discrepancies for other homologous series of polyoxyethylene alkyl ether surfactants. The reduction in the free energy of micellization for these long alkyl chain compounds is a consequence of intrusion of the oxyethylene chains into the micellar core. ^{1}H NMR studies on such compounds have indicated both line broadening and loss of intensity of the alkyl protons suggesting a considerable reduction in chain mobility (Elworthy & Patel 1984a; Lawrence 1985). The entropy decrease associated with the loss of chain mobility is partly responsible for the observed reduction in free energy change.

The $\Delta G_m^{\ominus}$ values calculated for the semi-polar surfactants are all lower than that of the $C_{18}E_{22}$ compound reflecting the influence of the semi-polar group in reducing the free energy of transfer to the micellar phase.

We thank ICI Pharmaceuticals Division for financial support of MJL.

References

Arnarson, T., Elworthy, P. H. (1980) Effects of structural variations of non-ionic surfactants on micellar properties and solubilization: surfactants based on erucyl and behenyl (C_{22}) alcohols. J. Pharm. Pharmacol. 32: 381–385

Arnarson, T., Elworthy, P. H. (1981) Effects of structural variations of non-ionic surfactants on micellar properties and solubilization: surfactants containing very long hydrocarbon chains. Ibid. 33: 141–144

Attwood, D., Florence, A. T. (1983) Surfactant Systems, Chapman and Hall, London. Chpt. 1

Attwood, D., Elworthy, P. H., Lawrence, M. J. (1989) Effects of structural variations of non-ionic surfactants on micellar properties and solubilization: surfactants with semi-polar hydrophobes. J. Pharm. Pharmacol. 41: 585–589

Barry, B. W., El Eini, D. I. D. (1976) Surface properties and micelle formation of long chain polyoxyethylene non-ionic surfactants. J. Colloid Interface Sci. 54: 339–347

Corkill, J. M., Goodman, J. F. (1969) The interaction of non-ionic surface active agents with water. Adv. Colloid Interface Sci. 2: 297–330

Elworthy, P. H., Florence, A. T. (1964) Chemistry of non-ionic detergents. VIII Critical micelle concentrations and thermodynamics of micellization of synthetic detergents containing branched hydrocarbon chains. Kolloid Z. 195: 23–27

Elworthy, P. H., Patel, M. S. (1982) Demonstration of maximum solubilization in a polyoxyethylene alkyl ether series of non-ionic surfactants. J. Pharm. Pharmacol. 34: 543–546

Elworthy, P. H., Patel, M. S. (1984a) A nuclear magnetic resonance (nmr) investigation of the micellar structure of a long-chain non-ionic surfactant. Ibid. 36: 565–568

Elworthy, P. H., Patel, M. S. (1984b) Evidence for the intrusion of polyoxyethylene into the hydrocarbon core of non-ionic micelles. Ibid. 36: 116–117

Lawrence, M. J. (1985) Physico-chemical and solubilization studies on aqueous solutions of synthetic non-ionic surfactants. Ph.D thesis, University of Manchester

Longman, G. F. (1978) The Analysis of Detergents and Detergent Products. Wiley, New York

Mukerjee, P., Mysels, K. J. (1971) Critical micelle concentrations of aqueous surfactant systems. NSRDC NBS-36, U.S. Government Printing Office, Washington

Patel, M. S. (1982) Effects of structural variations on the physico-chemical properties of non-ionic surfactants. Ph.D. thesis, University of Manchester

Patel, M. S., Elworthy, P. H., Dewsnup, A. K. (1981) Solubilization of drugs in non-ionic surfactants. J. Pharm. Pharmacol. 33: 64P

Rosen, M. J. (1978) Surfactants and Interfacial Phenomena. Wiley Interscience, New York, p. 100

Teo, H. H., Yeates, S. G., Price, C., Booth, C. (1984) Micellisation and surface properties of poly(oxyethylene) alkyl ethers. J. Chem. Soc. Faraday Trans. 1. 80: 1787–1794

J. Pharm. Pharmacol. 1990, 42: 583–585
Communicated February 14, 1990

Differential scanning calorimetry characterization of process-induced variations in an ointment base

PETER TIMMINS, IVAN BROWNING*, NICHOLAS I. PAYNE†, *Pharmaceutical Development, International Development Laboratory, Bristol-Myers Squibb, Reeds Lane, Moreton, Wirral, Merseyside L46 1QW, UK*

Abstract—Preparation of an experimental emollient wax-gelled ointment base by two processes differing only in cooling rate produced material with markedly different physical properties. Differential scanning calorimetry showed that a major endotherm, possibly related to a phase change in a major triglyceride wax component, Synchrowax HGLC, was different in the two products. Mean enthalpies for this major endotherm for the two products were 7·36 J g^{-1} (s.d. = 0·49, n = 5) in slow cooled samples and 4·35 J g^{-1} (s.d. = 0·21, n = 5) in fast cooled samples. The degree of order of the Synchrowax HGLC in the ointment is suggested as being different in the two preparations and it is this that controls the physical properties of the ointment.

