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EFFECT OF COATING ON THE FLOW, WETTING AND DISSOLUTION FOR DIMENHYDRINATE CRYSTALS

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Crystals of dimenhydrinate were coated with a gastric-soluble polymer (hydroxypropyl-methylcellulose) in a fluidized bed apparatus in order to increase the poor flowabilty of crystals. The amount of coating polymer can influence the wetting, the dissolution rate of the active ingredient and the sensitivity to heat. There was an increase in particle size due to the coating, but the increase is less than that during conventional granulation. The flow properties was increased by the film coating. The different wetting behaviour of the crystals is explained in terms of the contact angle of distilled water on the surface of tablets. Here different quantities of film forming polymer were examined. The characteristic water uptake reflects the wetting of the crystals. The thermal sensitivity, determined by a differential scanning calorimetry, was improved by the coating. The quantity of the polymer in the film plays an important part in the thermal sensitivity.

Keywords: dimenhydrinate, dissolution, flow properties, HPMC, melting point, wetting

Introduction

Solid dosage forms (tablets or capsules) are the forms most widely used in therapy. The main problem which arises during the preparation of the solid dosage form is when the particles exhibit an insufficient flow. Decomposition of the materials in the solid dosage form is another serious problem; it can be caused by heat, oxygen, moisture and light, and can happen during the preparation or storage of the product. Such problems can be avoided if the preparation is coated with a thin film. The aim of preformulation is to eliminate these problems.

Numerous factors affect the flow properties of powders, e.g. particle shape, size, size distribution, the roughness of surface of the particles, packing properties, etc. [1]. Various methods are applied to increase the flow properties of drugs, e.g. spherical crystallization [2-4], granulation [5], film coating [6], etc. Film coating is a very widespread method for protection, retardation and identification. Gastric-soluble polymers are used to protect ingredients from light, moisture and oxygen, and for identification. Intestine-soluble polymers or permeable polymers which provide drug diffusion are utilized for retardation [7]. A film coating can be used to increase the flowability of particles.

In this study, film coating with a gastric-soluble polymer was applied to increase the flowabilty of crystals with low-flow properties and to provide them with a protection by harmful factors. The thickness of such a polymer film is very important. The film smoothness and thickness determine the protective effect of the coating. These parameters are well measurable on the surface of tablets or pellets by means of image analysis [8]. 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. Therefore, the amount or quantity of polymer is used instead.

Three samples with different quantity of gastric-soluble polymer were prepared. The wettability of the preparations, the characteristic time of water uptake, the dissolution of the active agent, the flowability (flow time, mass by volume, and angle of repose) and the behaviour of the material on exposure to heat were examined. The effects of different amount of the polymer were studied.

The wetting of a solid dosage form is the first step in the dissolution of the active ingredient, and it can influence the bioavailability of the drug [9]. There is a relationship between the wetting of the particles and the bioavailability [10].

The aims of this study were to compare the above properties of untreated and treated crystals and to study how the amount of polymer influences these parameters.

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 [11]. The drug is well absorbed by the gastrointestinal tract. In the event of oral administration, the onset of the effect occurs after about 15 min [12]. This material is sensitive to heat: it decomposes at the melting point, as indicated by industrial experience and a previous study [13]. The film-forming agent was hydroxypropyl-methylcellulose (HPMC) (SEPIFILM LP 010®) (SEPPIC, Paris, France). SEPIFILM LP 010® was applied in an aqueous dispersion, containing binder, pigment and plasticizer.

Coating

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

Parameters:

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

Sample 1 (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.

Morphological study

Microscopy, and especially scanning electron microscopy (SEM), has been widely used to test the shape and surface of particles. A Hitachi S2400 (Hitachi Scientific Instruments Ltd, Tokyo, Japan) scanning electron microscope was utilised. A sputter coating apparatus (Bio-rad SC 502®, VG Microtech, UK) was applied to induce electric conductivity on the surface of the samples. The air pressure was 1.3-13 mPa.

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.

