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Differential scanning calorimetry studies of sebum models

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Synopsis

Human sebum is a mixture of triglycerides, fatty acids, wax esters, squalene, cholesterol, and cholesterol esters. *P. acnes,* a bacterium that is normally found on the skin, hydrolyzes certain triglycerides to fatty acids, thereby changing the sebum composition. The objective of this study was to examine the physical state of a model sebum and the effect of variations in its composition on its physical properties including (a) the carbon chain length of the components, (b) the ratio of unsaturated to saturated components, and (c) the ratio of triglycerides to fatty acids. A model sebum mixture was prepared based on a composition reported in the literature and evaluated by differential scanning calorimetry (DSC). Since cholesterol and cholesterol esters contribute insignificantly to sebum composition, they were not included. Squalene was kept constant (13%), while the concentration of the rest of the components was varied. Variations of sebum were prepared by dissolving all components in a 3:1 chloroform–methanol mixture for uniformity. Subsequently the solvent was evaporated at room temperature. The samples were then analyzed using DSC. Four distinct endotherms (namely, Mp-1, Mp-2, Mp-3, and Mp-4) were observed between −50°C and 100°C. Mp-1 and Mp-2 occurred below 0°C and were contributed by unsaturated components. Mp-3 and Mp-4, which represent the saturated components, occurred above 30°C. Thus, at normal skin temperature (skin surface temperature is 32°C), sebum contains both a solid and a liquid phase. All the transition temperatures increased with an increase in carbon chain length for the same ratio of unsaturation to saturation. A replacement of unsaturated components with corresponding saturated components led to a decrease in the transition temperatures for the former (Mp-1 and Mp-2) and an increase in the transition temperatures for the latter (Mp-3 and Mp-4). Replacement of triglycerides with corresponding fatty acids (mimicking the action of anaerobic bacteria) caused an increase in Mp-2 and a decrease in Mp-4. In all cases, the final melting temperature (Mp-4) was greater than the temperature of the human skin surface (32°C); thus components contributing to these endotherms are still solids at skin temperature. All variations in the sebum model led to mixtures of solids and liquids at skin temperature. Considering a reduction in Mp-3 and/or Mp-4 to represent sebum “fluidization,” it was achieved by a decrease in carbon chain length, an increase in unsaturation, or a substitution of triglycerides by corresponding fatty acids. Preferential enrichment with the saturated species will lead to enrichment of solids versus liquids in the sebum, presumably making it difficult for the liquid phase to dissolve the solids. It seems plausible that perturbation of the balance of solid and liquid components of sebum, such as by *P. acnes* action, may lead to blockage of the follicle. Future research will investigate strategies to dissolve and/or liquify the solid phase of sebum.

INTRODUCTION

Sebaceous glands produce an oily secretion, sebum, composed of non-polar lipids. These glands are holocrine (self-destructing), and the secreted sebum forms when the fully mature, lipid-rich cells die and disintegrate, discharging their contents to the skin surface via the follicular canal (1). Sebum is often thought to play a role in the pathogenesis of acne. This role has, however, not been clearly established (2). Some authors have suggested that the physical properties of sebum may be important in the pathogenesis of acne (3).

However, studies done on the physical properties of sebum have been scarce and inconclusive. Butcher and Coonin (4) studied some of the physical properties of sebum acquired from the forehead of a large number of subjects (presumably normal), and Burton (5) studied the properties of sebum obtained from the scalp of ten acne patients and seven normal patients. These properties have been summarized in Table I. Another study that investigated forehead sebum ascribed a melting point at 33°–35°C (6). These studies suggest that sebum collected from different sources or body sites have different viscosities and melting points. One of the reasons for these differences could be that scalp sebum is not involved in acne whereas forehead sebum is.

The physical properties of sebum, its melting point and viscosities in particular, are important, as they would mediate the blockage of the sebaceous follicle. To evaluate this theory, we have examined the physical properties of the sebum components and their mixtures using differential scanning calorimetry (DSC). There are, however, physical limitations to collecting large amounts of sample from the skin surface, and it is not easy to get "pure" sebum since it is contaminated with varying amounts of skin surface lipids. Furthermore, sebum varies quantitatively from person to person, contributing to the variability of the data. Hence we decided to carry out our experiments on a model sebum based on a composition given in the literature. We have evaluated a different sebum model and the effect of its components on its melting temperatures.

SEBUM COMPOSITION

The lipids from the skin surface are derived mainly from two sources, the sebaceous glands and the epidermis (7). The surface lipid from the gland-rich areas naturally contain a higher proportion of sebaceous lipid, whereas from gland-deficient areas such as arms and legs there is a greater proportion of epidermally derived lipid. Skin lipids from the face are derived in large part from sebum. The main components of sebum are triglycerides, wax esters, squalene, cholesterol esters, and cholesterol (7). The composi-

Table I
Physical Properties of Sebum

Property	Forehead sebum (ref. 4)	Scalp sebum (ref. 5)
Specific gravity	0.91 g/cm^3	0.90 g/cm^3 for three normal samples
Surface tension	24.9 dyne/cm from 26.5 to 31°C	22.9 dyne/cm for six normal samples at 30°C
Viscosity	0.55 poise at 38°C	0.32 poise at 35°C
	1.00 poise at 26.5°C	0.82 poise at 25°C
	Viscosity discontinuous at 30°C due to the separation of a precipitate in the sebum	
Freezing point	Sample started to freeze at 30°C and then solidified at 15°–17°C	15°–17°C

tion of skin surface lipids in Table II adapted from Downing (8) was used as a starting point for our experiments.