Present addresses: * Glaxo Operations, Barnard Castle, County Durham DL12 8DT, UK. † Cyanamid of Great Britain Ltd, Gosport, Hants PO13 0AS, UK.

Correspondence to: P. Timmins, Pharmaceutical Development, International Development Laboratory, Bristol-Myers Squibb, Reeds Lane, Moreton, Wirral, Merseyside L46 1QW, UK.

Ointment vehicles are greasy, usually anhydrous, semi-solid formulations used for topical application to provide for drug delivery or can be used unmedicated, for example, for their skin protecting properties. One simple approach to the formulation of an ointment base is to thicken or gel an oil such as mineral oil with a suitable agent. Like all semi-solid formulations, gelled oil vehicles might be susceptible to process-induced variation in finished product properties. In the case of a complex, emollient, wax-gelled oil ointment base developed for a novel topical corticosteroid (O'Laughlin et al 1989), the degree of agitation and also rate of cooling were found to produce marked differences in consistency in the finished product. Although it has been found possible to control the processing of this particular ointment to realize a reproducible product with desired physical properties, further investigation of the nature of the process-induced variation has been undertaken by application of differential scanning calorimetry (DSC) to discern the

nature of the various components in the ointment. Such studies might explain microstructural differences in the differently processed products and contribute to their understanding and avoidance of such process-related variation for other similar products.

Materials and methods

Materials. Mineral oil, propylene glycol, silicone fluid (350 cs), purified water, magnesium hydroxide, sodium metabisulphite, sodium citrate and butylated hydroxytoluene were of pharmacopoeial quality. Other formulation components were Synchrowax HGLC (C_{18}–C_{36} acid triglyceride CTFA, Croda, Humberside, UK) and cetearyl alcohol/ceateareth 20 (Promulgen D, DF Anstead, Southampton, UK) and polysynlane (Hydrogenated Polyisobutene CFTA, KWR Chemicals, Waltham Cross, UK).

Ointment preparation. Ointment composition is detailed in Table 1. Batches (0·5 kg) were prepared in a 1 L beaker with an electrically-heated water bath (Grant Instruments) providing the temperature control. The oily phase components were heated together at 75–80°C until fluid, mixing continuously using a propeller-bladed stirrer set at 100–150 rev min^{-1}. The oily phase was then allowed to cool to 65–70°C before the addition of aqueous phase maintained at the same temperature. This mixture was allowed to cool with continuous stirring to approximately 48°C before the remaining mineral oil and propylene glycol were added.

For 'fast cool' ointment batches the warm mixture was placed in a water bath at 20°C and left to stand without further stirring until firm. For 'slow cool' ointment batches the warm mixture was allowed to cool from 48 to 40–43°C with continuous stirring. Agitation was stopped and the water bath heater turned off. The ointment was then allowed to equilibrate to room temperature (20°C) over 12 h as the water bath cooled down, with occasional slow stirring with a flat blade.

To further characterize the nature of process-induced differences and relate them to a specific component, batches of ointment were prepared omitting one ingredient at a time for each lot. The slow cool process was used for these samples. All products were allowed to stand for no more than 24 h before being tested further to minimize any effects due to sample ageing.

Table 1. Composition (g) of emollient, wax-gelled oil ointment evaluated (per 0·5 kg).

Oily phase:	
Butylated hydroxytoluene	0·25
Magnesium hydroxide	1·25
Cetearyl alcohol/ceteareth 20	25·00
Synchrowax HGLC	60·00
Polysynlane	150·00
Mineral oil	167·65
Silicone fluid	15·00
Aqueous phase:*	
Sodium citrate	0·25
Sodium metabisulphite	0·10
Purified water	2·50
Propylene glycol	27·50
Remaining components:	
Mineral oil	25·00
Propylene glycol	25·00

* Aqueous phase is prepared by dissolving salts in purified water at 65–70°C before adding the Propylene glycol.

