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The influence of process-induced variations on the nature of stearic acid incorporation into an FAPG base

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Abstract

The major part of the FAPG base is a gel-like structure composed of propylene glycol and fatty alcohol with a crystalline network. Stearic acid is used as a penetration enhancer incorporated into FAPG base. Stearic acid's change of nature resulting from process-induced variation was investigated by differential scanning calorimetry, X-ray powder diffraction, infrared spectroscopy and polarized microscopy. Under a slow rate of cooling, the pure C form of stearic acid was obtained through propylene glycol in the presence of 5% w/w 1,2,6-hexanetriol and with increase in cooling rate, a mixture of forms B and C was produced. The polymorphic modifications are affected more strongly by the growth rate than by the stirring rate. When stearic acid is combined with stearyl alcohol, the supersaturation of stearic acid and precipated forms in propylene glycol no longer occurs, since stearic acid readily dissolves in the melting stearyl alcohol. Simultaneous IR and DSC measurements indicated that during the heating and cooling process, the components of the ointment did not chemically interact with one another. However, different manufacturing processes will result in markedly different physical properties, especially with respect to solubility.

Keywords: FAPG base; Stearic acid; Polymorphism; Solubility; Cooling rate; DSC; X-ray powder diffraction; Infrared spectrocopy

1. Introduction

For skin therapy, the employment of vehicle should not merely inhibit microbial growth and be aesthetically satisfactory, but also should possess optimum physico-chemical properties to ensure stability and the release of drug. A topical vehicle 'FAPG' base was reported to have more possible significant advantages than that of traditional ointments and cream (Barry, 1973). The base is a gel-like structure mixed with propylene glycol, stearyl alcohol, polyethylene glycol and glycerol through a crystalline network.

In order to promote percutaneous drug absorption, penetration enhancers either pretreat the skin before the application of drugs (Hsu et al., 1991) or unite in a formulation as additives (Hosoya et al., 1987; Hsu et al., 1993). Several

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fatty acids such as lauric, myristic and stearic acids, which are saturated common fatty acids, are capable of increasing the percutaneous absorption of co-administered drugs (Aungst et al., 1986; Komata et al., 1992).

In a preliminary study, stearic acid was chosen to be incorporated into FAPG base as a penetration enhancer on order to promote the absorption of quinolone antibiotics from ointment (Jaw, 1991). Simultaneously, the way to compare the effect of enhancement is to apply 5.0% (w/w) stearic acid/PG during the pretreatment of rat skin.

If the manufacturing processes are changed, the physical properties of ointment would be remarkably differentiated (Timmins et al., 1990). Stearic acid might be susceptible to process-induced variation in the final enhancing effect. As stated before (Gunstone, 1967), fatty acids are polymorphic and can exist in more than one crystalline form. Because the solubility of stearic acid in PG solution is low and its polymorphism could not be excluded, it became important to investigate the solid state of stearic acid. Although the relationship between the polymorphism and growth conditions of stearic acid has been previously examined (Garti et al., 1982), the present study was aimed at further investigation of the nature of the process-induced variation in the FAPG ointment through DSC, X-ray powder diffraction and IR spectroscopy, and at discerning the nature of the stearic acid in FAPG base.

2. Materials and methods

2.1. Materials

Stearic acid and propylene glycol were purchased from Sigma Chemical Co. Stearic acid of approx. 99% purity was recrystallized through isopropyl ether, and the C form, according to X-ray measurements, was thus produced. Stearyl alcohol and polyethylene glycol 6000 were purchased from E. Merk Co. 1,2,6-Hexanetriol was obtained from Riedel de Haen Co. α-Bromoacetophenone was purchased from TCI Co. All other chemicals were of analytical grade.

2.2. Preparation of samples

The fatty alcohol propylene glycol (FAPG) base is composed of stearyl alcohol (23.5% w/w), propylene glycol (61.9%), polyethylene glycol 6000 (4.8%) and 1,2,6-hexanetriol (4.7%); stearic acid was added at a concentration of 5%.