It is apparent from the table that there is great variation in the composition of the fatty acids and triglycerides. It could be because the free fatty acids are formed from the triglycerides through the action of *Propionibacterium acnes (P. acnes).* Bacterial lipases convert triglycerides to mono- and diglycerides as well as free fatty acids in the sebum, many of which are unique to the sebaceous glands (9). The extent of hydrolysis might vary in different persons, possibly due to variability in the *P. acnes* content on their skin.

For the DSC analysis, variations of the above composition were used. Diglycerides, cholesterol, and cholesterol esters were not used in our sebum models, as they made up a very small percent of the total. The percent of squalene was kept constant in all samples. Water was not part of the sebum model, as it is polar and would probably not be miscible with the non-polar lipid mixture. The aim of the study was to determine the effect of component characteristics on the phase behavior of the model sebum. In particular, we investigated the effects of the following on the melting behavior of a model sebum: (a) the carbon chain length of the components, (b) the ratio of unsaturated to saturated components, and (c) the ratio of triglyceride to fatty acid content.

EXPERIMENTAL

MATERIALS

The materials listed in Table III were obtained from Sigma Chemical Co., St. Louis, MO. They were at least 99% pure, according to the supplier. Chloroform and methanol were also obtained from Sigma.

PREPARATION OF LIPID SAMPLES AND DSC PROCEDURE

The ingredients for a particular model were weighed out and dissolved in a mixture of chloroform:methanol (3:1). Small portions of the above model sebum were withdrawn and put onto a pre-weighed DSC pan. The solvent was evaporated and the weight of the pan taken again. The difference gave us the weight of the lipid mixture, and this weight was entered on the DSC run by computer. In the absence of chloroform–methanol co-solvent, the samples withdrawn were not uniform, since there was a separation of the different phases. The DSC pan was then covered with an aluminum lid and run at a scan

Table II
Average Composition of Human Skin Surface Lipid for 17 Subjects (ref. 8)

Lipid class	Mean (%)	Range
Triglycerides	41.0	19.5–49.4
Diglycerides	2.2	2.3–4.3
Fatty acids	16.4	7.9–39.0
Wax esters	25.0	22.6–29.5
Squalene	12.0	10.1–13.9
Cholesterol	1.4	1.2–2.3
Cholesterol esters	2.1	1.5–2.6

Table III
Ingredients Used to Examine the Effect of Carbon Chain Length

	Carbon chain length		
Components	14	16	18
Wax ester (unsaturated)	Oleyl oleate	Oleyl oleate	Oleyl oleate
Triglyceride (unsaturated)	Trimyristolein	Tripalmitolein	Triolein
Fatty acid (unsaturated)	Myristoleic acid	Palmitoleic acid	Oleic acid
Wax ester (saturated)	Myristyl myristate	Palmityl palmitate	Stearyl stearate
Triglyceride (saturated)	Trimyristin	Tripalmitin	Tristearin
Fatty acid (saturated)	Myristic acid	Palmitic acid	Stearic acid

rate of 5°C/min from −50°C to 100°C, using a Perkin Elmer DSC-7. Each of the compositions was run in triplicate. For all the individual components, DSC runs were done in pure form and after dissolving in chloroform–methanol and evaporating the solvent. This was done to facilitate identification of the peaks. Polymorphic changes might occur when the individual components are dissolved in the co-solvent mixture, which is consequently evaporated. The above step identifies if any such change occurs.

EFFECT OF CARBON CHAIN LENGTH

The effect of three different carbon chain lengths (namely 14, 16, and 18) was examined. Major free fatty acids (FFA) of sebum fall in the carbon chain length of 14, 16, and 18 (C-14, C-16, and C-18, respectively) category, with negligible amounts of other carbon chain lengths (10). To investigate the effect of one carbon chain length (14, for example), the triglycerides, fatty acids, and wax esters were all of carbon chain length 14 (see Table III). The same was done for carbon chain lengths 16 and 18 also. According to Table II, the amount of triglycerides is 41%, wax esters are 25%, and fatty acids are 16.4% of the total lipid, and we used approximately that composition for each carbon chain length. The total triglycerides are, however, a mixture of unsaturated and saturated components, and so those were varied also for our second objective. In Table III, we have listed the ingredients used in each experiment. The quantities used are shown in Table IV.

