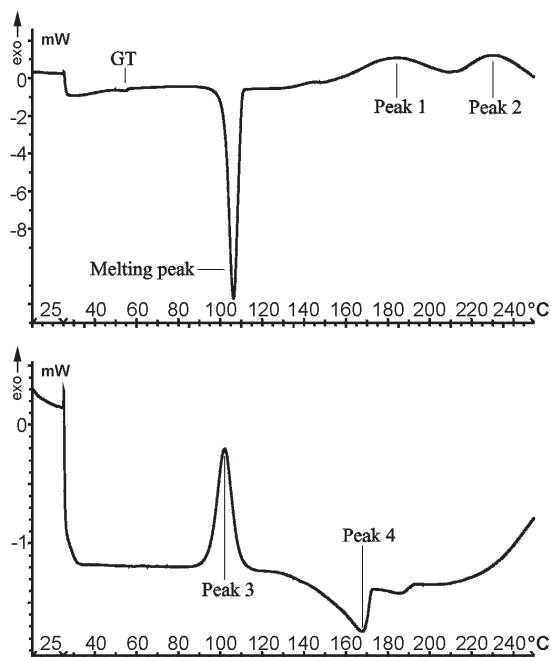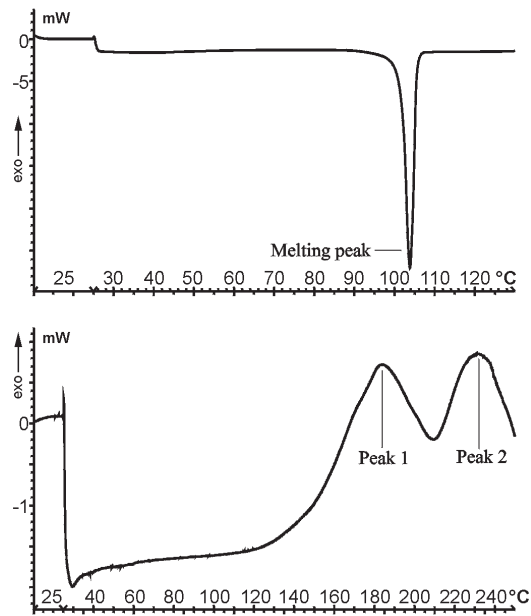

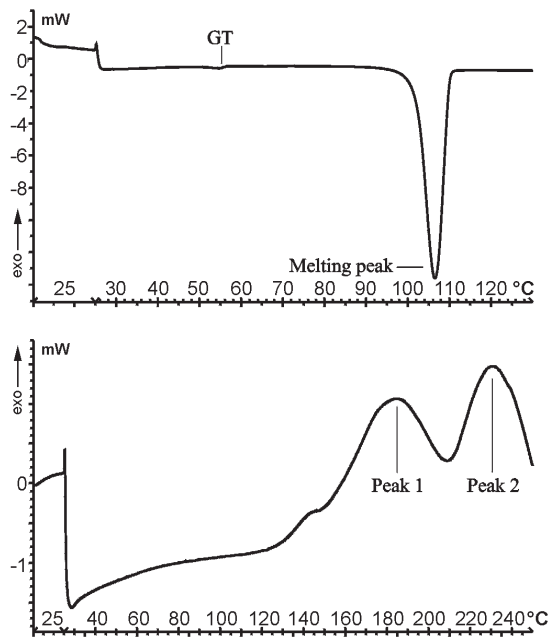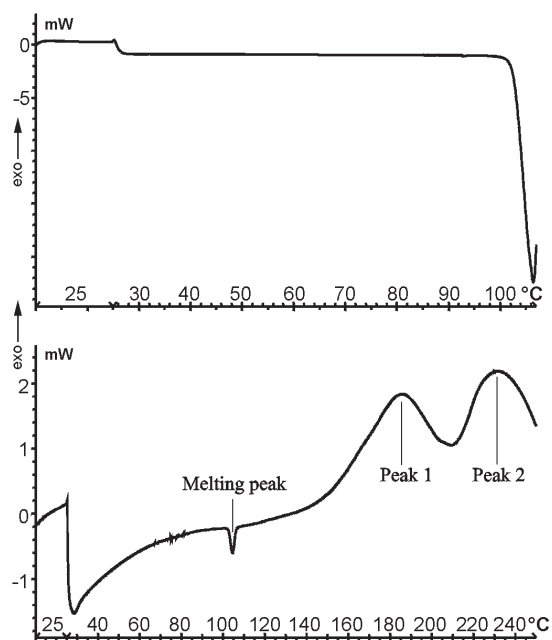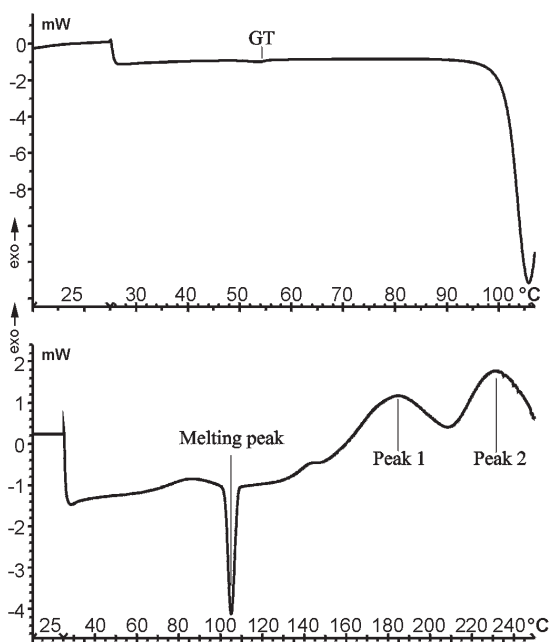**Fig. 1** DSC curves in experiment I