The ointments were prepared according to a reported method (Kaiho et al., 1987) with slight modification: the so-called 'supercooling operation' meant to stir the melting mixture at paddle speeds of 400, 800 and 1200 rpm with a paddle radius of 2.0 cm. Using a Heidolph electronic stirrer, these treatments were carried out and samples were kept in a thermostated water bath (maintained at 25 and 0°C, respectively). The so-called 'slow cooling operation', intended to keep the melting mixture under room temperature (27°C), was employed with good agitation, until some homogeneous ointments were formed.

The stearic acid/PG suspensions for pretreating the skin were prepared by crystallizinhg stearic acid from propylene glycol in the presence of 5 wt% 1,2,6-hexanetriol. The cooling operations could be divided into quiescent and drastic conditions, the latter being described in the previous section.

To further elucidate the nature of process-induced differences, and to evaluate the relationship between stearic acid and other ointment components, one or two ingredients were removed from each bath of ointment, but the stearic acid was retained. All products were filtered through 0.45 μm nylon membranes (Msi. Micro Separation Inc.) under vacuum, and then collected. The precipitated crystals were washed 8–10 times with double-distilled water to remove the remaining PG and then were dried in vacuum overnight at room temperature. The amount of stearic acid dissolved in PG solution was determined as stated under section 2.7.

2.3. DSC

DSC thermograms were obtained using a Perkin-Elmer DSC-7 differential scanning calorimeter. Sample sizes were in the range of 3–5 mg and were sealed in an aluminum pan.

Thermograms were recorded from 35 to 85°C at a heating rate of 2°C/min.

2.4. IR spectroscopy

Infrared spectra were taken on a Hitachi 270–30, using KBr discs over the wavenumber range 4000–400 cm^{-1}.

2.5. X-ray powder diffraction (XRPD)

Diffraction patterns were obtained with a Siemens D5000 diffractometer using Cu radiation and a Ni filter. The copper target X-ray tube was operated at a power of 40 kV and 30 mA. The measuring range of the general patterns was 5–60° 2θ with a step size of 0.05° and a measuring time of 3°/min.

2.6. Photomicroscopy

Photomicrographs were obtained by taking thin films of ointment that was spread over a microscope slide, and then by using a Nikon Optiphot microscope with a polarized camera attachment.

2.7. Solubility study

PG solution (1.00 g) was placed in a screw-top test tube, 50 μl of C2 (acetic acid) was added as the internal standard (2 mg/ml acetone), and extraction was performed with 3 ml of toluene. The mixture was shaken for 1 min and centrifuged for 5 min at $2000 \times g$. A 0.5 ml sample was transferred from the upper toluene layer to the second tube and subsequently evaporated to dryness with dry purified nitrogen at 40°C. 200 μl of an α-bromoacetophenone solution (10 mg/ml acetone) and 200 μl of a triethylamine solution (10 mg/ml acetone) were added to the tube, the screw-top capped tightly, and the tube placed in a boiling water bath for 15 min. The tube contents were then cooled to room temperature. A 1 μl aliquot of the derivatives was removed and subjected to TLC scanning (Camag TLC Scanner II, V3. 04) for analysis. The TLC method has been described previously (Yen et al., 1991) with a mobile system consisting of heptane/acetone (60:40).