EFFECT OF PERCENT SATURATED

To study the effect of percent saturated, the carbon chain length of all the components

Table IV
Sample Compositions With Varying Ratios of Unsaturation to Saturation of Each Lipid Class

Components	% Weight						
Unsaturated:saturated	0:1	1:1	2:1	3:1	1:2	1:3	1:0
Squalene	13	13	13	13	13	13	13
Wax ester (unsaturated)	0	13.5	18	20.25	9	6.75	27
Wax ester (saturated)	27	13.5	9	6.75	18	20.25	0
Triglycerides (unsaturated)	0	21.5	28.66	32.25	14.33	10.75	43
Triglycerides (saturated)	43	21.5	14.33	10.75	28.66	32.25	0
Fatty acids (unsaturated)	0	8.5	11.33	12.75	5.66	4.25	17
Fatty acids (saturated)	17	8.5	5.66	4.25	11.33	12.75	0
Total	100	100	100	100	100	100	100

was kept constant and variation was done in the unsaturated and saturated portions. As an example for the fatty acids, which made up 17% of the total, the ratio of unsaturated to saturated fatty acids was varied, keeping the total to 17% of the mixture, as shown in Table IV.

EFFECT OF CHANGE IN TRIGLYCERIDE AND FATTY ACID RATIOS

Triglycerides are hydrolyzed to fatty acids by *P. acnes.* The total amount of triglycerides and fatty acids, however, is 60% (10). For these experiments, the carbon chain length was 16 and the ratio of unsaturation to saturation was 1:2, as given by Nordstorm *et al.* (11). In these experiments only the saturated wax ester (palmityl myristate) was used. The rest of the ingredients were in the same quantities as in Table IV.

RESULTS AND DISCUSSION

A typical DSC thermogram of model sebum has four distinct transitions that are assigned to different components in the sebum, as shown in Figure 1. Their melting temperature, referred to as Mp-1 through Mp-4, characterizes each of these transitions. While Mp-1 and Mp-2 occur below 0°C and represent the unsaturated portion, Mp-3 and Mp-4 occur above 0°C and represent the saturated portion. From Figure 1, as the temperature is increased from −50°C, a fraction of the lipid mixture melts at approximately −20°C, which is seen as transition Mp-1. As the temperature is increased further, another transition occurs at approximately −15°C, which is designated as Mp-2. As the temperature is further increased, another fraction of the model sebum melts (at about

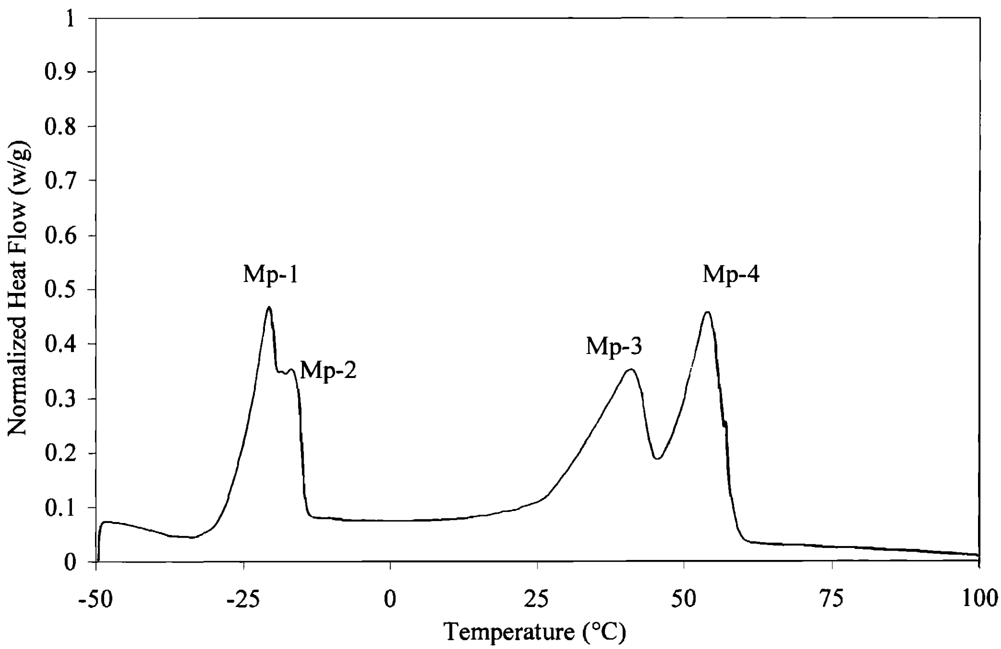
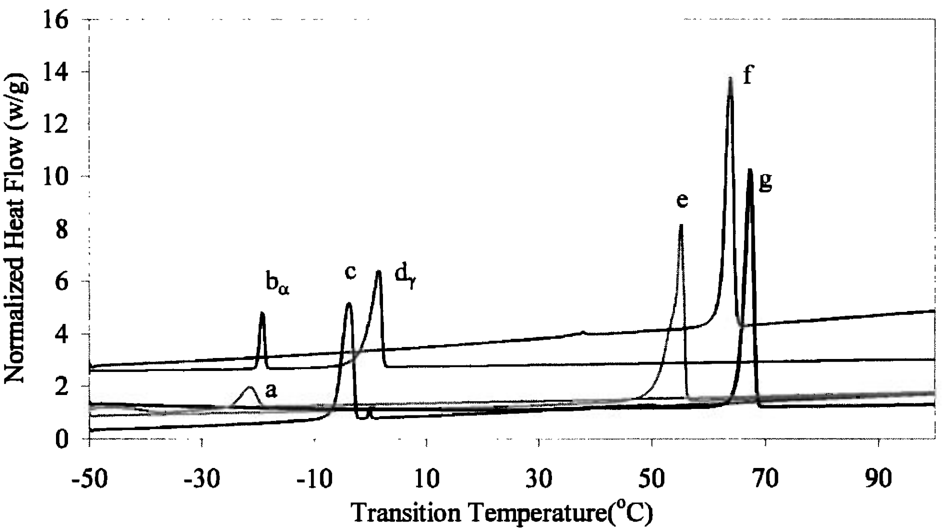


