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Aminophylline suppository decomposition: an investigation using differential scanning calorimetry

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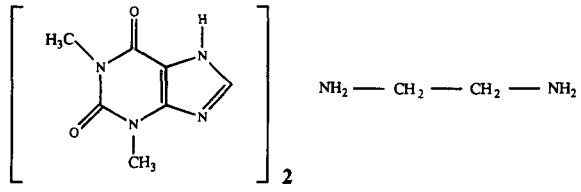
Summary

The decomposition of aminophylline suppositories has been investigated using differential scanning calorimetry (DSC) in an attempt to develop a rapid and sensitive detection method for the appearance of the decomposition products. The thermal properties of (a) fresh aminophylline suppositories and their component materials, (b) commercial aminophylline suppositories stored at room temperature for up to 4 years, (c) aminophylline suppositories stored at 32°C for 12 weeks, (d) freshly prepared and aged or heated ethylenediamine and theophylline suppositories, (e) extracted decomposition products and (f) a synthetic bishexadecanamide (diamide) were investigated. It was concluded that DSC can be used to detect the presence of decomposition products in aminophylline suppositories and that the ageing process can be simulated by storage at elevated temperatures. The DSC endotherms were consistent with the interaction of ethylenediamine with the suppository base. The evidence suggests that diamide decomposition products produced by the aminolysis of the triglycerides are responsible for the observed changes in the thermograms on ageing and that these may interact physically with suppository bases.

Introduction

Suppositories formulated with aminophylline, a mixture of theophylline and ethylenediamine (Fig. 1), are unstable (Peterson and Guida, 1953; De Blaey and Rutten-Kingma, 1976, 1977). The elevation of the melting ranges and large increases in melting times of suppositories after storage result in a reduction of the release rate of theophylline in vitro and an unpredictable response in vivo (De Blaey and Rutten-Kingma, 1976, 1977). These problems have led to the recent withdrawal of the U.K. licence for amino-



Theophylline — Ethylenediamine

Aminophylline

Fig. 1. The composition of aminophylline; two molecules of theophylline and one of ethylenediamine.

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phylline suppositories until further studies to assess the bioavailability are complete (Taylor, 1990), even though many consider theophylline to be the drug of choice in asthma treatment (Costello, 1991) and the rectal route has advantages for delivery of drugs with a narrow therapeutic index (Taylor and Simpkins, 1981).

The instabilities which occur on storage are not completely understood, but are assumed to be related to the interaction of the ethylenediamine component of the aminophylline with the triglyceride base (Fig. 2) to produce diamide decomposition products by aminolysis (Cieszynski, 1975; Brower et al., 1980; Van Dop et al., 1981). A major problem when attempting to correlate suppository decomposition with the fall in bioavailability is the lack of a sensitive and robust method for the detection of decomposition products. Melting point determinations are insensitive to the early stages of decomposition (De Blaey and Rutten-Kingma, 1976, 1977; Pryce-Jones et al., 1979) and methods to monitor either release of theophylline or decrease in ethylenediamine content are complex and time-consuming (Pryce-Jones and McGuffie, 1980; Van Dop et al., 1981). Although TLC was reported to indicate the presence of diamides (Cieszynski, 1975; Brower et al., 1980; Van Dop et al., 1981), no quantitative method has been reported to indicate the degree of deterioration. The present work describes an investigation into the use of differential scanning calorimetry (DSC) as an analytical method for the detection of the decomposition of aminophylline suppositories.

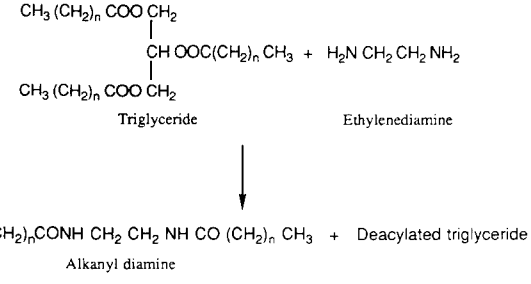

Fig. 2. Postulated reaction sequence for the formation of diamides by aminolysis of triglycerides by ethylenediamine.