3. Results and discussion

Table 1 lists the precipitated forms of stearic acid, which were produced from propylene glycol in the presence of 5 wt% 1,2,6-hexanetriol, and from this quiescent and stirred solution under different cooling rates. It can be seen that, in quiescent solution at slow cooling rates, no significant change was induced in the crystal structure, the C form predominating in this case. However, with increase in cooling rate, significant amounts of the B form were produced. The X-ray diffraction pattern is displayed in Fig. 1. The infrared spectra of polymorphic forms B and C did not show any significant difference. The DSC ther-

Table 1
The effect of growth conditions on the crystal structure and solubility of stearic acid crystallized from propylene glycol in the presence of 5% w/w 1,2,6-hexanetriol

Flow regime	Stirring rate (rpm)	Cooling rate (°C/min)	C (μg/g)	C_s (μg/g)	Crystal modification by X-ray
Quiescent	0	1.5	81.8 ± 2.5	213.0 ± 1.9	C
Quiescent	0	10	84.3 ± 2.2	325.9 ± 2.2	C
Quiescent	0	40	98.0 ± 2.7	393.5 ± 3.1	B, C
Stirred	400	5	83.7 ± 1.8	135.1 ± 1.2	C
Stirred	400	10	81.1 ± 1.1	157.7 ± 1.4	C
Stirred	400	40	96.3 ± 2.3	251.8 ± 2.0	B, C
Stirred	800	50	99.6 ± 2.9	289.0 ± 1.2	B, C
Stirred	1200	50	98.5 ± 2.8	259.4 ± 1.5	B, C

C, concentration at the onset of crystallization; C_s, supersaturation concentration at 27°C.

mograms, normalized and adjusted to the same baseline, are given in Fig. 2. DSC measurements showed that there is only one endothermic peak at its melting point, however, the melting point of the form which crystallized under supercooling was lower than that under conditions of slow cooling. Generally, the lower melting form would be a more energetic species which would result in faster dissolution as well as greater initial solubility (Lindenbaum et al., 1985). The DSC thermogram also showed that the lower melting form B and C mixture had a larger heat of fusion and therefore greater solubility in PG solution (Table 1).

For the stirred solution, when drastic conditions were applied to the system, the pure C form was obtained under a slow cooling rate. As the cooling rate increased, the supersaturation was

