Thermochimica Acta, 95 (1985) 425—430
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

PRECIPITATION AND PHYSICO-CHEMICAL PROPERTIES OF A DRUG SUBSTANCE

P.G.H. NYQVIST[1] and T. WADSTEN[2]

[1]Research and Development Laboratories, Pharmaceutics, Solid Systems, Astra Läkemedel AB, S-151 85 Södertälje (Sweden)

[2]Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, (Sweden)

ABSTRACT

The usefullness of thermoanalytical techniques in early preformulation studies of drug substances is demonstrated with a substituted benzamide derivative precipitated from solvents containing various amounts of water. Slow ageing of the crystalline products registered as changes in the bonding of water could be registered with TA-techniques only.

INTRODUCTION

The preformulation studies of a drug compound are conducted in order to select a candidate drug for the development of new pharmaceutical preparations (ref.1). The possibility to influence crystal form and structure of the candidate drug by variation of the precipitation medium is essential to investigate at this stage of the development work (ref.2). The aim of this work was to study the use of thermal analysis methods in combination with some other physico chemical characterization methods in an early preformulation program.

MATERIALS

The (+)-tartrate salt of a substituted benzamide derivative , FLA 870(-), (S)-(-)-3,5-Dichloro-N-(1-ethyl-2-pyrrolidinyl-methyl)-2-hydroxy-6-methoxy benzamide was precipitated from 2-propanol/water mixtures or acetone/water mixtures (Table 1).

METHODS

Precipitation

Batches of 10 to 100 g were precipitated according to the solvent systems found in Table 1.

0040-6031/85/$03.30

Powder characterization

Pictures of gold coated samples were taken in a JEOL JSM 25 SII scanning electron microscope (SEM).

True density (D_t, g • ml^{-1}) was determined in an air comparision pycnometer (Beckman model 930).

Thermal analysis

Differential scanning calorimetry measurements (DSC), thermogravimetric analysis (TG) with registration of the first derivative of the weight loss (DTG) were carried out on Perkin-Elmer DSC-2 and TG-2 instruments.

X-ray diffraction

X-ray powder diffraction measurements (XRD) were performed in a Guinier Hägg camera with photographic recording. Symmetry and unit cell dimensions were calculated with Weissenberg technique. The crystallographic density (D_x, g • ml^{-1}) was calculated based on single crystal data.

Water sorption

Water adsorption and desorption isotherms were determined gravimetrically on 0.500g samples at 25 °C by storage in hygrostats for 48 hours at different relative humidities (RH).

TABLE 1

Characteristics of FLA870(-)(+)-tartrate precipitated from different solvent combinations.

Solvent system	Hydrate	Crystal symmetry	Structure type	Cell volume	Density (g • ml^{-1})	
				Å	D	D
2-propanol 99 %	Anhydrate	Monoclinic	A	1122	1.46	1.45
2-propanol-water 95-5 %	Anhydrate	Orthorombic	B	2240	1.48	1.45
2-propanol-water 90-10 %	Monohydrate	Orthorombic	C	2240	1.49	1.47
Acetone-water 95-5 %	Anhydrate	Orthorombic	B	2240	1.48	1.45
Acetone-water 93-7 %	Monohydrate	Orthorombic	C	2240	1.49	1.46
Acetone-water 90-10 %	Monohydrate	Orthorombic	C	2240	1.49	1.46