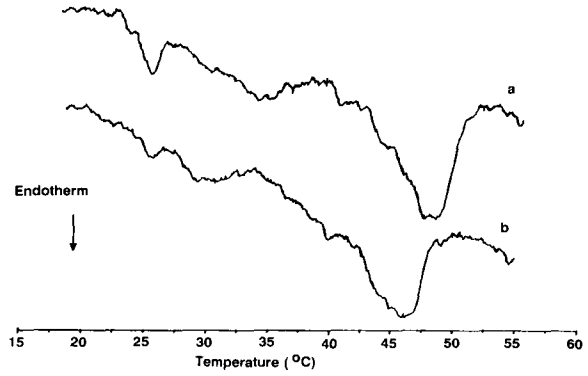

FIG. 1. DSC curves for (a) slow cooled ointment batch, (b) fast cooled ointment batch. Heating rate 2°C min^{-1}.

Differential scanning calorimetry (DSC). DSC evaluation was undertaken on a Dupont 9900 instrument. Preliminary experiments indicated suitable heating rates of 2°C min^{-1} over the range 15–60°C for ointments prepared by fast and slow cool methods and 10°C min^{-1} over the range 15–80°C with cooling rates of 2°C min^{-1} to 25°C min^{-1} during heating–cooling cycling studies. Maximum information was obtained with a cooling rate of 2°C min^{-1}. All studies were undertaken in hermetically sealed aluminium pans with a pinhole pierced in the pan lid, using nitrogen gas atmosphere and samples of 5–15 mg of ointment.

In experiments comparing enthalpies for endotherms in fast and slow cool samples, the enthalpies were calculated by computer software available with the instrumentation used. Isothermal baselines were carefully constructed by the operator to ensure comparable results from run to run and over as much of the melting range as possible. Melting ranges for fast and slow cool samples were virtually identical.

As virtually identical samples were being compared under equivalent conditions, error due to undetected early melting was assumed to be a constant and no correction was applied.

Photomicroscopy. Photomicrographs were taken of thin films of ointment spread over a microscope slide using a Nikon Optiphot microscope with a Polaroid camera attachment.

Results and discussion

The two manufacturing processes produced ointments of markedly different physical properties. The fast cool method produced a stiff wax-like product that was difficult to apply to skin and did not appear elegant. The slow cool method produced an elegant, more fluid, ointment with the consistency of petrolatum that was easy to apply to the skin.

DSC analysis of slow cooled ointment over the range 15–60°C revealed some minor endotherms and one major endotherm, onset at around 45°C. The same endotherms were present in the fast cooled ointment (Fig. 1a, b).

There are few literature data on the thermal analysis of ointments although there are reports on other semi-solid topical applications (Junginger et al 1979, 1984; Eccleston 1985; deVringer et al 1986). DSC of other semi-solids has demonstrated endotherms due to phase transitions and polymorphic transitions of triglyceride and fatty alcohol components (Ford & Timmins 1989). By running DSC analysis of samples of the current ointment omitting one different component in each sample and observing changes in endotherms it was observed that the major endotherm at around 45°C was absent only in ointments without Synchrowax (Table 2, Fig. 2).

Table 2. Onset temperature (°C) of significant endotherms in ointment batches prepared omitting specific components.

Component omitted	Significant Endotherms
—*	22, 32, 44, 58
Synchrowax HGLC	23
Silicone fluid	45, 59
Propylene glycol	43, 59
Mineral oil	43, 58
Polysynlane	45, 58
Cetearyl alcohol/ceteareth 20	43, 59
Butylated hydroxytoluene	30, 43, 59

* Control ointment containing all components.

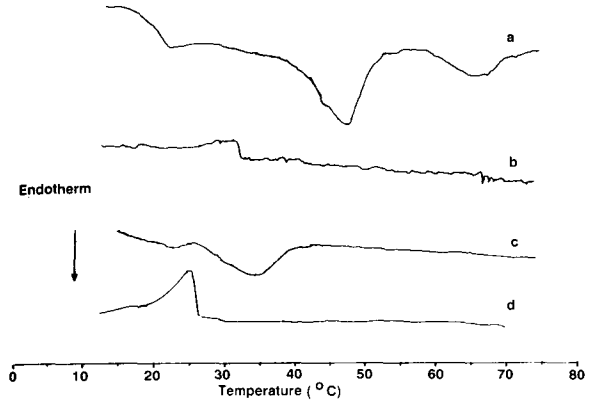

FIG. 2. Heating/cooling cycle DSC curves for (a) heating cycle control ointment, (b) cooling cycle control ointment, (c) heating cycle for ointment without Synchrowax HGLC, (d) cooling cycle for ointment without Synchrowax HGLC.