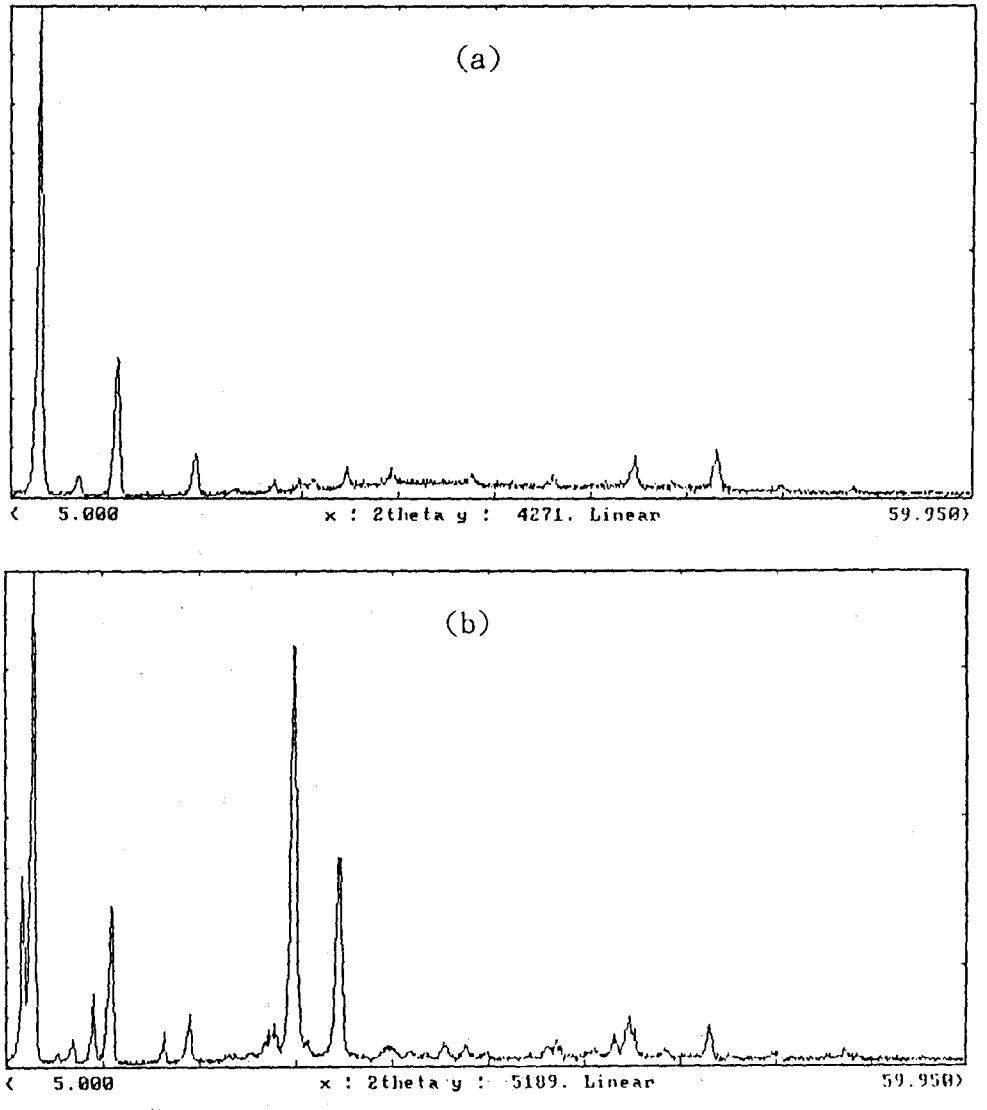

Fig. 1. X-ray diffraction pattern of stearic acid crystallized from propylene glycol in the presence of 5% 1,2,6-hexanetriol: (a) C form crystals under slow cooling; (b) a mixture of B and C form under supercooling.

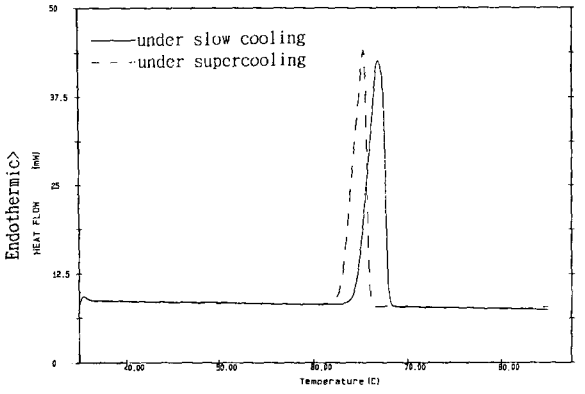

Fig. 2. DSC thermograms of stearic acid crystallized from propylene glycol in the presence of 5% 1,2,6-hexanetriol.

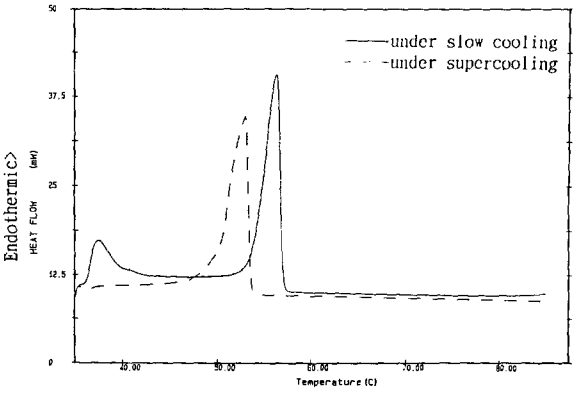

Fig. 4. DSC thermograms of solid dispersion prepared by incorporating stearic acid into stearyl alcohol and then crystallized from propylene glycol in the presence of 5% 1,2,6-hexanetriol.

stabilized, and thus greater solubility resulted. However, the formation of the C form was only partial. It appeared admixed with the B form. Thus, polymorphic modifications are affected more strongly by the growth rate than by the stirring rate.