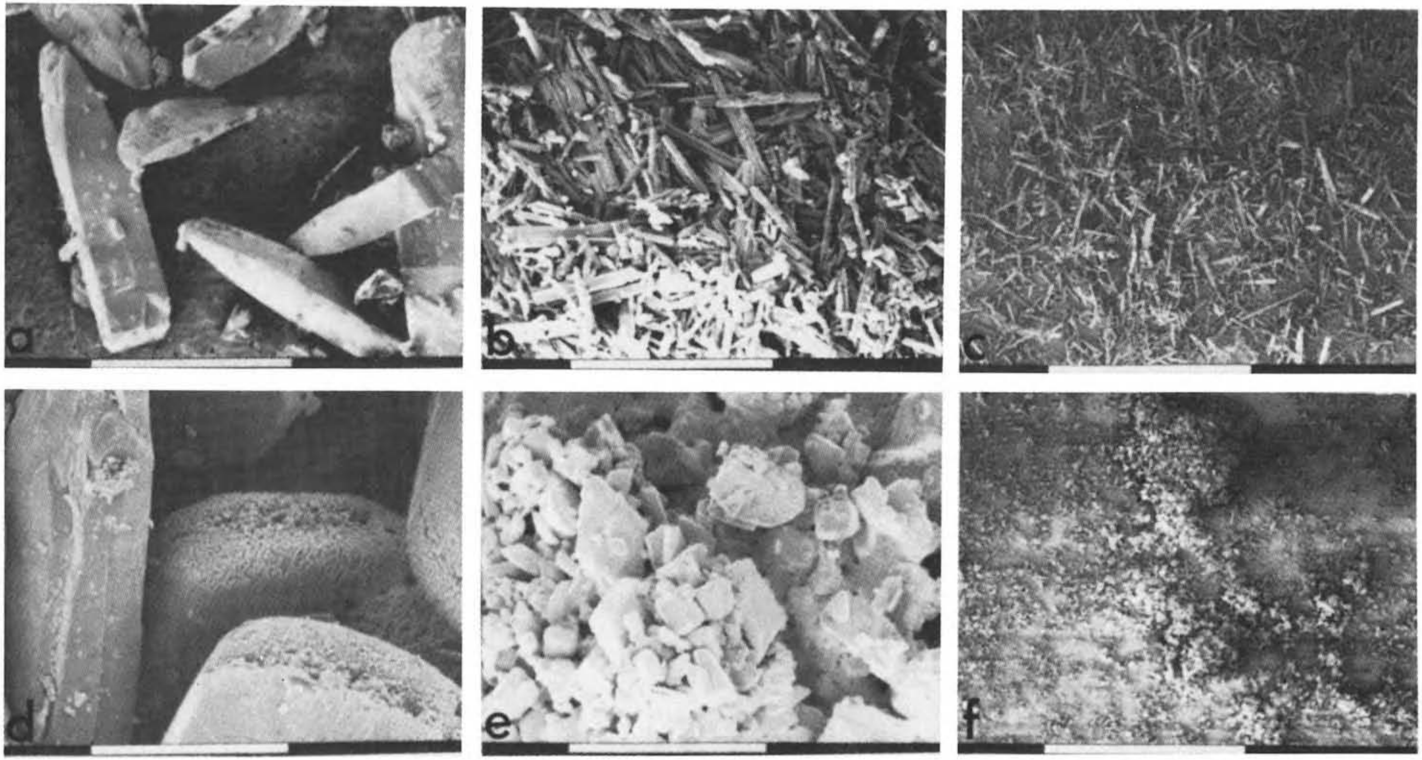

Fig. 1. SEM pictures (all with magnification 450X, bar=0.1 mm) of FLA870(-)(+)-tartrate precipitated from a) Isopropanol 99 %, b) Isopropanol-water 95-5, c) Isopropanol-water 90-10, d) Acetone-water 95-5, e) Acetone-water 93-7, f) Acetone-water 90-10.

RESULTS

With increasig water content in the mother liquid the particle size decreases (Fig. 1).

At a water content of less than 1% in the precipitation medium, an anhydrate product is obtained with monoclinic symmetry (type A). An increased water content up to 5% gives another anhydrate with orthorombic symmetry (type B). When the water amount exceeds 7% a monohydrate is crystallized with another orthorombic symmetry (type C).

The observed D_t-values with reference materials give slightly higher figures than D_x which suggest that the batches studied here all seem to be free from amorphous component (Table 1).

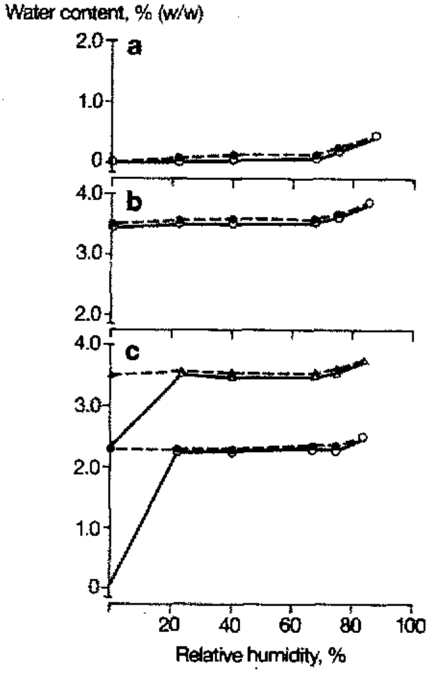

Fig. 2. Water adsorption (open symbols) and desorption (closed symbols) isotherms for a) Anhydrate precipitated from 2-propanol 99 %, b) Monohydrate precipitated from acetone-water 90-10, c) Anhydrate precipitated from acetone-water 95-5 and stored 2 days at various relative humidities (○) and thereafter 6 months at various relative humidities (Δ).

