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Comparative thermal properties of the monohydrates of sodium theophylline and theophylline

ABU T. M. SERAJUDDIN

St. John's University, College of Pharmacy and Allied Health Professions, Jamaica, NY 11439. Present address: Pharmacy R & D Department, Revlon Health Care Research, Tuckahoe, NY 10707, USA

The thermal properties of sodium theophylline monohydrate, as determined by differential scanning calorimetry (DSC), thermogravimetric (TG) analysis and hot stage microscopy, were studied and compared with those of theophylline monohydrate. The onset of dehydration of sodium theophylline monohydrate varied between 170 and 264 °C depending on the atmospheric conditions surrounding the sample. Under similar conditions, dehydration of theophylline monohydrate occurred at 18 to 65 °C. Sodium theophylline melted with the onset of a DSC endotherm at 391 °C. Possible effects of the physicochemical properties of sodium theophylline monohydrate on its dosage forms and the expected superiority of the sodium salt over theophylline and aminophylline are discussed.

Theophylline is widely used as a bronchodilator. Various salts and derivatives of it have been prepared to increase its solubility and dissolution rate (Martindale 1982). Aminophylline, which has variously been referred to as a salt (Weinberger & Hendeles 1979), a compound (Merck Index 1983) or a stable mixture (Martindale 1982) of theophylline and ethylenediamine, has been in use since the early twentieth century (Dessauer 1908). However, it has recently been shown by Cotgreave & Caldwell (1983a, b) that the pharmacological activity of aminophylline may be due to the presence of theophylline alone; the two components of aminophylline are handled independently by the body and there is no molecular association between these components in biological systems. In aqueous solution of aminophylline, theophylline remains as neutral molecules as well as negatively charged aggregates (Tashma 1984). Thus, it appears that the high aqueous solubility of aminophylline may be related to ionization of theophylline (pK_a = 8·4) at alkaline pH conditions (9·0–9·3). The high aqueous solubility of theophylline monoethanolamine (US Pharmacopeia 1985) may also be due to the same reason. Sodium salt formation is able to increase the solubility and the dissolution rate of theophylline by similar ionization in aqueous media (Serajuddin & Jarowski 1985); however, there is no commercial preparation using sodium theophylline. Although theophylline sodium glycinate (U S Pharmacopeia 1985) and theophylline sodium acetate (Martindale 1982) may contain sodium theophylline in physical mixtures with glycine and sodium acetate, respectively, there is no recognition of sodium theophylline in any official pharmacopoeia. Before the recent study by Serajuddin & Jarowski (1985) on the solubility and the dissolution rate of sodium theophylline, there was no published report on the physicochemical properties of this salt. In continuation of the characterization of sodium theophylline monohydrate for its possible use in dosage forms, its thermal properties were studied and then compared with those of theophylline monohydrate. The results are presented herein.

MATERIALS AND METHODS

Compounds

Sodium theophylline (monohydrate) was received as a gift from Boehringer Ingelheim, West Germany, through the courtesy of Henley & Co., New York. Anhydrous theophylline was purchased from Eastman Kodak, USA. Theophylline monohydrate, used in the present study, was freshly prepared by mixing anhydrous theophylline with water (2 : 1) and then air-drying at room temperature (20 °C) for 3 days. Preliminary studies showed that the physicochemical properties of theophylline monohydrate prepared by this method were similar to those of the crystals obtained by cooling a saturated aqueous solution. These properties were also essentially similar to those of samples obtained from commercial sources; however, the commercial theophylline monohydrate was not used because it was partially dehydrated.