Fig. 2 DSC curves in experiment II

alterations in the shape of the curve was explained by decomposition of the material at this high temperature. The second exothermal peak of first heating related to the material involved in the decomposition: if the heating was stopped after the first peak, then only an exothermal peak was detected at about 230°C, which accorded with the second exothermal peak of first heating of the untreated crystals. Therefore, the material was not decomposed after the first exothermal peak, but was not transformed to the crystalline state after the cooling, and the process continued as on the first heating. There was a significant difference between the temperature of melting and the two peaks observed in the reheating period of experiments I and II. The virtual melting point of the coated crystals was higher, which could be caused by reduction of the thermal conductivity of the crystals with a macromolecular film (Table 4).

Table 4 Analysis of DSC curves in experiments I and II

		Melting peak	Peak 1	Peak 2	Peak 3	Peak 4
I	Mean/°C	103.35	183.94	229.54	114.56	162.65
	SD	0.57	1.02	1.15	1.03	1.03
II	Mean/°C	105.98	183.67	231.05	101.64	167.69
	SD	0.25	0.75	0.44	0.35	0.23

Fig. 3 DSC curves in experiment III

Fig. 4 DSC curves in experiment IV

Fig. 5 DSC curves in experiment V

Fig. 6 DSC curves in experiment VI

In the next experiment the maximum first heating temperature was only 130°C. The two exothermal peaks remained, but the endothermal melting peaks disappeared after the reheating in experiment III and IV (Figs 3 and 4). The cause of this phenomenon may be that the dimenhydrinate was not decomposed, but was not transformed to the crystalline state after cooling, and therefore the melting peak was not involved in the second heating. The melting peak could not be detected after a week. The virtual melting points were similar than in experiments I and II and the difference between experiments III and IV was significant (Table 5).

Table 5 Analysis of DSC curves in experiments III and IV

		Melting peak	Peak 1	Peak 2
III	Mean/°C	103.31	184.01	229.86
	SD	0.65	1.35	1.81
IV	Mean/°C	105.91	183.80	230.62
	SD	0.66	0.51	0.29

In experiments V and VI the heating was interrupted on the increasing part of the endothermal melting peak and, after cooling, the effect of heating to 250°C was examined (Figs 5 and 6). The melting point in the first period was not evaluated statistically, because the peak was not full. A significant difference was detected only in the melting point in the second heating period (Table 6). There was a difference in the shape of the curves of reheating in experiments V and VI. A lower value was observed for the area under the curve (AUC) of the endothermal melting peak of second heating for the uncoated crystals than coated crystals. The change was significant (Table 7). This alteration was explained by the differing thermal conductivity of the crystals. Since a thin macromolecular film separates the crystals in experiment VI this can impede the spread 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, smaller fraction of the dimenhydrinate decayed than for the uncoated crystals. This difference was observed if the same mass of crystals was measured. The more the active ingredient remaining in a volume, the higher the AUC.

Table 6 Analysis of DSC curves in experiments V and VI

		Melting peak	Peak 1	Peak 2
V	Mean/°C	104.20	183.99	229.99
	SD	0.37	0.48	0.12
VI	Mean/°C	104.89	183.74	230.62
	SD	0.09	0.34	0.27

Table 7 Analysis of AUC of melting peak of reheating parts of DSC curves in experiments V
and VI

