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USE OF SUB-AMBIENT DSC TO COMPLEMENT CONVENTIONAL DSC AND TG

The study of water adsorption of drug substances and excipients

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Abstract

Several drug substances or excipients are hygroscopic. The uptake or loss of water of such substances is generally difficult to control during processing or storage of drug products. DSC instruments with sub-ambient temperature equipment allow the determination of the amount of freezable water by measuring the corresponding melting enthalpy.

The determination of freezable water adds valuable information complementary to TG analysis for understanding the processing and storage of raw materials and drug products. Several substances were tested as is, without treatment, after storage at 92% r.h. and after equilibration with water. The results of these experiments showed that it was possible to demonstrate defined hydrate formation, to determine the upper level of binding of water in amorphous substances and to confirm reversible hydrate formations demonstrated by temperature resolved X-ray diffraction.

Keywords: bound water, drug substance, excipients, freezable water, hydrates

Introduction

The uptake or loss of water in raw materials and dosage forms is often difficult to control, especially if one considers climatic fluctuations of temperature and relative humidity (r.h.). Moisture adsorption plays an important role in physical and chemical stability of raw materials and dosage forms [1]. The measurement of adsorption-desorption isotherms [2] allows one to know the behaviour of substances, but only the use of appropriate methods like X-ray diffraction, DSC or TG allows one to know if water is bounded to the substance and if defined hydrates are formed.

A large number of drugs crystallize as hydrates [3]. Kankari and Grant [4] recently published a review upon pharmaceutical hydrates. Hydrates may lose water and anhydrous forms may take up or lose water reversibly depending of the ambient level of moisture (Theophylline [5–7], Medetromine [8]). A change of crystal structure in a reversible process without hysteresis can only be detected by in situ X-ray analysis. The dehydration/rehydration behaviour of pharmaceutical hydrates has been recently studied by Elder [9] and Morris *et al.* [10]. Furthermore amorphous substances and especially amorphous polymeric excipients bind water and the glass transition temperature is lowered [11].

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During crystallization processes in aqueous media, it is often difficult to understand which hydrated form crystallizes first since generally drying follows the crystallization. In the case of different hydration levels, the form with the highest number of water molecules will be the stable form at the lowest temperature. Knowledge about hydration can be essential since the activity of water in organic solvents is the critical factor for the preferential crystallization of hydrates [12].

Since DSC instruments allow measurements at sub-ambient temperatures, the melting enthalpy of freezable water in samples cooled to –20°C in order to allow water to crystallize, can be used for the calculation of the content of freezable water in samples. Thermogravimetry allows one to calculate the total loss on drying.

The purpose of this study is to treat samples with moisture in a 92% r.h. atmosphere and by equilibration with water in order to obtain the maximum possible hydration. The amount of bounded water is calculated by substracting the amount of free water from the TG value.

Experimental

Instruments: DSC: calibrated DSC-7, Perkin Elmer with aluminium tight sample pans (sealed pans v.s.p.). Thermobalance TGA-7, Perkin Elmer with aluminium samples and pure nitrogen. The samples were analyzed as is and after treatment. Great care was given to analyze the samples simultaneously by DSC and TG.

The treatment were:

– exposure 1–2 days at 92% r.h. (saturated solution of sodium carbonate decahydrate)

– equilibration with water by the phase solubility technique [13].

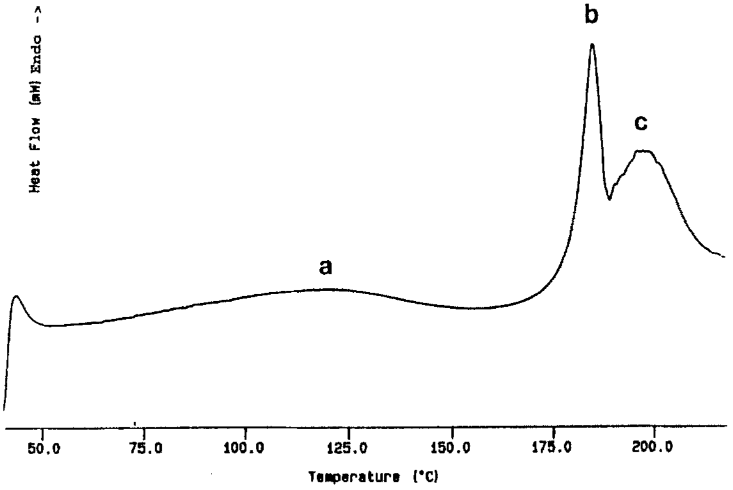

Fig. 1 DSC curve of a monohydrate (substance 2), crimped pan, 20°C min^{-1} heating rate. a – dehydration, b – melting, c – decomposition