Flow properties

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

Thermal analysis

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 sample were measured into the pans (40 µl, aluminium). The heating method involved an isothermal segment (25 °C, 3 min) and a dynamic segment (from 25 °C to 130 °C at a heating rate of 5 °C/min). Three parallel experiments were performed.

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 characteristic water uptake time ($t_{63.2\%}$) is the time which is necessary for the uptake of 63.2% of the maximum quantity of water. The RRSBW equation was used. This equation can be used for the determination of characteristic dissolution time of active ingredient from solid dosage forms [14]. Since the mechanism of water uptake is similar to dissolution this equation can be used in this case.

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

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

$$\ln\ln\frac{M_0}{M_0 - M} = \beta \ln t - \ln a \qquad (2)$$

where β is the slope and the ln *a* is the intercept.

This equation was linearized by Langenbucher [15]:

$$\ln a = \beta * \ln t_{63.2\,\%} \qquad (3)$$

Table 1 Particle sizes of samples

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

Linear regression ($p<0.05$) was carried out for the determination of $t_{63.2\%}$. Three parallel experiments were performed.

Wettability

Measurements on wetting of fine particles are very difficult, and therefore several methods are used for its determination [16]. Comprimates were made from materials under high pressure in this study. High pressure causes the deformation and breaking of crystals, which can alter the wetting. On the other hand, high pressure causes a lower porosity, which can cause disturbances during the measurements. The disintegration of comprimates did not influence the measurements, as indicated by the use of an Erweka USP disintegration tester (Erweka GmbH, Frankfurt am Main, Germany). The tablets were not disintegrated in distilled water at 37 °C within 15 min. This test procedure was used because dimenhydrinate is commercially available in tablet form.

The same parameters of the tablet machine were applied in every case. Each sample contained only treated or untreated dimenhydrinate.

Parameters:

Tablet machine: Korsch EK0 instrumented eccenteric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany)
Tablet diameter: 10 mm flat bevelled edge
Pressure force: 18±1.5 kN
Volume of die cavity: 100 mm^3

A sessile drop analysis system (Tropfenkonturanalyse-System G 10/DSA 10, KRÜSS GmbH, Hamburg, Gemany) was used to determine the contact angle of distilled water on the tablet surface. The measurements were made at room temperature. The same parameters were applied in every case. Five parallel experiments were performed.

The results were compared to the characteristic water uptake times.

Dissolution test

The dissolution of dimenhydrinate was studied with a paddle method.

Test parameters:

Apparatus: Pharma Test PTWII (equipped with a rotating paddle) (Pharma Test GmbH, Germany)

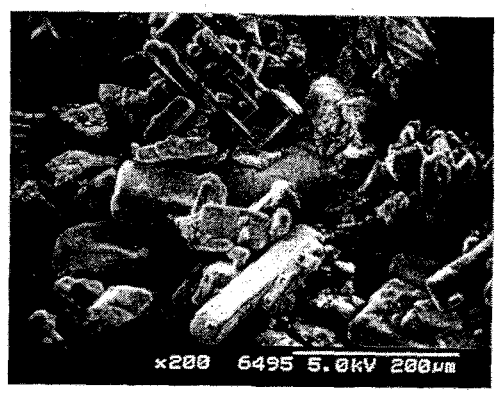

Fig.1 Dimenhydrinate crystals (SEM)

Paddle speed: 100 rpm
Dissolution medium: 900 ml artificial gastric juice (pH=1.2±0.1)
Temperature: 37.0 ± 1 °C
Samples taken at: 1, 3, 5, 10, 20, 30, 45 and 60 min
Number of samples: 6
Mass of sample: 0.50 g
Measurement: with a UV spectrophotometer (Spectromom 195D, MOM, Hungary) at 275 nm.