Thermal analysis

The thermal properties of the samples were determined by differential scanning calorimetry (DSC), thermogravimetric (TG) analysis, and hot stage microscopy. A DuPont 990 thermal analyzer was used for DSC and TG studies. The atmospheric condition of the sample (5 mg) was varied during DSC study by placing the sample in an open aluminium pan under a flow of N_2 (50 ml min^{-1}), in an aluminium pan without purging of N_2, and in crimped and hermetically sealed aluminium pans. The hot stage microscopic study was conducted by heating the sample at a rate of 1 °C min^{-1} with and without silicone oil in a Mettler FP52 microfurnace fitted with a FP5 controller, and observing it under a microscope fitted with polarizing lenses.

RESULTS AND DISCUSSION

Dehydration of sodium theophylline monohydrate

Sodium theophylline received from the commercial source as well as some samples prepared by raising the pH of a saturated solution of theophylline to about 10 (Serajuddin & Jarowski 1985) gave a water content of 8·0–8·4% by Karl-Fischer analysis. This percentage of water also agrees with the reported water content of 8·2–8·3 per cent in sodium theophylline monohydrate prepared by Kawashima et al (1982). Even when the sample was heated at 100 °C for 24 h, the loss of water was <10% of the initial water content. Thus, sodium theophylline exists as a monohydrate. Fig. 1 shows the DSC thermograms of sodium theophylline (monohydrate) with varying atmospheric conditions of the sample inside the DSC cell. The first endotherm in each thermogram represents the dehydration of the sample. This was confirmed, in separate experiments, by moisture analysis of the samples before the onset and after the end of this endotherm. The onsets of dehydration in an open pan with purging of nitrogen, in an open pan without nitrogen purging, in a crimped pan, and in a hermetically sealed pan are at 170, 207, 226 and 264 °C, respectively. The variation in dehydration temperature of sodium theophylline monohydrate may be explained on the basis of the partial pressure of water vapour. If a reaction involves the evolution of gas, e.g.

$$A_{solid} \rightleftarrows B_{solid} + C_{gas}$$

the onset and peak temperature and the shape of DSC thermogram are affected by the gas pressure of the system (Stone 1960). Thus, according to the van't Hoff equation,

$$\ln \frac{(K_p)_2}{(K_p)_1} = \ln \frac{(P_c)_2}{(P_c)_1} = \frac{\Delta H\,(T_2 - T_1)}{R\,(T_2 T_1)} \qquad (1)$$

where K_p, P_c and T are, respectively, equilibrium constant for the reaction, partial pressure of C_{gas}, and temperature. The subscripts 1 and 2 represent lower and higher temperature conditions, respectively, and H and R are, respectively, enthalpy and gas constant. According to Equation 1, the decrease in the onset of dehydration temperature by the purging of nitrogen (Thermogram 1, Fig. 1) is due to a

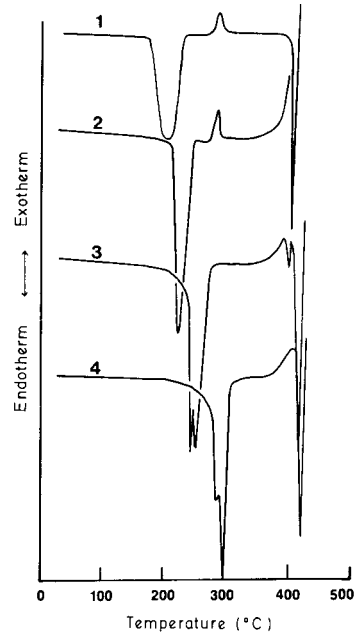

FIG. 1. DSC thermograms of sodium theophylline monohydrate recorded at a heating rate of 5 °C min^{-1} by subjecting the samples to various atmospheric conditions. The atmospheric conditions were varied by placing the samples (1) on an open aluminium pan with purging of nitrogen (50 ml min^{-1}), (2) on an open pan without purging of nitrogen, (3) in a pan closed by crimping, and (4) in a hermetically sealed pan.

lowering of the partial pressure of water vapour. The partial pressure of vapour and, as a result, the dehydration temperature increased when the sample was heated in crimped and hermetically sealed pans. Recently, Paulik et al (1983a, b) also observed large variation in dehydration temperature of the hydrates of calcium nitrate by changing the sample holders. A hydrate generally loses its water molecule by a two-step process: (1) water is liberated by breaking the solid-water hydrogen bond (Byrn 1982), (2) the liberated water forms a solution which dries by evaporation (Paulik et al 1983a).