Materials and Methods

Materials

A range of suppository bases of European Pharmacopoeia grade (Witepsols H15, H12, W35 and S55 and Suppocires OS1L, AML, AIML, BP) were donated by Huls Troisdorf (Ruhr, Germany) and Gattefosse (Cedex, France), respectively. Theophylline and ethylenediamine (laboratory reagent grades) were obtained from BDH Ltd (Poole, Dorset), aminophylline was obtained from Sigma Chemical Co. Ltd (Poole, Dorset) and aminophylline (E.P. grade) from Macarthys' Medicals (Romford, Essex). All solvents used were either analytical reagent grade (BDH Ltd, Poole, Dorset) or puriss (Aldrich, Gillingham, Dorset). Ethylenediamine and hexadecanoyl chloride were obtained from both Fluka Chemicals Ltd (puriss, Glossop, Derbyshire) and Lancaster Synthesis (Morecambe, Lancashire).

Preparation of suppositories

Fresh suppositories were prepared from all of the suppository bases by a standardised procedure which involved melting the base (weighed to make the equivalent of 22 g Aminophylline Suppositories B.P.) in a stainless-steel dish on a thermostatically controlled water bath maintained at about 42°C. The appropriate amount (accurately weighed) of theophylline (5.84 g), aminophylline (7.2 g) or ethylenediamine (0.8 g) was incorporated into the melt to give approx. 40 g of suppository mass. Calculations assumed displacement values of 1.5 for theophylline and aminophylline and 1.0 for ethylenediamine. The dish was removed from the water bath and the mass poured into traditional suppository moulds and the suppositories stored in airtight containers.

Extraction of decomposition products from suppositories

Decomposition products of aminophylline suppositories were obtained by extraction: (1) from commercial aminophylline suppositories stored at

room temperature for four years or longer; (2) from aminophylline or ethylenediamine suppositories made as above and stored (i) at 32°C for a period of 12 weeks or (ii) heated at 105°C for 4.5 h over an oil bath.

The extractions were performed by stirring 5 g of the aged suppositories with 50 ml of ethyl ethanoate (in which ethylenediamine diamides are insoluble (Pryce-Jones et al., 1987)) for 15 min at ambient temperature to dissolve any remaining tri-, di- and monoglycerides and glycerol. The off-white amorphous powder residue was found to dissolve at low concentrations (< 1% w/v) in hot $CHCl_3$/MeOH (50:50), $CHCl_3$/DMF (50:50), pentyl ethanoate, ethyl butanoate or benzene. Higher concentrations were achieved in hot methoxyethanol or butanol which were used to recrystallise the products. A low concentration of water (less than 5%) helped form clear solutions in the hot solvents during the first crystallisation.

Preparation of synthetic diamide

A sample of the even carbon number homogeneous synthetic diamide of hexadecanoic acid was prepared by cautiously adding a solution of 4.32 g hexadecanoyl chloride in 30 cm^3 of benzene to 0.68 g ethylenediamine (hydrate) in 10 cm^3 benzene, i.e., a 2:1 molar ratio. Under these conditions the reaction was not dangerously vigorous. The white flocculent precipitate which formed immediately was filtered off and crystallised from hot methoxyethanol or butanol.

For some experiments an accurately weighed (0.43 g) sample of the synthetic bishexadecanamide (diamide) was melted on a heater and a mass of suppository base (3.57 g) calculated to be equivalent to two 360 mg Aminophylline Suppositories B.P. added. The molten mass was removed from the heat and stirred until cool. This procedure was performed with a minimum of heat because excessive temperatures are known to cause the decomposition of diamides to the corresponding imidazolines (Linfield, 1984).

Analytical procedures

C, H, Cl and N microanalysis was carried out on the decomposition products extracted from the suppositories.

Hot stage microscopy

Melting temperatures of the diamide and the decomposition products extracted from suppositories were determined using a hot stage (Reichert) fitted to a Karl Zeiss microscope. Other melting ponts were determined using a capillary melting point apparatus.