Furthermore, in order to examine the effects of process-induced differences on the dispersion of stearic acid in the FAPG ointment, the interaction between stearic acid and FAPG base in the solid state was investigated by IR and DSC measurements. The DSC recording of stearyl alcohol alone is shown in Fig. 3. Two endothermic peaks could be detected with onset temperatures at 42.0°C (70.5 J/g) and 55.6°C (100.1 J/g), respectively. On comparison between the enthalpies in rapidly and slowly cooled samples, there were no significant differences. Fig. 4 depicts the thermograms when stearic acid was added into stearyl alcohol. It was observed that the major endotherm of stearic acid at around 65°C was completely absent. As shown in Fig. 5, similar results could be observed in the physical mixture of stearyl alcohol and stearic acid (2:1), however, the higher endothermic peak tailed off. The reason for this observation is perhaps that the stearic acid can readily dissolve in melting stearyl alcohol and then form a solid dispersion on cooling; in contrast, the supersaturation of

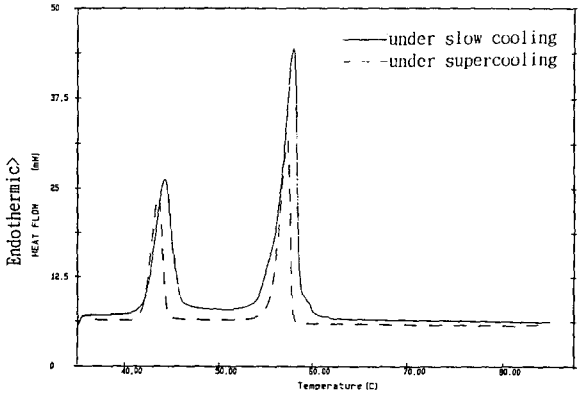

Fig. 3. DSC thermograms of stearyl alcohol crystallized from propylene glycol in the presence of 5% 1,2,6-hexanetriol.

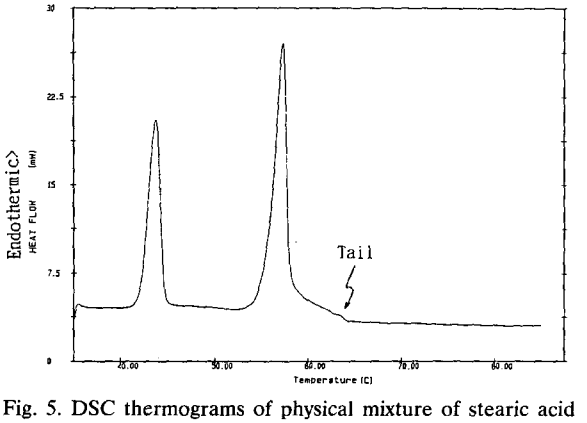

Fig. 5. DSC thermograms of physical mixture of stearic acid and stearyl alcohol (1:2 w/w).

Table 2
Onset temperatures and heats of fusion in stearyl alcohol combined specific components of ointment prepared at various cooling rates (stirring rate 400 rpm)

Component	Cooling rate (°C/min)	Onset temperature (°C)	Sum of endotherms (J/g) ($n = 3$)
St	5	42.0, 55.6	173.13 ± 0.48
St	40	42.0, 55.3	168.23 ± 0.35
St + SA	5	36.1, 53.9	182.82 ± 0.44
St + SA	40	–, 49.9	185.84 ± 0.27
St + SA + PEG	5	39.6, 53.5	182.20 ± 0.86
St + SA + PEG	40	35.1, 48.8	184.95 ± 0.97

St, stearyl alcohol; SA, stearic acid; PEG, polyethylene glycol 6000.

stearic acid and the precipated forms in propylene glycol no longer took place. Therefore, the enthalpies for endotherms of eutectic mixture were greater than that of stearyl alcohol alone. These data are summarized in Table 2. The above results may be explained on the basis that the content of stearic acid in stearyl alcohol is susceptible to process-induced variation and is increased by supercooling. Hence, the melting point of a supercooled product is lower than that of the slowly cooled product or physical mixture. When PEG 6000 was incorporated into the solid dispersion of stearyl alcohol and stearic acid, there was no significant changes in endotherms, as demonstrated by the thermograms in Fig. 6.