The two steps may overlap and form one endotherm, or may separate to form two endotherms

at different temperatures. The observation of two peaks in the dehydration endotherms of sodium theophylline monohydrate in crimped and hermetically sealed pans may be due to separation of these two steps.

The dehydration endotherm of sodium theophylline may also be correlated with the weight loss observed by TG (Fig. 2). A weight loss of 7·6% was observed at 175–221 °C under a flow of nitrogen (Fig. 2). The onset of this weight loss approximately corresponds to the onset of dehydration endotherm in Thermogram 1 of Fig. 1.

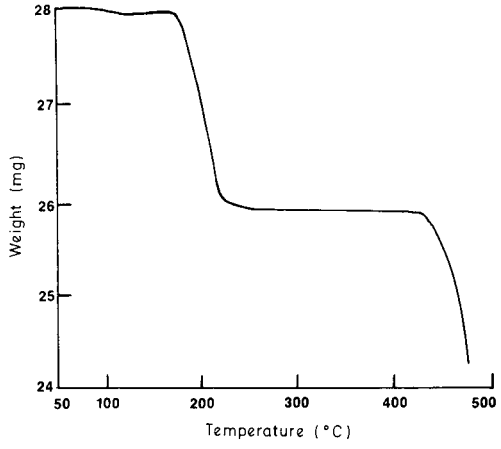

FIG. 2. TG thermogram of sodium theophylline monohydrate recorded at a heating rate of 5 °C min^{-1} with purging of nitrogen at a rate of 50 ml min^{-1}.

In hot stage microscopy using silicone oil, evaporation of water vapour was observed at 221–254 °C. This temperature range is higher than that of the dehydration endotherm in an uncovered pan without purging of nitrogen (Thermogram 2, Fig. 1), because higher vapour pressure developed on the surface of the solid submerged in silicone oil. Elemental analysis and thin layer chromatography showed no significant chemical change in sodium theophylline due to dehydration.

Melting and decomposition of sodium theophylline

Thermogram 1 in Fig. 1 gives the onset of the melting endotherm of sodium theophylline at 391 °C. The melting was followed by an exotherm and decomposition of the material. The material almost charred at ~440 °C. The second weight loss in Fig. 2 is possibly due to the evaporation of charred material. Sodium theophylline decomposed before its melting when heated without purging of nitrogen (Thermogram 2, Fig. 1). The sample gradually turned brown at a temperature above 300 °C, and ultimately charred. The difference between the thermograms with and without purging of nitrogen (Thermograms 1 vs 2, Fig. 1) suggests that the decomposition of the salt is due to oxidation. Although air was present with the samples in crimped and hermetically sealed aluminium pans (Thermograms 3 and 4, respectively, Fig. 1), its volumes inside the pans were limited. As a result, both exothermic oxidation and melting endotherms were observed in Thermograms 3 and 4.

An exotherm was observed at 270–290 °C in each of Thermograms 1 and 2 of Fig. 1. Possibly this was due to recrystallization and/or crystalline transformation of the sample after dehydration. However, such exotherms were not seen in Thermograms 3 and 4, although the melting endotherms in Thermograms 1, 3 and 4 appear to be identical. It is possible that the recrystallization in Thermograms 3 and 4 occurred during dehydration, and, as a result, the exotherm was overlapped by the endotherm.