Figure 1. Typical thermogram of a model sebum.

40°C) and is designated as Mp-3, and then finally the last solid fraction of the model sebum melts at approximately 55°C and is designated as Mp-4. At −50°C the lipid mixture is a solid, and by 100°C all components have completely melted and the mixture is a liquid. From the DSC profiles and melting endotherms, we can conclude that the model sebum is crystalline in nature. Generally, pure lipids or homogeneous systems yield single sharp peaks whereas heterogeneous systems produce broad multiple peaks (12). If sebum was a homogeneous mixture, there would be one melting transition, but the presence of multiple melting transitions indicates that there are multiple phases. From the temperatures of these melting transitions, it appears that at skin temperature (32°C), some of the components of sebum are solids and some are liquids, which are not completely miscible with each other.

In order to identify the component associated with each transition, singular components were run through the DSC under the same conditions as the model sebum. The components used for carbon chain length 16 are given in Figure 2. Adding other substances



a. Tripalmitolein m.p. = -21.184°C

b α-Palmitoleic acid m.p. = -18.7°C

c. Oleyl Oleate m.p.= -4.234°C

d γ–Palmitoleic acid = 2.1°C

e. Palmityl Palmitate = 55.166°C

f. Palmitic acid = 63.866°C

g. Tripalmitin = 67.326°C

Figure 2. Thermograms showing transition temperatures of individual components.

to pure compounds usually decreases their melting point. In the DSC thermogram, investigating the effect of C-16 (Figure 3), the peak, Mp-4, is possibly a combination peak of the triglyceride tripalmitin (m.p = 67.316°C; DSC run shown in Figure 2), and the fatty acid is palmitic acid (m.p = 63.866°C; Figure 2). The peak for Mp-3 in C-16 can be assigned to the peak of the wax ester, palmityl palmitate (m.p = 55.166°C). Palmitoleic acid exists in the form of two isomers, γ (m.p = −18.7°C) and α (m.p = 2.1°C) (13). Mp-2 can be a mixture of the unsaturated wax ester, oleyl oleate (m.p. = −4.234°C) and the α form of palmitoleic acid. Mp-1 may be a mixture of the triglyceride tripalmitolein (m.p = −21.184°C) and the γ form of palmitoleic acid. Squalene has a m.p of −75°C and does not show any transitions. Its only role is probably that of a solvent, and it may be affecting all the peaks in decreasing their melting temperatures. Similarly, for the carbon chain lengths of 14 and 18, the peaks can be assigned to their individual components (DSC runs done separately, not shown here). In general, Mp-1 is the peak of the unsaturated triglyceride and unsaturated fatty acid, Mp-2 is the peak of the unsaturated wax ester, Mp-3 is the peak of the saturated wax ester, and Mp-4 is the peak of the saturated triglyceride and fatty acid. It is safe to assign the peaks to this mixture of compounds as the individual compounds show their peaks around these melting transitions. In Figure 3, investigating C-14, an extra peak is seen before Mp-3. This can be attributed to a polymorphic form of one of the components.

CARBON CHAIN LENGTH

From Figure 4, it is obvious that as the carbon chain length increases, all the melting temperatures increase, which would be expected. The slopes of the unsaturated compo-