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

Results and Discussion

The habit of the crystals is shown in the SEM photo. The dimenhydrinate consisted of crystals with mainly columnar form and a wide size distribution (*Fig.1*) (*Table 1*). Many particles were broken. An increase in the size of the crystals was detected during coating, but this was different from that in general during granulation or pelletization (*Figs.2-4, Table 1*). The 2.5-3.0 times increase in dimensions correspond to aggregation of 15-27 (2.5^3-3.0^3) crystals in a coated particle. The shape of the coated crystals were not similar to that of granules or pellets. An increase in particle size occurs during the coating of the fine particles and this is difficult to avoid [17]. This method therefore does not involve a conventional granulation, but a few particles can stick together and fluid bridges can be formed, which will become solid bridges during drying [18, 19]. There was obviously no relationship between the solid content of the coating film and the particle size. This can be explained by the a simultaneous breaking of the crystals and of the breaking film during the coating.

Flowability tests revealed, that the flow properties of the original crystals were inappropriate (*Table 2*). These crystals were unsuitable for the tabletting process [20]. It can be seen from the data, however, that the coated crystals displayed excellent flow properties.

An increase of the amount of polymer decreases the flowability of the treated crystals. This can be explained by the deterioration of the shape, which can be seen in the SEM photos (*Figs.2-4*). The disadvantageous change in the shape of the particles decreased the

Table 2 Flow properties of samples

Sample	Flow time (s)	Angle of repose (°)	Mass of heap (g)
Dimenhydrinate	No measurable	52.53 (SD=1.13) (RSD=2.2)	41.73 (SD=0.31) (RSD=7.3)
Dim 1	6.4 (SD=0.05) (RSD=0.8)	32.4 (SD=0.63) (RSD=1.9)	43.9 (SD=0.29) (RSD=0.7)
Dim 2	7.1 (SD=0.09) (RSD=1.3)	33.4 (SD=0.64) (RSD=1.9)	41.5 (SD=0.83) (RSD=2.0)

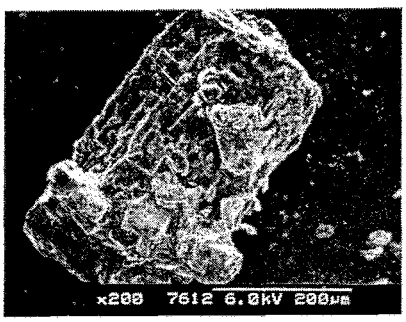

Fig.2 Dim 1 sample (SEM)

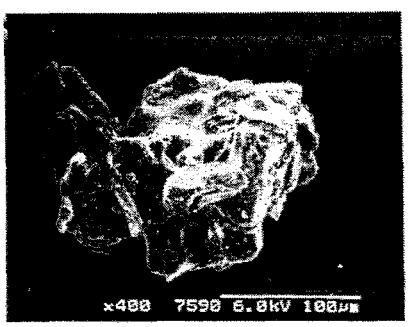

Fig.3 Dim 2 sample (SEM)

flowability because the possibility of adhesion of the particles increased.

The behaviour of the material on exposure to heat is very important. DSC experiments were therefore performed and the melting of the samples was observed. The coated crystals displayed a significantly ($p<0.05$) higher virtual melting point than that of the uncoated crystals, which could be caused by the reduction of the thermal conductivity of the crystals by the macromolecular film (*Table 3*). This was supported by another experiment. A thin (55±10.2 µm) SEPIFILM LP 010 film was laid on the bottom of the pan and he powder was then measured into the pan. The detected virtual melting point, calculated by the software, significantly increased, from 103.35±0.57 °C to 106.62±0.39 °C. These experiments demonstrated that this SEPIFILM LP 010 even film decreases the heat conductivity to the crystals, the heating program continues and therefore the software detects a higher virtual melting point.