Table 1 Summary of results

Substance	TG	Freezable water		
		ΔH/J g^{-1}	free water	comment
Sodium tartrate·$2H_2O$	15.6%	0	0%	dihydrate theory 15.7%
Calcium oxalate·H_2O	12.0%	0	0%	monohydrate theory 12.3%
$CuSO_4$·$5H_2O$	36.0%	0	0%	pentahydrate theory 36.1%
Substance 1 amorphous				
Batch 96815	3.0%	0	0%	3.0% bound water
96815 92% r.h.	23.2%	0	0%	23.2% bound water
96815 equilibrated in water	31.8%	8.5	2.55%	29.2% bound water
Substance 2 monohydrate				
Batch 89921	3.5%	0	0%	3.5% bound water
89921 92% r.h.	3.5%	0	0%	3.5% bound water
89921 equilibrated in water	20.3%	58.5/60.1/61.2	18.0%	diff.=2.3%
87901 equilibrated in water	33.8%	104.6	31.4%	diff.=2.4% monohydrate: 3.45%

Approx. 100–150 mg of substance were introduced with 1 ml water in closed bottles fixed to a vibromixer in a water bath at 25°C. After 1 day of vibration, the samples were filtered and analyzed.

The amount of freezable water is calculated by taking into account the heat measured by DSC in the sample and the melting enthalpy of water: 6.0 kJ mol^{-1}.

Results and discussion

The results are summarized in Tables 1 and 2. The sub-ambient DSC curves of substance 2 are given in Fig. 2 as example of the curves obtained: no event is observed when water is bound and the melting peak of water is observed if freezable water is present.

As expected sodium tartrate dihydrate, calcium oxalate monohydrate and copper sulphate pentahydrate are defined hydrates and contain only bound water.

Substance 1 is amorphous and can take up moisture up to 20–30%.

Substance 2 is crystalline (X-ray diffraction). The DSC curve of substance 2 in a crimped is given in Fig. 1. A very broad endotherm at 75–150°C, corresponding

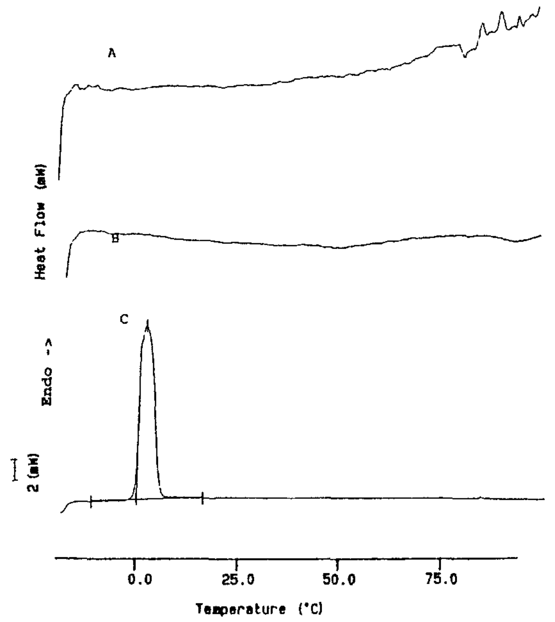

Fig. 2 Substance 2. DSC sub-ambient curves of sample as is and of samples after treatment at 92% r.h. and after equilibration in water. Tight closed pans (sealed pans), 10°C min^{-1} heating rate. A – sample as is, B – sample 1 day at 92% r.h., C – sample equilibrated with water

to the loss of water, is observed before the melting which occurs with degradation. The TG curve gives a loss of mass of 3.5% in one step. The same value is obtained by Karl Fisher titration. The dehydration in a crystalline anhydrous form before the melting was demonstrated by temperature resolved X-ray diffraction [14]. The sub-ambient DSC curves in sealed pans between –20 and 90°C are given in Fig. 2. No thermal events are observed for the samples as is or after treatment in 92% r.h. The melting peak of freezable water is observed for the sample equilibrated with water.

