Thermochimica Acta, 93 (1985) 125-127 ,
Elsevier Science Publishers B.V., Amsterdam

CAN AGEING EFFECTS IN DRUGS BE MEASURED AND INTERPRETED BY TA-TECHNIQUES?

Håkan Nyqvist, Astra Läkemedel AB, Pharmaceutics, Solid Systems
Södertälje, Sweden
Tommy Wadsten, Arrhenius Laboratory, University of Stockholm,
Sweden

A large number of crystalline substances are obtained as hydrates and in the pharmaceutical field the hydrate form of new chemical entities is dominating. From our experiences a ratio of hydrated to nonhydrated compounds is ~ 3:1.

During the last five years we have scrutinized about 25 compounds and three of these have shown unusual ageing effects. The slow changes have been clearly observed with thermal analytical methods where other techniques have failed.

Our cases were all monohydrates, Raclopride (INN), Zimeldine (INN) and Amiflamine (INN).

Fig. 1 shows the characteristic feature of a young and and an old sample of two precipitations of Raclopride.

Proceedings of ICTA 85, Bratislava

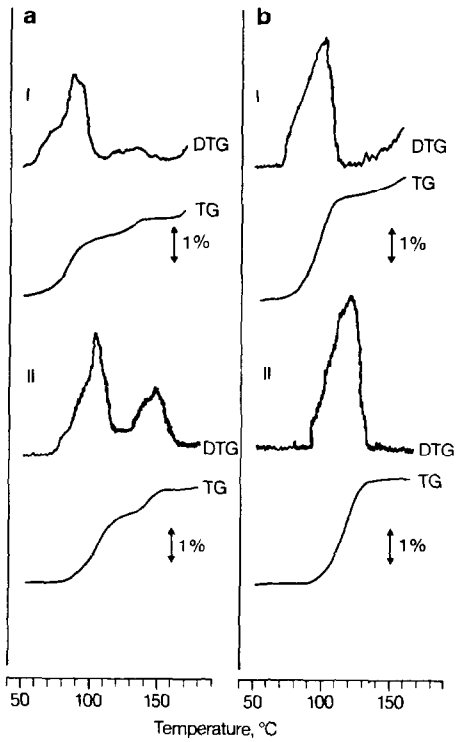

Fig.1 TG and DTG characteristics for a) freshly precipitated and b) stored samples (6 months, 25°C, 75% RH) I. Anhydrate precipitated from acetone-water 95:5 (this salt takes up water from the atmosphere immediately after precipitation and forms a monohydrate). II. Monohydrate precipitated from acetone-water 90:10.

The most remarkable effect occured with zimeldine which effloresced upon storage, resulting in an increased surface area as measured by gas adsorption. The increased surface area gave rise to an enhanced surface water adsorption. The process could be treated in accordance with first order kinetics and the rate of efflorescens increased at higher temperatures following the Arrhenius equation.

By using a combination of thermogravimetrical analysis and XRD it was found that the crystal water in zimeldine dihydrochloride, i.e. four molecules per unit cell, seems to change within the crystal lattice. Such a change, or ageing, may be responsible for the cracking of the crystals, resulting in the increased surface area, and at higher temperatures the cracking is more rapid. Repeated heating and cooling cycles of freshly precipitated material in order to speed up the ageing caused the crystals to effloresce, and no detectable change in surface area occurred on storage.

The "rearrangement" phenomenon of water molecules within the crystal lattice during storage was observed also for Amiflamine. This effect is probably not unique for the three drug substances studied here but may be relevant for many hydrated compounds. In the preformulation work it is of great importance to gain knowledge of the physico-chemical properties of the candidate drug substances and to take into consideration how they can change at storage. The slow changes demonstrated in this work have been clearly observed with TA-methods where other techniques have failed. Much effort is also put into selection of substance saving test methods due to the limited amounts often available in the preformulation phase. The TA-methods used her can be used to study physico-chemical properties on minute quantities of candidate drug compounds, around 10 mg.

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