The bulk crystals and the treated crystals exhibited very similar DSC curves, but two differences can be seen in the DSC curve for the coated (Dim 2) crystals

Table 3 Detected virtual melting points of samples

Sample	Melting point (°C)
Dimenhydrinate	103.35 (SD=0.57)
Dim 1	105.53 (SD=0.34)
Dim 2	105.98 (SD=0.25)
Dim 3	104.97 (SD=0.09)

Fig.4 Dim 3 sample (SEM)

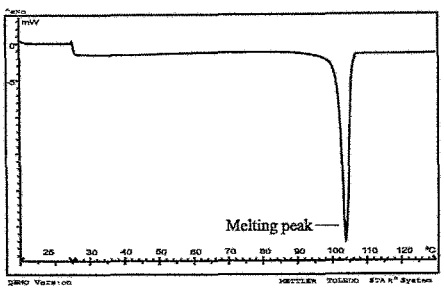

Fig.5 DSC curve of uncoated crystals

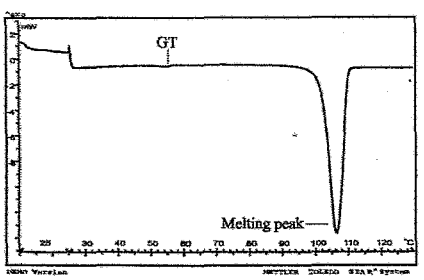

Fig.6 DSC curve of coated crystals (Dim 2)

(*Figs.5* and *6*). The slight change at about 50 °C can be explained by the glass transition (GT) of coating polymer for coated crystals. Both the other coated samples gave similar curves. DSC methods are widely used for the determination of glass transition [21-23]. The second difference is the wider peak, which indicates that the coating film disturbs the thermal conductivity. This was verified by in a previous study [13].

We also examined the water uptake and the wetting of the samples. The characteristic water uptake time ($t_{63.2\%}$) of the bulk crystals was the shortest (*Table 4*). A

Table 4 Characteristic time of water uptake of the samples

Sample	Characteristic water uptake time(s)	R value	lna	β
Dimenhydrinate	9.83	0.9910	-2.0340	0.8796
Dim 1	18.90	0.9977	-2.8617	1.0122
Dim 2	38.65	0.9690	-3.5414	0.9716
Dim 3	45.80	0.9970	-3.9039	1.0217

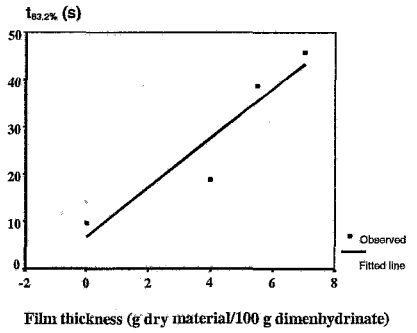

Fig.7 Relationship between film thickness and characteristic water uptake time

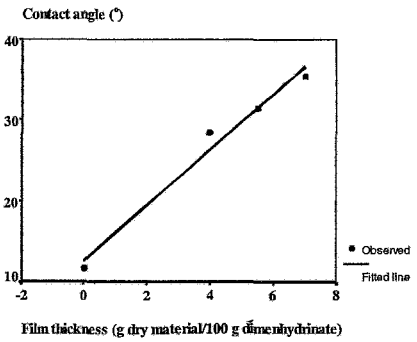

Fig.8 Relationship between film thickness and contact angle

higher amount of polymer causes a longer wetting time, as indicated by a linear regression ($p<0.1$), where the R value was 0.9374, the slope was 5.22 and the intercept was 6.76 (*Fig.7*).

The untreated crystals were the most difficult to compress because the filling of the die and therefore the pressure force were uneven. 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 relative standard deviation (RSD) of pressing force measured on the upper punch. The RSD of the upper punch force was 18.03% for dimenhydrinate, 1.97% for Dim 1, 3.23% for Dim 2 and 5.76% for Dim 3.

The untreated crystals displayed the smallest contact angle and the largest standard deviation in the wettability test (*Table 5*). The polymer film decreased the wetting of the crystals. The contact angle of distilled water increased with increase of the polymer content, as demonstrated by linear regression ($p<0.05$), where the R value was 0.9899, the slope was 3.43 and the intercept was 12.57 (*Fig.8*).