DSC

A Du Pont Instruments Model 9900 Thermal Analyser and Model 910 Differential Scanning Calorimeter were used to investigate thermal properties of the suppository bases, of aminophylline and its components, ethylenediamine and theophylline. Tests were also carried out on fresh, aged and heated suppositories, the extracted decomposition products, the synthetic diamide, and synthetic diamide added to suppository bases (Pryce-Jones et al., 1987). Sample weights of between 7 and 9 mg were placed in sealed metal pans and tested against similar sealed reference pans containing Alumina (Al_2O_3). The test runs were all carried out using a heating rate of 10°C per min as this was found to provide the best balance between sensitivity and background noise.

Results and Discussion

DSC thermograms for aminophylline, theophylline, ethylenediamine and a typical suppository base (Witepsol H15) are shown in Fig. 3. All the fresh triglyceride suppository bases exhibited a broad, irregularly shaped DSC endotherm (negative) peaking at around 33–38°C (cf. Fig. 3a). This peak corresponded to the melting temperature of the base. The broad shape is attributed to the fact that the triglycerides are a heterogeneous mixture of compounds of similar properties but with a polydisperse molecular mass distribution. The endotherm for ethylenediamine at 119°C (Fig. 3b) corresponded to its boiling temperature and that for theophylline at 272°C (Fig. 3c) to the melting temperature found by hot stage microscopy. Aminophylline (Fig. 3d) showed three sharp transitions, two of which were attributed to the ethylenediamine (119°C) and theophylline (272°C) components and the third at

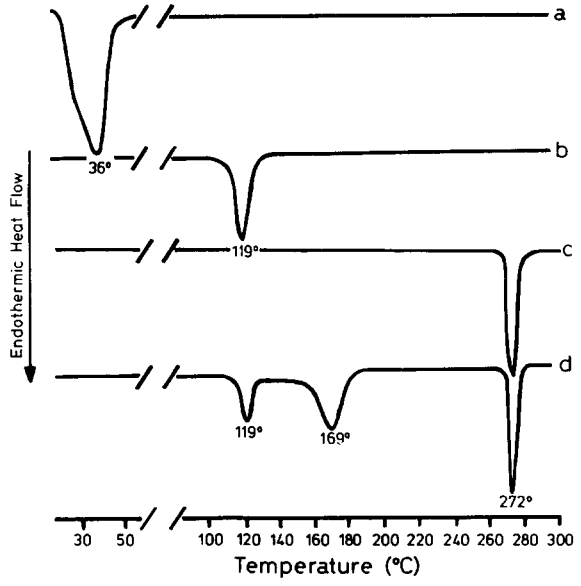

Fig. 3. DSC thermograms of the components of aminophylline suppositories: (a) typical suppository base (Witepsol H15), (b) ethylenediamine, (c) theophylline and (d) aminophylline.

169°C to an association complex of ethylenediamine (strong base) and theophylline (weak acid).

Fig. 4 compares thermal data for freshly prepared and aged Witepsol H15 suppositories of aminophylline and theophylline and freshly prepared and heated (105°C for 4.5 h) suppositories of ethylenediamine. Comparison of thermograms for fresh and aged suppositories confirm that the decomposition of the aged aminophylline suppositories can be detected by DSC. Fresh suppositories (Fig. 4a–c) showed the expected endotherms due to the base and appropriate components (cf. Fig. 3d). In contrast, for aged aminophylline suppositories (Fig. 4d,e), although the endotherm due to the theophylline (272°C) remained the same, the endotherms due to the ethylenediamine/theophylline complex (169°C) and ethylenediamine (119°C) had disappeared and been replaced by transitions at lower temperatures (approx. 95 and 110°C). The endotherm for the suppository base, although similar in shape and temperature range to that of the fresh suppository was smaller, indicating a reduction in the amount of free suppository base. This suggests that the 'melting range' observed in aged aminophylline suppositories by De Blaey and Rutten-Kingma (1976) is not a continuous process, but the result of at least two distinct melting processes; the first due to the melting of any remaining unreacted base and the second at much higher temperatures due to the decomposition products. These observations were confirmed by capillary melting point determinations.