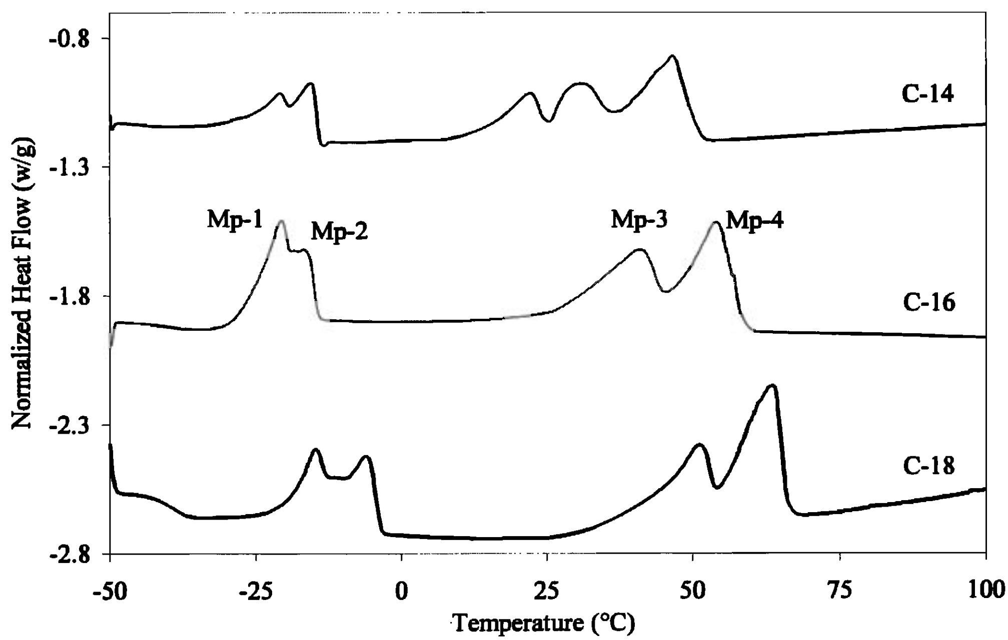


Figure 3. Thermogram showing the effect of carbon chain length in the model sebum (ratio of unsaturation to saturation 1:1).

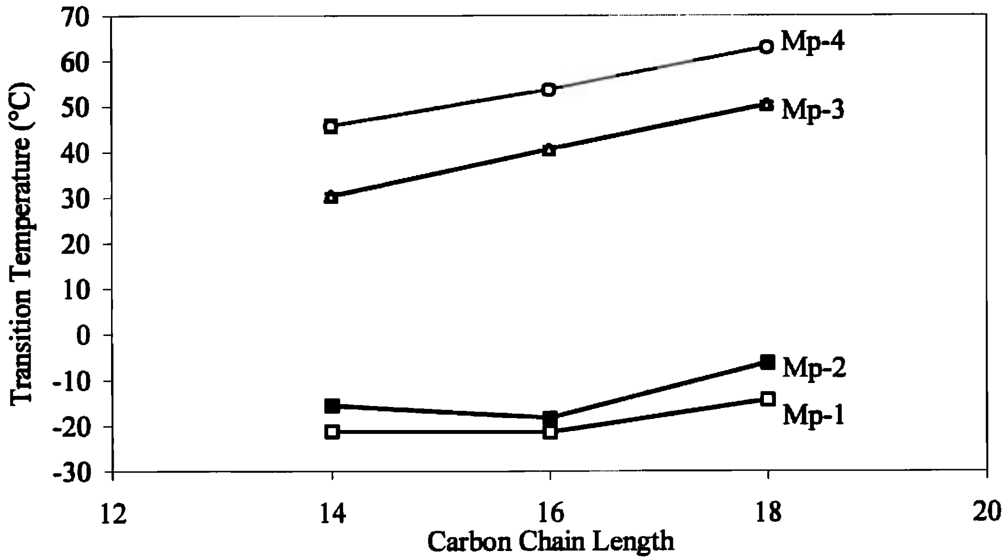


Figure 4. Effect of carbon chain length on the transition temperature (ratio of unsaturation to saturation 1:1). Error bars indicate the standard error of the mean of three replicates.

nents are significantly smaller than the slopes of the saturated components, which means that the increase in carbon chain length affects the saturated portion more than the unsaturated portion.

EFFECT OF PERCENT SATURATED

The effect of saturation (corresponding to Table IV) on the melting temperatures is

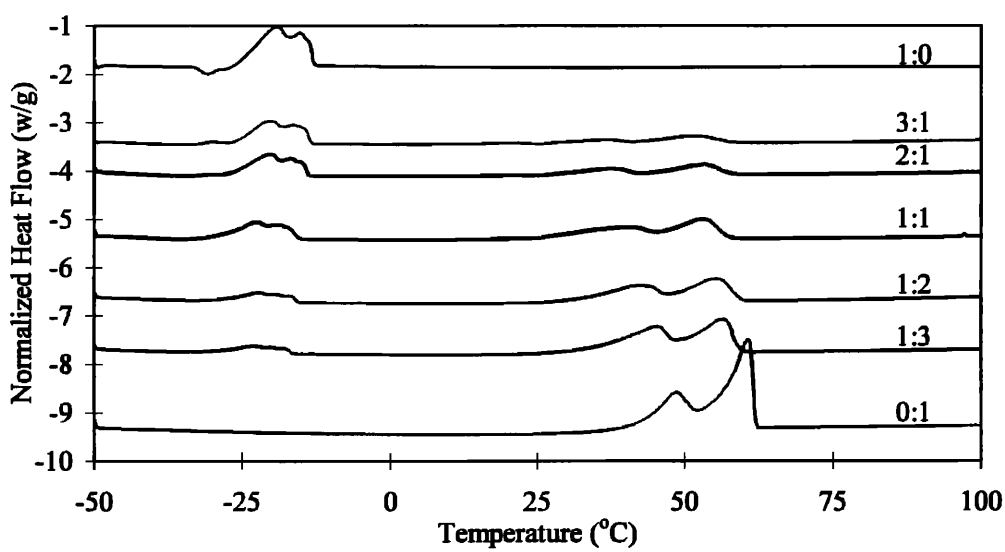


Figure 5. Thermogram showing the effect of percent saturated in the model sebum for carbon chain length 16. Numbers on the side of thermograms indicate the ratio of unsaturation to saturation.