Table 5 Contact angle of distilled water on different tablets

	Dimenhydrinate	*Dim 1*	*Dim 2*	*Dim 3*
Contact angle(°)	11.68	28.40	31.42	35.43
SD	4.22	0.63	1.20	0.43

Table 6 Rate constant of drug release from preparation

Sample	k	R value
Dimenhydrinate	0.0325	0.9801
Dim 1	0.2832	0.9918
Dim 2	0.5000	0.9652
Dim 3	0.0926	0.9849

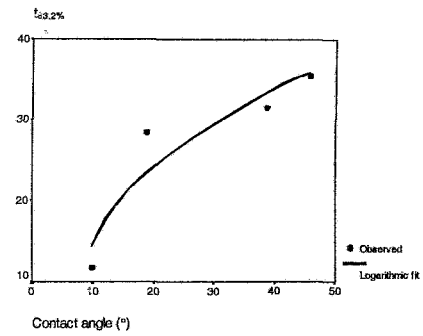

Fig.9 Relationship between characteristic water uptake time and contact angle

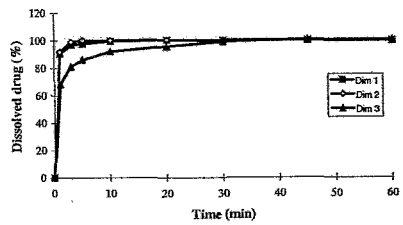

Fig.10 Dissolution of dimenhydrinate from samples

Regression analysis revealed a relationship between the characteristic water uptake time and the contact angle (*Fig.9*). More results are required for the determination of an exact relation, but the tendency is observed to a logarithmic regression curve ($p<0.1$) where the R value is 0.9438, the slope is 13.94 and the constant is -17.55.

Since the onset of the effect of dimenhydrinate after oral administration is quick, the dissolution of the active ingredient from the preparation must be very rapid. This phenomenon can be seen in *Fig.10*. There was no significant difference in the shapes of the curves of dissolution from the coated crystals with different amounts of polymer. Each sample displayed first-order kinetics (*Table 6*). A plot of the logarithm of thequantity of undissolved material against time yielded a straight line, which was supported by the linear regression ($p<0.05$) [24]. The uncoated crystals exhibited the slowest dissolution, which was confirmed by the drug release rate constant (k). This is explained by the sticking of the wet crystals, which could then disintegrate only after a few minutes. The coated crystals underwent rapid dissolution. There was a well-

soluble polymer film on the surface of the treated crystals which influences the eroding of the crystals. A slight sticking of the wet crystals was observed for Dim 1, but the disintegration of these agglomerates was rapid. The dissolution was slower for Dim 3 than for the other two samples, which was explained by the polymer content of the film and possibly by slow wetting. The Dim 2 sample underwent the most rapid dissolution, because the particles did not display sticking and did not contain too high amount of polymer.

The stirring effect of the paddle and the sticking of particles in the gastric fluid influences the wetting of the samples. Therefore, there was no way to perform a mathematical comparison of the results of water uptake and contact angle measurements and the dissolution of dimenhydrinate.

Finally, it can be stated that the coating increases the dissolution of dimenhydrinate from these samples.

Conclusion

The coating of dimenhydrinate crystals improved the low-flow properties of the original particles. There was an increase in particle size, but this was not as large as that after the granulation. The increase of the polymer content of the film did not alter the size significantly. There are relationships between the characteristic water uptake time, the contact angle of distilled water on the surface of tablets made from different samples, and the amount of polymer. The use of this gastric-soluble film for coating does not significantly influence the dissolution. The detected virtual melting point of the coated crystals was higher, which is very useful if a drug decomposes at its melting point. The quantity of the polymer did not significantly influence this alteration.

Finally, it can be concluded that the presence of a gastric-soluble polymer film disturbs the wetting of the material. It is therefore important to determine the ideal amount of polymer, because tablet wetting can be decreased and thus delays the disintegration of the tablet and finally the bioavailiability. Crystal coating with a suitably quantity of polymer can be more useful for crystal preparation for tabletting than crystal agglomeration because the polymer coating provides additional possibilities to influence positively the disadvantageous properties of the materials (light, moisture and oxygen sensitivity, or a very unpleasant odour and taste).

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