The heated ethylenediamine suppositories (Fig. 4f) showed similar thermal behaviour to the aged aminophylline suppositories (Figs. 4d,e), for the endotherm at 118°C in fresh ethylenediamine suppositories had also disappeared on heating to be replaced by endotherms at approx. 95 and 110°C, and the triglyceride endotherm had reduced in intensity. These similarities between aged aminophylline and heated ethylenediamine suppositories, together with the disappearance of the 169°C peak (associated with the interaction

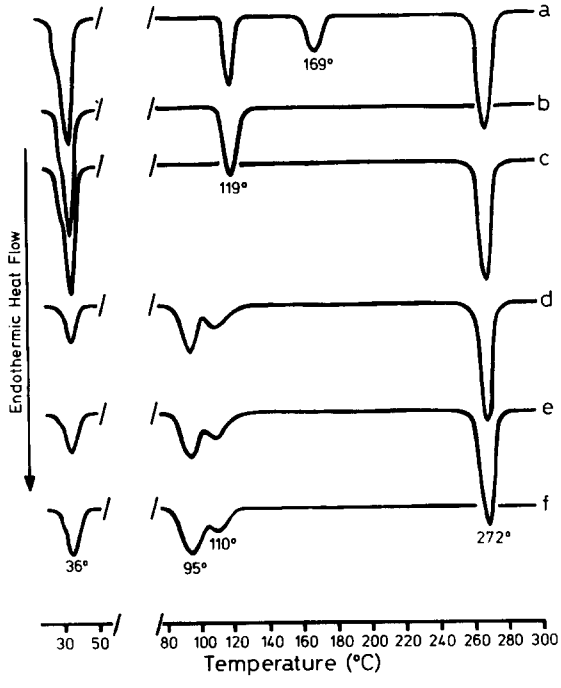

Fig. 4. Representantive DSC data of fresh and aged suppositories prepared with Witepsol H15. (a) Fresh aminophylline suppositories, (b) fresh ethylenediamine suppositories, (c) fresh and aged theophylline suppositories, (d) commercial aminophylline suppositories stored for 4 years, (e) aminophylline suppositories stored at 32°C for 12 weeks and (f) ethylenediamine suppositories heated at 105°C for 4.5 h.

between ethylenediamine and theophylline) provide strong evidence that the changes seen in aminophylline suppositories are due to interaction between the triglyceride suppository bases and ethylenediamine. This conclusion is further supported by the observation that the DSC thermograms of the aged (32°C for 12 weeks) theophylline suppositories (Fig. 4c) were no different from those when fresh, i.e.,the theophylline component did not appear to cause any changes in the aminophylline suppositories.

Similar trends on ageing were shown by suppositories prepared with all the triglyceride bases investigated, although the position of the decomposition peaks varied between 85–95 and 100–110°C according to the base used. The similarities between the thermograms of aminophylline suppositories aged for 4 years at room temperature and those aged for 12 weeks at elevated temperature (Fig. 3d,e) confirm that storage at a higher temperature is a satisfactory method of simulating the natural ageing process over a shorter time scale.

To investigate whether aminolysis of the triglyceride suppository bases by ethylenediamine to form fatty acid diamides is responsible for their decomposition, DSC thermograms of the decomposition products extracted from aged suppositories and a synthetic fatty acid diamide were compared. Thermograms for decomposition products extracted from aminophylline (Fig. 5a) and ethylenediamine (Fig. 5b) suppositories are indistinguishable, providing further evidence that these products are a result of interaction between ethylenediamine and the suppository base.

The endotherms exhibited by the materials extracted from aged suppositories, however, did not match those exhibited by the parent suppositories (cf. Figs 4 and 5), implying that there may be a further interaction between the decomposition product and the suppository base. Although the lower endotherms of the decomposition products (96–97°C) were close to those given by the suppositories (95°C) their upper endotherms (at 145–146°C) were substantially higher and were much sharper and more consistent in shape than the higher endotherms of the suppositories (110°C). It may be significant that the thermo-