shown in Figure 5. The transition temperatures are plotted versus the percent saturated in Figure 6. As the saturation increases (or unsaturation decreases), the temperatures of the unsaturated components (Mp-1 and Mp-2) decrease with a concurrent increase in the Mp-3 and Mp-4. Since the slope of Mp-3 is significantly higher than that of Mp-4, it would seem that the unsaturation seems to affect the wax ester portion of the model sebum more than the triglyceride and fatty acid portion of the mixture. It appears that Mp-1 and Mp-2 are affected to a lesser extent in terms of their melting point than both Mp-3 and Mp-4 (from slopes). As mentioned earlier, the presence of other substances decreases the melting point of the pure compounds. When there is more unsaturation than saturation, by the time the temperature is reached for the melting of the saturated compounds, some of the saturated portion dissolves in the already-melted unsaturated portion and their melting point decreases. The more the unsaturation, the more the dissolving and hence the higher decreases in the melting point. In these cases, the unsaturated portion acts as the solvent. When the percent of saturated fraction is greater,

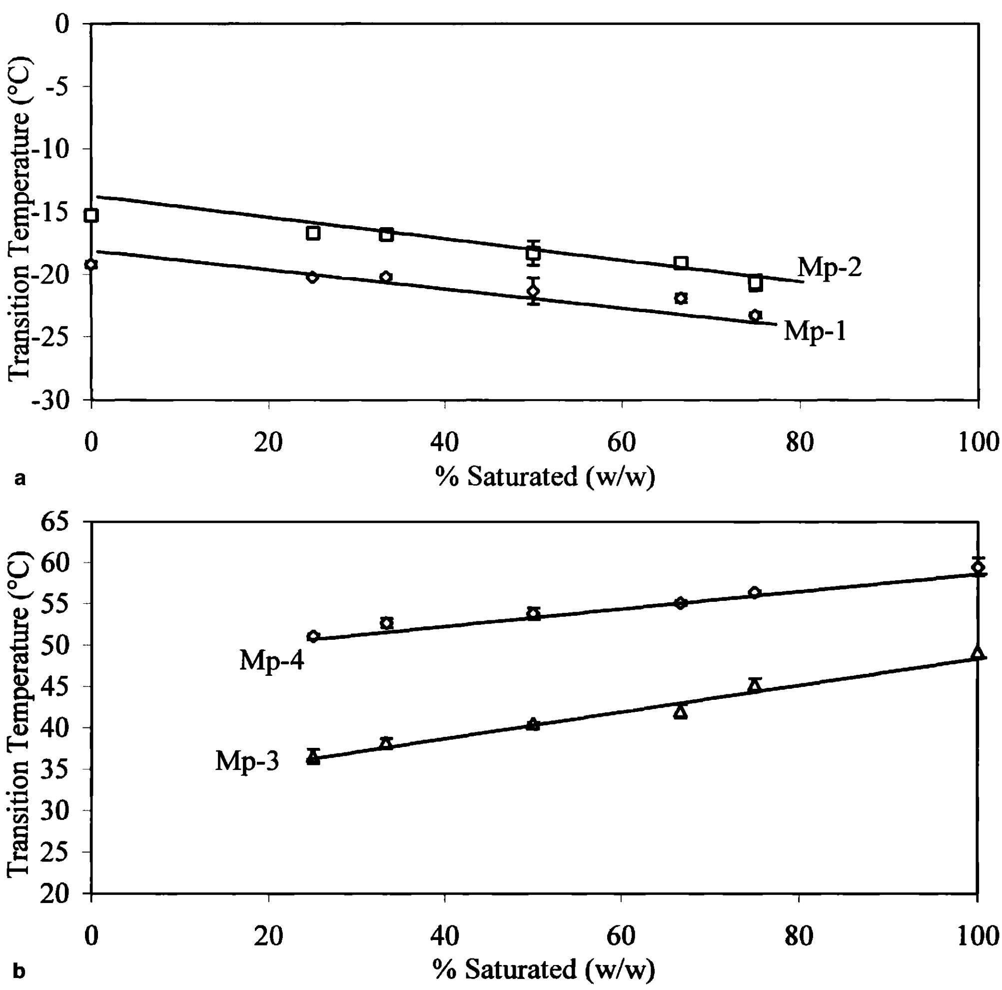


Figure 6. Effect of percent saturated on transition temperatures (a) Mp-1 and Mp-2 and (b) Mp-3 and Mp-4 for C-16. Error bars indicate the standard error of the mean of three replicates.

it dissolves partially in the diminished percent of the unsaturated portion. This is probably the reason that Mp-1 and Mp-2 are not affected as much as Mp-3 and Mp-4 by the increase in the percent saturated. The decrease in Mp-3 more than in Mp-4 means that the unsaturated portion is a "better" solvent for the wax ester than for the triglycerides and fatty acids. We are not sure as to why there is preferential dissolution of the wax ester fraction as compared to the combined fatty acid and triglyceride fraction. Similar results were also obtained for carbon chain lengths 14 and 18.