The monoclinic anhydrate (A) and the monohydrate (C) do not adsorb any significant amounts of water from the atmosphere (Fig. 2a and b). The orthorombic anhydrate (B), however, adsorbs rapidly ~2.5 % water and upon long time storage (several months) a water content of ~3.5 % is obtained which corresponds to the monohydrate (theoretically 3.51 %, Fig. 2c). Changes in the DSC and TG measurements are observed with respect to the water interaction (Figs. 3 and 4). The change in TG and DTG-curves with storage suggest that the water molecules rearranges in the crystal lattice (Fig. 4).

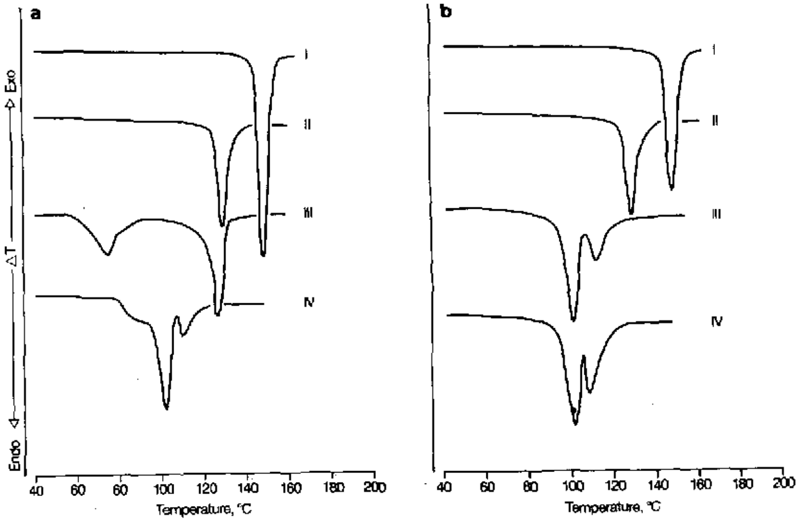

Fig 3. DSC-curves of a) freshly precipitated and b) stored samples (6 months 25 °C 5 % RH). I=Anhydrate precipitated from 2-propanol 99 %, II=Anhydrate 2-propanol-water 95-5, III=Anhydrate 2-propanol-water 95-5 stored at 84 % RH 2 days, IV=Monohydrate, isopropanol-water 90-10.

CONCLUSIONS

By a rather small variation in the solvent to water ratio of the mother liquid either stable anhydrate or monohydrate of FLA 870(-) (+)-tartrate is obtained or an unstable anhydrate that is converted to a stable monohydrate at long time storage. The slow ageing registered as a change in the bonding of water for some of the solid preparations, could be registered with TA-techniques only. By X-ray diffraction methods no change could be observed. The combination of different techniques in this study (except for the air pyknometer) can be run with less than totally 1g of substance and is well suited for use in the early preformulation studies.

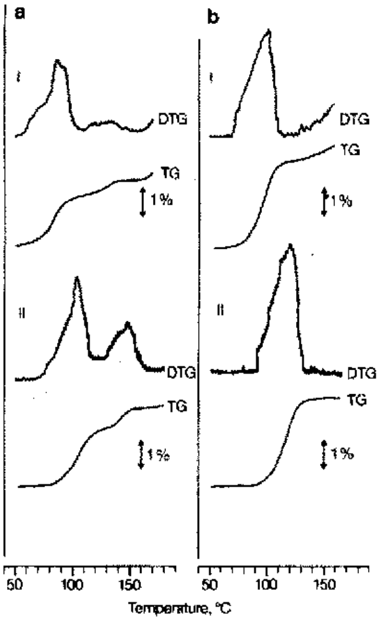

Fig. 4. TG and DTG-curves of a) freshly precipitated and b) stored samples (6 months, 25 °C, 75 % RH). I=Hemihydrate formed from anhydrate precipitated from acetone-water 95-5 stored at 84 % RH 24 hours. II=Monohydrate, acetone-water 90-10.

REFERENCES

1. C. Graffner, M. Johansson, M. Nicklasson and H. Nyqvist, J. Pharm. Sci., 74 (1985) 16-19
2. S. Byrn, Solid State Chemistry of Drugs, Academic press New York, 1977, 346 pp.