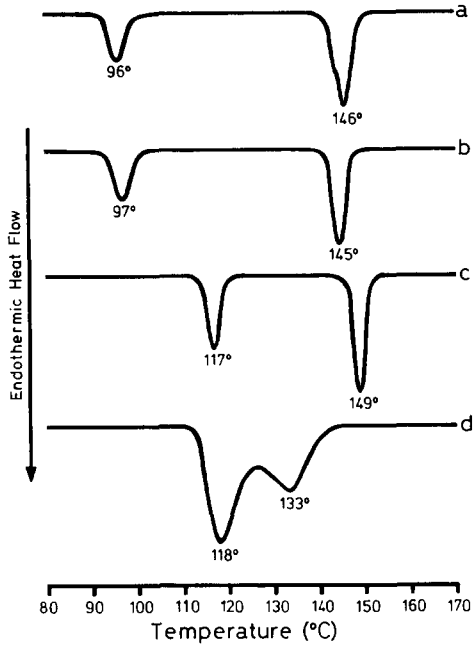

Fig. 5. Comparison of DSC endotherms of decomposition products extracted from (a) aminophylline suppositories, (b) ethylenediamine suppositories with (c) a pure crystalline synthetic diamide (*N,N'*-ethylenediyl bishexadecanamide) and (d) the same synthetic diamide incorporated into Witepsol H15 base.

gram of the synthetic *N,N'*-ethylenediyl bishexadecanamide (Fig. 5c) was very similar to those of the extracted decomposition materials although none of the endotherms coincided exactly. The synthetic diamide displayed two sharp and well defined phase transitions, the higher one corresponding to the melting point (hot stage) at 149°C, only 3°C higher than that of the extracted decomposition product. However, the lower endotherm at 117°C was about 20°C higher than the lower endotherm of the decomposition product. Such large differences in the lower endotherm do not rule out the possibility that the extracted materials are diamides as such materials formed by the reaction sequence shown in Fig. 2 would be expected to have a polydisperse molecular mass reflecting the heterogeneous alkanoyl composition of the triglycerides from which they were formed. This possibility is supported by the observation that the C, H, and N content of the decomposition products extracted from the aged

suppositories were equivalent to a diamide of tridecanoic acid and tetradecanoic acid (found: C 74.66%, H 13.79%, N 6.01%; calculated: C 74.61%, H 12.53%, N 6.00%).

The hypothesis that the diamides entered a special form of bonding with the suppository bases was tested. Addition of the synthetic diamide to the triglyceride suppository bases produced a DSC thermogram (Fig. 5d) which was different from that of the crystalline diamide in Fig. 5e, and although close, was still not identical to those of the aged suppositories (Fig. 4). The lower endotherm (approx. 118°C) had not changed from that of the pure form. The biggest difference was that the upper endotherm at 149°C had disappeared and been replaced by one at about 133°C and which was shaped more like those found in the aged aminophylline and heated ethylenediamine suppositories. This implies that changes seen in the aged suppositories were due to the reaction of ethylenediamine with the suppository bases to form a heterogeneous mixture of diamides with polydisperse molecular mass. The diamides then appear to interact with the triglycerides during the high temperature of the DSC test in such a way that they differ from the crystalline structure of the pure synthetic diamides. This might be because solid diamides at temperatures below their melting points dissolve in the molten triglyceride bases. The mechanism of this interaction and the chemical structure of the decomposition products that cause the new endotherms are currently under investigation.

Conclusions

(1) DSC can be used to detect changes in aminophylline suppositories. As the suppositories age some endotherms reduce in size (triglyceride base) or disappear (ethylenediamine, association complex) and are replaced by others due to the decomposition products.

(2) Storage for short times at elevated temperatures successfully simulates the effects of aging on the DSC thermograms.

(3) Although it was not possible to prove categorically that the diamides of the fatty acids from the triglyceride suppository bases and ethylenediamine were responsible for the appearance of the new endotherms, the thermal data strongly support this hypothesis.

(4) The evidence suggests that if diamides are the decomposition products responsible for the changes in the DSC thermograms then they also enter into some form of physical interaction with the suppository bases to change their thermal properties.

Further studies are in progress to elucidate (i) the mechanism of this interaction, (ii) the chemical structure of the decomposition products that cause the new endotherms, (iii) whether these endotherms can be used quantitatively and (iv) whether there is a correlation between the DSC endotherms and the dissolution rate of theophylline.

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