EFFECT OF CHANGE IN TRIGLYCERIDE AND FATTY ACID RATIOS

P. acnes hydrolyzes triglycerides to fatty acids in the skin. It was hence necessary to examine the transition temperature of the model sebum when it contained different percentages of triglycerides and fatty acids. In these experiments the ratio of the unsaturated to the saturated portion was 1:2 and the carbon chain length was 16. The wax ester fraction used in these experiments was palmityl myristate, and there was no unsaturated wax ester added. This wax ester was selected because, according to Nordstorm *et al.* (11), this was the fraction that occurred most frequently. In Figure 7, Mp-4 is ascribed to a mixture of palmitic acid (m.p = 63°C) and tripalmitin (m.p = 68°C). Figure 8 shows the effect of decreasing the relative amount of triglycerides and increasing the fatty acids. MP-4 decreases from 59°C to 48°C as the percentage of triglycerides decreases, as shown in Figure 8b. Mp-3 can be assigned to the wax ester palmityl myristate (m.p = 49.4°C) and decreases from 44°C to 39°C (Figure 8b) as the percentage of triglycerides decreases (fatty acid increases). Mp-3 is not affected as much as Mp-4 by the altered triglyceride to fatty acid fractions because it is a wax ester peak. From Figure 8, it can be concluded that as the percentage of triglycerides increases, Mp-4 increases, whereas Mp-3 is affected to a lesser degree.

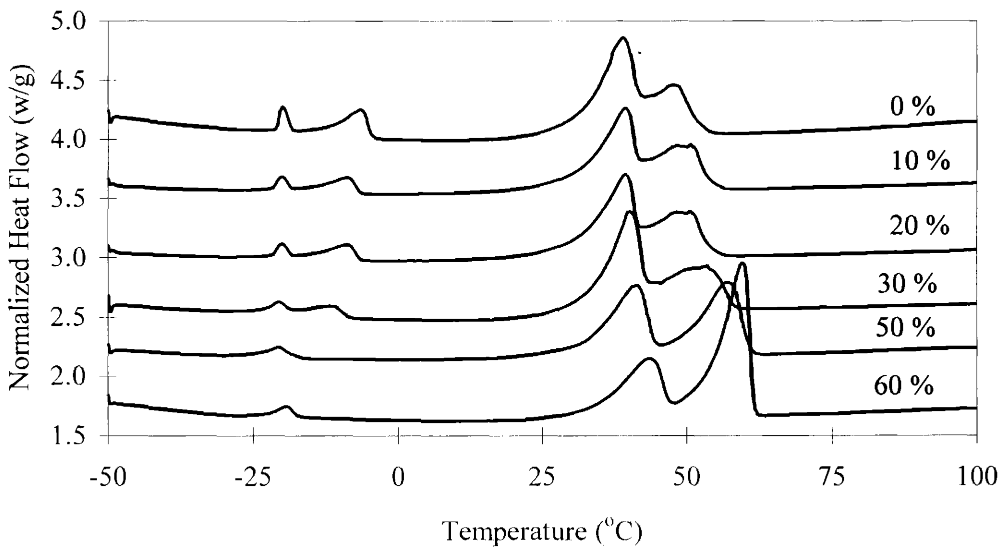


Figure 7. Representative thermogram showing the effect of percentage of triglycerides in the model sebum. Numbers on the side of thermograms indicate the percent of triglycerides.