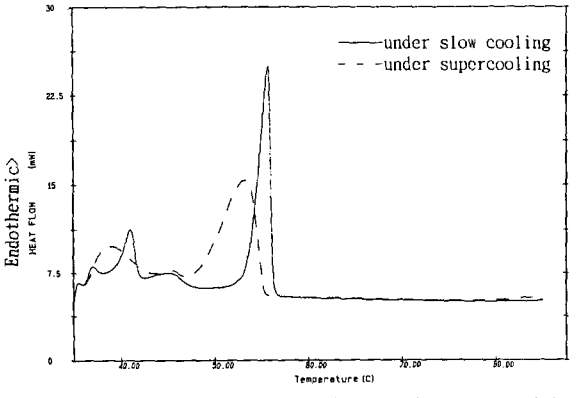

Fig. 6. DSC thermograms of solid dispersion prepared by combining stearic acid with stearyl alcohol and polyethylene glycol 6000, and then crystallized from propylene glycol in the presence of 5% 1,2,6-hexanetriol.

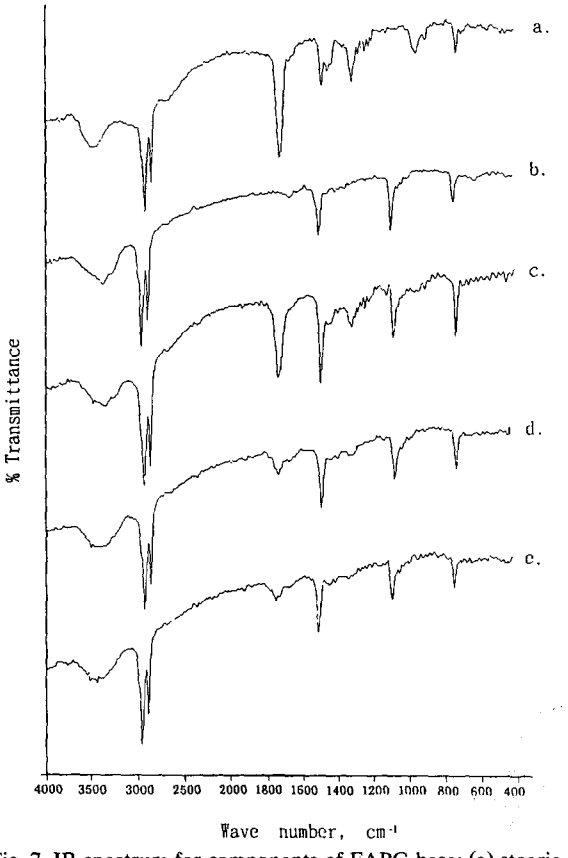

Fig. 7. IR spectrum for components of FAPG base: (a) stearic acid alone, (b) stearyl alcohol alone, (c) physical mixture of stearic acid and stearyl alcohol, (d) solid dispersion prepared by combining stearic acid with stearyl alcohol, and (e) solid dispersion prepared by combining stearic acid with stearyl alcohol and PEG 6000.

Simultaneous IR and DSC measurements indicated that the chemical interaction does not occur among the components during heating or cooling, as shown in Fig. 7. However, the various manufacturing processes would result in markedly different physical properties, especially in the case of solubility. Hence, we can conclude that in order to achieve a greater enhancement effect on penetration, it would be more effective to use the supersaturation of an enhancer suspension to pretreat the skin before the application of ointment rather than to take fatty acids as additives or to add them into FAPG bases.

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