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INFLUENCE OF SUBSTANCE PROPERTIES ON SCALING UP OF TABLET FORMULATIONS

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ABSTRACT

The influence of water content of furosemide in a direct compressible tablet formulation was studied in pilot plant production. Small variations in the water content of furosemide as determined by thermogravimetry was found to have a substantial influence on the compaction properties of the direct compressible formulation.

A study of furosemide per se revealed that an increase in water content from 0.06 % to 0.24 % resulted in an increased elastic recovery and decreased net work at compaction. By adjusting the water content of furosemide in the direct compressible formulation it was possible to avoid the capping tendency at tablets.

INTRODUCTION

The diuretic substance furosemide is slightly soluble in water with a pH dependent solubility. It is normally crystallized from water or ethanol-water mixtures in the final purification. This yields rod-shaped crystals, 2-30 μm, with a lenght-width ratio of approximately 3:1.

During the development of a tablet formulation of furosemide a direct compressible system was tested. It was found during the scaling up that this formulation sometimes gave soft tablets and sometimes harder tablets with a tendency to cap. This variation in binding properties were not observed in the early formulation work where tabletting was studied on small batches, normally not more than 3,000 tablets in an excenter press. In the pilot plant batches, where 10 to 50 kg of tablet mass were compressed on a small production rotary machine, this batch variation in binding properties was observed.

This study was undertaken in order to find the reasons for this batch variation in binding properties. It was considered important to study the solid state properties of furosemide per se, such as particle size, surface area, water content, crystallographical properties and compaction properties.

EXPERIMENTAL

Materials

Furosemide[1] was milled in a pin disc mill[2] to a mean particle size of less than 10 μm as determined by permeametry.

The direct compressible tablet was produced by drymixing furosemide with lactose as carrier in a double cone mixer whereafter the rest of the excipients including lubricant was added.

Methods

Surface area

The surface area of furosemide was determined by gas adsorption in an Alpha Mec-6[3] using krypton (1).

Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out on a Mettler TA 3000[4] and thermogravimetry (TG) was

performed on a Perkin-Elmer TG-2 instrument[5]. All measurements were performed at a heating rate of 10°C/min in air.

x-ray powder diffraction

Furosemide samples were analyzed on a Guinier-Hägg camera with photographic recording using KCl (a=6.2930 A) as an internal standard and with $CuK_{\alpha 1}$-radiation.

Water adsorption

Water adsorption isoterms were determined at 20°C by storage of powder samples in hygrostats with various relative humidities (RH) for up to 30 days. The amount of adsorbed water was determined by thermogravimetry.

Tablet compression

Tablets of pure furosemide and of the tablet formulation were compressed in an instrumented excenter press[6] at a maximum upper punch pressure of 150 ± 8 MPa. External lubrication with magnesium stearate was used for the pure furosemide. From Heckel plots elastic recovery (ER) was determined and the net work at compression (w_{net}) from force displacement curves. The crushing strength of the tablets was determined in a Heberlein hardness tester.

The pilot plant tabletting of the direct compressible formulation was performed in a rotary tablet machine[7] using round, slightly curved punches. Batches of 10 to 50 kg were manufactured.

RESULTS

The water content of furosemide as recieved from the supplier was found to be low, less than 0.3 % as determined by thermogravimetry.Exposure to high RH did not bring about any substantial water adsorption as shown in Fig. 1. DSC-measurements showed, however, that the onset temperature of melting/decomposition increased with increased amounts of adsorbed water (Table 1).

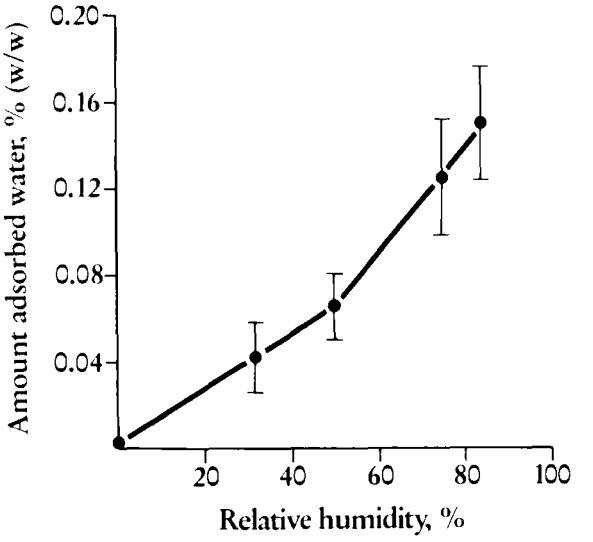

Fig. 1 Water adsorption of furosemide at 25°C. Amount water adsorbed (%, w/w) as determined by thermogravimetry. Mean values with 95 % confidence intervals.

Simultaneously an endothermic signal at 120-150°C appeared which was not present in the dried sample (Fig. 2). This signal corresponded to a weight loss recorded by the TG-analysis.

The XRD-analysis of furosemide revealed that the intensity of the second strongest reflection line (d=3.587 A) decreased with increased water content (Table 1). However, the diffraction pattern of all samples were similar indicating that no change in the internal crystal structure occurs at exposure to high RH. These results are in accordance with the data by W.H. de Camp (2) where less reproducible diffraction patterns were obtained for undried samples of furosemide.