Dehydration of theophylline monohydrate

Both anhydrous theophylline and theophylline monohydrate are recognized in various pharmacopoeias (Martindale 1982). It was observed in the present investigation that the anhydrous form is converted to a hydrate when mixed with water or exposed to high humidity (85% r.h.). The monohydrate, in turn, has variously been reported to lose its water molecule at relatively low temperatures of 35–50 °C (Byrn 1982), 40–50 °C (Shefter & Kmack 1967), 52–80 °C (Abou-Shaaban & Simonelli 1978), 70–80 °C (Kuhnert-Brandstätter 1971), and ~90 °C (Bogardus 1983). However, no systematic study of the dehydration of theophylline monohydrate has been reported in the literature. Fig. 3 shows that the onset of the release of water molecule may vary depending on the experimental conditions. As mentioned earlier, the two peaks observed during dehydration may be due to the release and the evaporation of water. The onsets of the release of water from samples placed on open pan, with and without purging of nitrogen, and in crimped and hermetically sealed pans were at 18, 28, 50 and 65 °C, respectively. Similarly to sodium theophylline, the increase in the onset of dehydration of theophylline monohydrate was due to the increased vapour pressure at the surface of the sample. The conversion of anhydrous theophylline to a monohydrate in presence of water or humidity and the dehydration at a relatively low temperature suggest that the existence of one particular form of the compound may

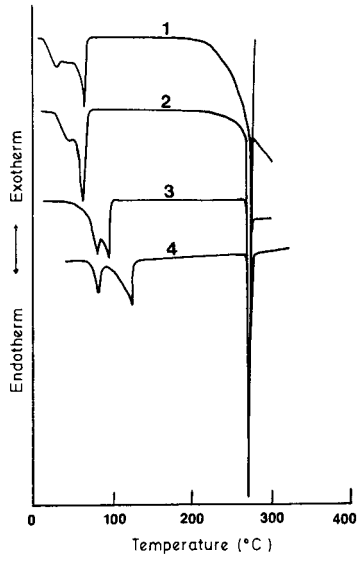

FIG. 3. DSC thermograms of theophylline monohydrate recorded at a heating rate of 5 °C min^{-1} by subjecting the samples to various atmospheric conditions. The atmospheric conditions were varied by placing the samples (1) on an open aluminium pan with purging of nitrogen (50 ml min^{-1}), (2) on an open pan without purging of nitrogen, (3) in a pan closed by crimping, and (4) in a hermetically sealed pan.

not be likely during processing of its solid dosage forms. For example, in the case of wet granulation, the degree of dehydration during drying at a particular temperature may also depend on the atmospheric conditions of the material, e.g. type of dryer, presence of air current in the dryer, type of granules, thickness of granule bed, etc. The variable hydrate $\longleftrightarrow$ anhydrate conversion may adversely affect the physicochemical (Yamaoka et al 1982; York 1983) and biopharmaceutical properties of dosage forms.

Abou-Shabaan & Simonelli (1978) reported weight loss of theophylline in the vicinity of its melting temperature due to sublimation. Thus, the lowering of the onset of melting endotherm of theophylline monohydrate in an open pan, with and without purging of nitrogen, is due to this sublimation process.

Dosage form consideration

The results of the present investigation show that sodium theophylline forms a monohydrate which would not dehydrate under normal processing conditions of solid dosage forms. Serajuddin & Jarowski (1985) reported that the dissolution rate of sodium theophylline monohydrate in the gastrointestinal pH range is about five-fold higher than that of theophylline monohydrate. Thus, in addition to the stability of the hydrate form, the sodium salt may be used in solid dosage forms for its high dissolution rate. The salt may be preferable to aminophylline due to the absence of ethylenediamine with potential pharmacological activity of its own. The high solubility of sodium theophylline may also be advantageous in designing dosage forms with osmotically controlled drug release (Theeuwes 1975). In addition, sodium theophylline may be used in solution. The precipitation of theophylline may be prevented if the pH of the solution is maintained above 9·2 (pH_{max}), because at such a pH the solubility of the compound is limited by the ionized species (Serajuddin & Jarowski 1985).

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