The use of heating/cooling cycle experiments suggested that the major endotherm at around 44 C and a lesser one at 58 C were probably melting transitions associated with Synchrowax HGLC whereas some of the minor lower temperature endotherms may well be polymorphic transitions of this synthetic triglyceride. Fig. 2a illustrates a heating/cooling cycle curve for a sample of ointment evaluated by DSC. On heating, the major endotherm is seen at 45 C and on cooling an exotherm centred on 32°C is observed. Re-running this sample shows a major endotherm now at 33 C, which possibly represents a polymorphic transition of the Synchrowax HGLC in the ointment base (Fig. 3).

Pure Synchrowax HGLC showed a melting endotherm at 57°C and an exotherm on cooling centred on 49°C. On re-

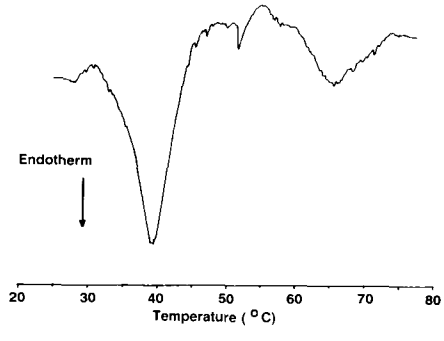

FIG. 3. DSC curve for sample from Fig. 2a–b rerun after heating and cooling cycle completed. Heating rate 10 C min^{-1}.

heating the sample the melting endotherm occurred at 55°C and an exotherm on cooling at 49°C. The melting endotherm was probably depressed in the final ointment due to it being an admixture with other components and possibly because of the interactions between Synchrowax HGLC and some of these components. The proposed polymorphic transition is not observed in the pure material evaluated as described, but the polymorph involved may be more stable in the ointment base environment as compared with pure Synchrowax HGLC. Alternative, eutectic type interactions might explain the changes in endotherms seen.

DSC of fast cool and slow cool-processed ointments showed reproducible differences in the heat of transition association with the endotherm attributed to melting of Synchrowax HGLC in the ointment base. In the case of slow cooled ointment the heat of transition was always greater than with the fast cooled ointment. Mean enthalpies for this endotherm were 7·36 J g^{-1} (s.d. = 0·49, n = 5) for slow cooled ointments and 4·35 J g^{-1} (s.d. = 0·21, n = 5) for fast cooled ointments. This suggests that the material contributing to this endotherm is in a more ordered state in the slow cooled ointment than in the fast cooled ointment.

Although the nature of the products, and therefore the exact causes of the phenomena, are different, Patel et al (1985) also suggested the degree of crystalline order for a critical formulation component was responsible for process-induced differences in an aqueous cetrimide/cetearyl alcohol ternary gel. The nature of the order and degree of order proposed may control physical properties in addition to consistency such as texture (granular or smooth) and tendency to syneresis (separation of fluid oily phase) which can occur in gelled-oil-type ointments. It was not possible to completely confirm these ideas by use of optical microscopy under crossed polarizers, as in the case of fast-cooled and slow-cooled ointments they presented similar appearance of patches of anisotropic material shining brightly against a dark background. Hence ordered material is present in ointment prepared by both processes but quantification of differences suggested by DSC was not possible by microscopy.

In the current work DSC has indicated differences between batches of a wax-gelled ointment prepared by different processes which could be correlated with differences in physical properties of the ointment. Confirmation of the nature of these differences would require application of other more sophisticated techniques including freeze-fracture scanning electron microscopy and X-ray diffraction, to confirm and elaborate the proposed microstructure for these types of ointment. Such further understanding could contribute to control of physical properties such as consistency, texture and tendency to syneresis.

References

deVringer, T., Joosten, J. G. H., Junginger, H. E. (1986) A study of the gel structure in a non-ionic o/w cream. Coll. Polym. Sci. 264: 691–700

Eccleston, G. M. (1985) Phase transitions in ternary systems and oil-in-water emulsions containing cetrimide and fatty alcohols. Int. J. Pharm. 27: 311–323

Ford, J. L., Timmins, P. (1989) Pharmaceutical Thermal Analysis. Ellis Horwood, Chichester, pp 248–258

Junginger, H. E., Fuhrer, C., Ziegennege, J., Friberg, S. (1979) Structure study of ointments. J. Soc. Cosmet. Chem. 30: 9–23

Junginger, H. E., Akkermans, A. A. M. D., Heering, W. (1984) The ratio of interlamellary fixed water to bulk water in o/w creams. Ibid. 35: 45–57

O'Laughlin, R., Pannagio, A., Varia, S. (1989) US Patent 4868168

Patel, H. K., Rowe, R. C., McMahon, J., Stewart, R. F. (1985) Properties of cetrimide/cetearyl alcohol ternary gels: preparation effects. Int. J. Pharm. 25: 237–242