The results (Table 1) confirm that water is bound in the samples as is and after exposure to 92 % r.h. and that the monohydrate is the upper hydrated form. The amount of water after equilibration with water are high, 20 to 30%, and the calculated amount of bound water is lower than expected (2.3–2.4% *vs.* 3.5%).

Substance 3 was obtained as two different crystalline hydrated forms A and B. TG values complied with water content determined by Karl Fisher titration.

For both hydrated forms, temperature resolved X-ray diffraction was done previously [14] and a reversible dehydration in one step was observed. The very hygroscopic anhydrous forms were different. Results obtained in this study are given in Table 2 (batch 94922, form A, batch 94923, form B). Form A contains 1.5 moles water and Form B is a tetrahydrate.

All batches of substance 4 contain water, in different amounts. A X-ray single structure analysis demonstrated that the substance is a monohydrate [14]. Batch

95912 was analyzed in this study. The results given in Table 2 confirm the monohydrate formation.

Glucose is available as anhydrous or as monohydrate. The TG value (7.0%) of the original sample declared as monohydrate was lower than the value expected for a monohydrate (9.08%). The sub-ambient DSC experiments demonstrate that water is bound to the sample and that the sample converted totally to the monohydrate after 4 h at 92% r.h. (TG: 9.0%, no freezable water).

Tetracaine hydrochloride [15] converts at 92% r.h. to the monohydrate. After crystallization in water the sample contains a high level of water corresponding to a tetrahydrate (TG, Karl Fisher, elemental analysis). DSC sub-ambient curve confirms this statement: water is bound and the hydrated form is the tetrahydrate.

Table 2 Summary of results

Substance	TG	Freezable water		
		ΔH/J g^{-1}	free water	comment
Substance 3 modifications A and B				
Batch 94922 (Mod. A)				2.0%
94922 92% r.h.	2.0%	0	0%	monohydrate: 1.4%
				1.5 water: 2.0%
Batch 94923 (Mod. B)	4.8%	0	0%	4.8 bound water
94923 92% r.h.	5.0/5.2%	0	0%	5.1 bound water
94923 equilibrated in water	50.7/51.3%	160.2	48.1%	diff=3% tetrahydrate: 5.4% water
Substance 4 crystalline				
Batch 95912	1.5%	0	0%	hydrated form
95912 equilibrated in water	2.2%	0	0%	monohydrate: 2.17%
Substance 5 amorphous				
Batch 96940	3.4%	0	0%	3.4% bound water
Glucose monohydrate				
As is	7.0%	0	0%	7.0% bound water
4 h 92% r.h.	9.0%	0	0%	monohydrate: 9.08%
Tetracaine hydrochloride tetrahydrate				
Crystallized in water	20.4/18.6%	0	0%	tetrahydrate: 19.3%
Substance 6				
Batch 96603	<0.1%	0	0%	anhydrous
96603 15' 92% r.h.	98.6%	0	0%	partly liquid bound water

Substance 6 is very hygroscopic and turns rapidly to a liquid at r.h. >60%. The sub-ambient DSC curve of the sample treated 5 min at 92% r.h. shows that no freezable water is available. The TG curve does not allow one to distinguish loss of water from the decomposition of the compound.

Some results after equilibration with water gave lower values than expected in two cases (substances 2 and 3) where the retained water was very high (20–50%). This behaviour can be related to analytical errors (difference of values) or to a change in the structure of the sample. This will be investigated further.

Conclusion

The use of sub-ambient DSC of samples treated in different ways with moisture or water is very interesting for a better insight in the interaction of water with raw materials and dosage forms.

Defined hydrates are confirmed: sodium tartrate dihydrate, calcium oxalate dihydrate, copper sulphate pentahydrate, tetracaine tetrahydrate, glucose monohydrate. The upper level of hydration for three substances is determined. The binding of water in amorphous drug substances is confirmed and the maximal amount of water bound can be determined.

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