	V	VI
$AUC/J\ g^{-1}$	3.51	25.45
SD	4.72	10.62

It is important to know the sensitivity of the material moisture, because coating with an aqueous dispersion is a wet method. DSC was used to detect the decomposition of dimenhydrinate. The wet crystals were prepared in an Enslin apparatus. The monoparticular layer of particles took up the maximal quantity of water possible through a filter paper under these conditions. The wet crystals yielded a changed DSC curve (Fig. 7A) , but the alterations had disappeared after drying for 24 h at room temperature (Fig. 7B). It can therefore be stated that dimenhydrinate was not decomposed if it is processed by wet methods followed by mild drying. The fluidized method used corresponded to these requirements, because the drying temperature was 40°C.
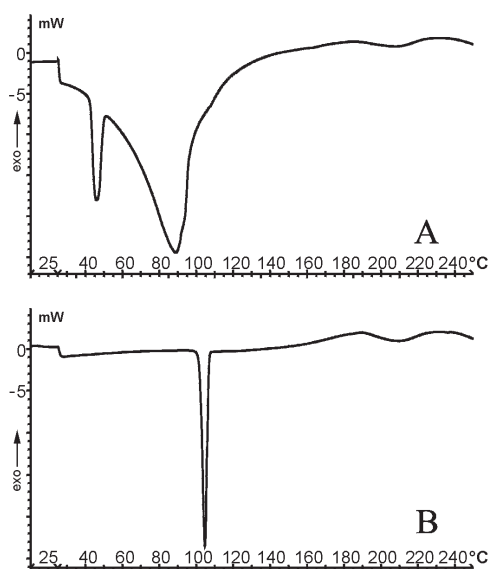
Fig. 7 A – DSC curve of wet dimenhydrinate crystals. B – DSC curve of dried (room
temperature, 24 h) water-treated crystals

Conclusions

Thermoanalytical measurements and NMR studies reveal that dimenhydrinate crystals are sensitive to heat. A brown glass-like spot develops if the material is heated above its melting point and left to cool. If this happens during compression, then it disturbs the uniform, exact and rapid tablet making. Different DSC heating methods show that this change is caused by decomposition. A higher temperature of (250°C) causes the decom-

position of dimenhydrinate, while a temperature of 130°C (above the melting point, but below the temperature of the second exothermal peak of the first heating of dimenhydrinate) does not decompose the material, but the dimenhydrinate loses its crystal state. Film coating method a widely used in pharmaceutical technology, does not alter the shape of the DSC curve of dimenhydrinate, but increases the melting point. A change of about 50°C from the curve for the uncoated crystals can be explained by the film glass transition and changes in other components. The presence of a macromolecular film reduces the thermal conductivity, because it separates the particles. The film coating can be achieved in a fluidized bed apparatus, because these conditions do not cause decomposition of this material. Further experiments must be carried out to establish the detailed complete effects of coating in reducing heat formation. These examinations may involve measurement of the forces during compression, the friction work, the flow properties and compactibility. The thickness of the film on the surface of the particles may be important, and these experiments must therefore extend to the influence of change in the thickness of the macromolecular film. Finally, it may be stated that the film coating of crystals may facilitate the tablet making of heat-sensitive materials.

* * *

References

1 P. Ridgway Watt, Tablet Machine Instrumentation in Pharmaceutics: Principles and Practice, Ellis Horwood Ltd., Chichester, UK 1988, p. 23.

2 A. Lieberman and L. Lachman, Pharmaceutical Dosage Forms, Tablets, Vol. 2, Marcel Dekker Inc., New York, USA 1981, p. 168.

3 S. Rankell and T. Higuchi, J. Pharm. Sci., 57 (1968) 574.

4 G. Kedvessy and M. Garamvölgyi-Horváth, Pharmazie, 28 (1973) 748.

5 C. Führer and W. Parmentier, Acta Pharm. Technol., 23 (1977) 205.

6 U. Bogs and E. Lenhardt, Pharm. Ind., 33 (1971) 850.

7 USP 23, United States Pharmacopeial Convention Inc., Rockville, USA 1994, p. 228, 781, 1210, 526.

8 E. Graf and A. Sakr, Pharm. Ind., 41 (1979) 86.

9 K. Thoma and K. Bechtold, Eur. J. Pharm. Biopharm., 47 (1999) 39.

10 G. Cole, Pharmaceutical Coating Technology, Taylor & Francis Ltd., London, UK 1995, p. 27.

11 M. T. DeCrosta, J. B. Schwartz, R. J. Wigent and K. Marshall, Int. J. Pharm., 198 (2000) 113.

12 K. Pintye-Hódi, P. Szabó-Révész, M. Miseta and B. Selmeczi, Acta Pharm. Hung., 54 (1984) 127.

13 K. Parfitt, Martindale, The Complete Drug Reference, Thirty-second edition, Pharmaceutical Press, London, UK 1999, p. 408.

14 H. McPhillips, D. Q. M. Craig, P. G. Royall and V. L. Hill, Int. J. Pharm., 180 (1999) 83.

15 J. L. Ford, Int. J. Pharm., 179 (1999) 209.