The amount of water adsorbed at 75 % RH corresponds to a surface area of approximately 4,3 m^2/g for the studied batch of furosemide as calculated from the molecular cross-sectional are of water (10.8 A^2) (3). The gas adsorption surface area as

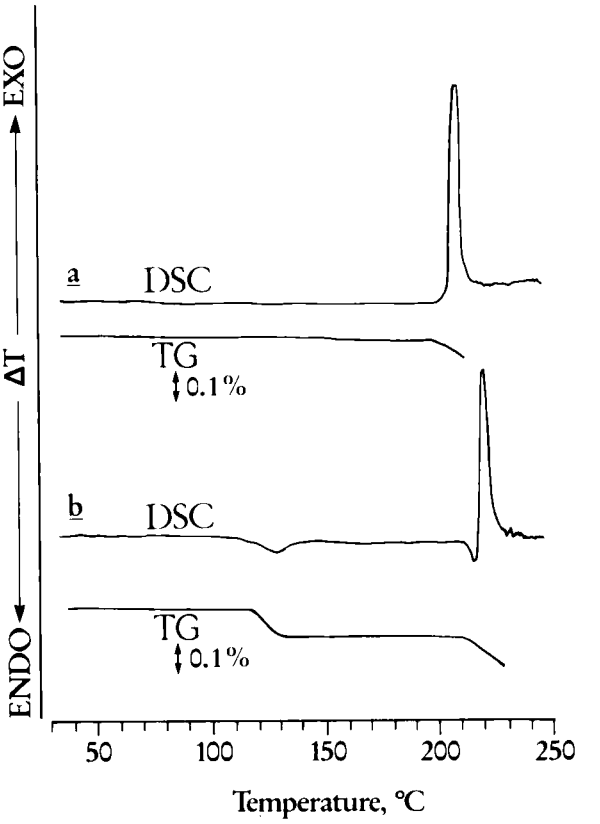

Fig. 2 DSC- and TG-curves of furosemide a) dried (0 % RH), b) sample exposed to 75 % RH for 30 days.

Table 1

DSC-, TG- and XRD-data for Furosemide Exposed to Various Relative Humidities at 25°C.

RH (%)	Onset temp. (°C)	Weight loss, TG (%, w/w)	dA, 3.587 (Rel. int)
0	206	< 0.010	Strong
33	209	0.045	Middle
50	209	0.066	Weak
75	219	0.125	Very weak

Table 2

Compaction Properties of Furosemide With Various Water Contents.

Water content (%, w/w)	Wnet (Nm)	Elastic recovery (%)	Crushing strenght (N)
<0.010	20.2	8.6	87
0.045	18.1	9.2	88
0.066	14.5	10.8	92
0.125	8.8	15.1	92

determined by krypton adsorption was found to be 4.8 m^2/g. At the same time the DSC-and TG-analysis indicate that the adsorbed water is bonded to the surface of the crystals with such a high force that a distinct signal for loss of water could be registred at 120-150°C.

At tablet compression of furosemide per se, w_{net} decreased at increased water content and an increased elastic recovery was observed (Table 2). No variation in crushing strenght could, however, be observed.

In a pilot plant manufacture test series of the direct compressible tablet formulation, portions of furosemide pretreated to contaion various water contents were mixed with the excipients in the tablet formulation. These batches were then compressed in the rotary tablet machine and the results are summarized in Table 3. This test series was then repeated with another batch of furosemide and similar results were obtained.

Table 3

Pilot Plant Tabletting of Furosemide Direct Compressible Tablets.

Water content furosemide (%, w/w)	Water content tablet mass (%, w/w)	Crushing strenght (N)	Capping frequency (%)
<0.01	1.1	34	0
0.05	1.2	52	0
0.08	1.0	69	3
0.14	1.2	95	7

DISCUSSION

Furosemide adsorbs minor amounts of water which tends to be bonded to the crystal surface with weak, but detectable forces as measured with thermal analysis. Adsorption of water does not seem to change the internal structure of the crystals but alters the compaction properties. Thus, at higher water contents the crystals show a higher elastic recovery and also a decreased net work at compaction. These results suggest that the surface structure of a crystal can be of importance for its compaction behaviour. In the case of furosemide, the amount of adsorbed water was found to be of great importance also in a direct compressible tablet formulation. By controlling the water content of furosemide within a narrow range it is possible to obtain tablets with an acceptable crushing strength without any capping.

For the formulating pharmacist it is well known that many problems with a formulation are recognized as late as in the scal-

ing up part of the development work. By performing thorough preformulation studies, both on the drug substance and the excipients intented to be used, some problems can be avoided and prevented that, otherwise, would show up during scaling-up.

FOOT NOTES

1. Dumex A/S, Denmark
2. Alpine 63C, F.R.G.
3. Studsvik Energiteknik, Sweden
4. Mettler Instrumente AG, Greifensee, Switzerland
5. Perkin Elmer Corp. Conn. Norwalk, USA
6. Korsch EKO, F.R.G.
7. Manesty, Betapress, Great Britain

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2. W.H. de Camp, J. Ass. off. Anal. Chem., 67, 927 (1984).
3. H.K. Livingston, J. Colloid Sci., 4, 1447 (1949).