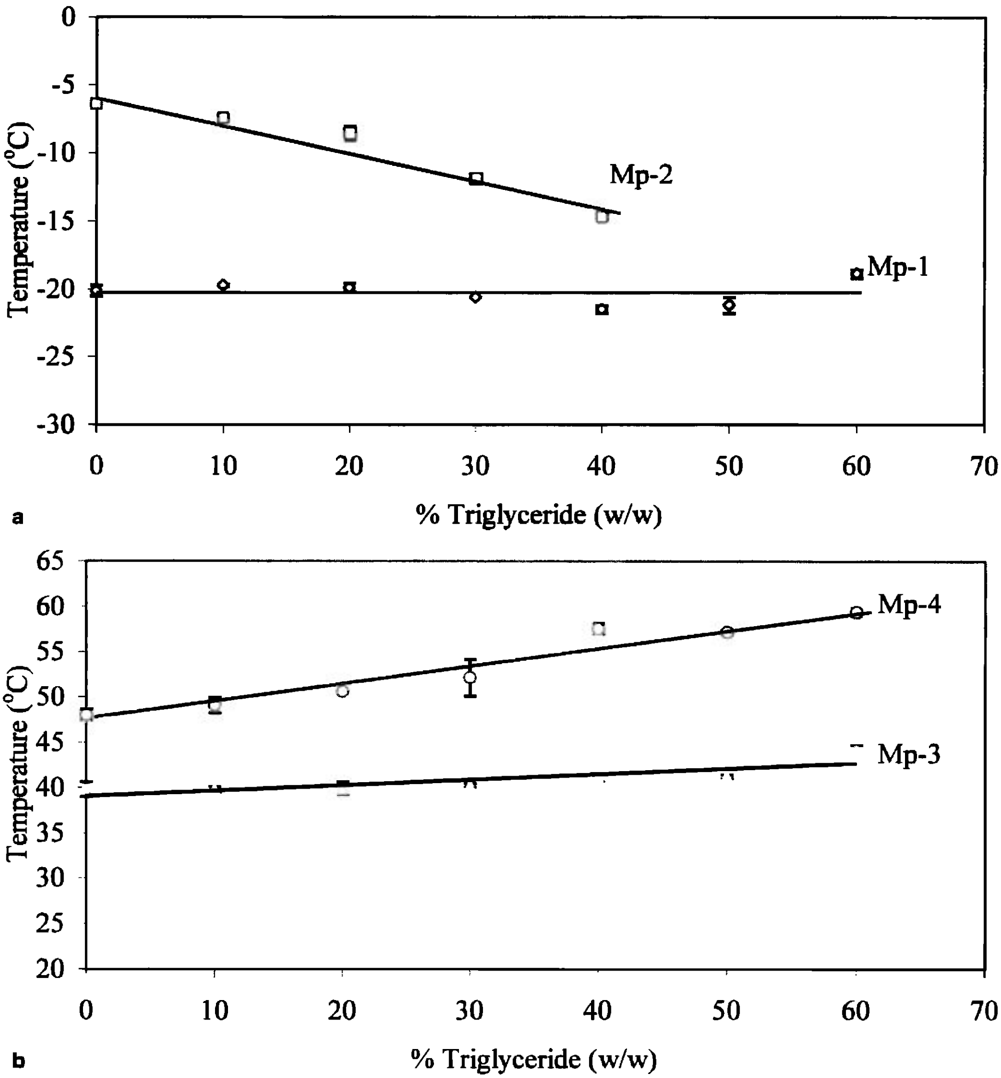


Figure 8. Effect of percentage of triglycerides on the transition temperatures (a) Mp-1 and Mp-2 and (b) Mp-3 and Mp-4 for C-16 (ratio of unsaturation to saturation = 1:2). Error bars indicate the standard error of the mean of three replicates.

Mp-2 decreases with the increase in percentage of triglycerides (Figure 8a). It was mentioned earlier that the Mp-2 peak is the mixture of the unsaturated wax ester and the unsaturated fatty-acid α form of palmitoleic acid. In these experiments, we did not use an unsaturated wax ester, and so Mp-2 is not a combination peak but just a peak of the unsaturated fatty acid. Mp-2 does not appear until the 30% triglyceride level, and is not seen in compositions of 50% and 60% triglycerides. The peak decreases in area as the percent of triglycerides increases and as its percentage in the lipid mixture decreases. Mp-1 appears more or less constant (Figure 8a). Due to the fact that Mp-1 is a combination peak of the unsaturated fatty acid and the unsaturated triglyceride, this result is difficult to resolve.

CONCLUSIONS

We conclude that under the experimental conditions explained earlier, the unsaturated lipids help dissolve the saturated lipids. As the proportion of the saturated, solid components (associated with the Mp-3 and Mp-4 peak) increase, it is more unlikely that the liquid components will be able to dissolve the solid under natural conditions of skin. Hence if *P. acnes* preferentially changes the relative percent of the longer chain, more saturated constituents, producing more solids, these will not be dissolved by the skin's natural liquid oils and may plug the pilosebaceous ducts. Some evidence suggests that comedonal material is relatively more saturated while sebum collected from the skin surface is more unsaturated (10). Additionally, it is well published that there is a deficiency in polyunsaturated fatty acids such as linoleic and sebaleic acids in acne (14). Converting triglycerides to free fatty acids by *P. acnes* may not have the largest consequences as far as the physical properties of sebum are concerned, since the saturated forms of both are still solids above skin temperature and the unsaturated species of both are still liquids below skin temperature. However if relatively more of the saturated fatty acid species are produced by bacterial hydrolysis, the balance between the liquid and solid phase will be altered.

Actual sebum may lie somewhere in between all the model sebum that we have investigated, and a portion of it may be solid at 32°C. Furthermore, the presence of the solid portion depends in a large part of the presence of the unsaturated or liquid portion of the sebum. The fact that sebum may exist in different phases has also been suggested by Burton (5). Butcher and Coonin (4) showed that while some components of forehead sebum started to solidify at 30°C, it completely solidified at 15°–17°C. These studies are in agreement with our observations that sebum does not exist as one phase, but rather as a mixture of a solid and a liquid at skin temperature. DSC of scalp sebum has been performed by Bore and Goetz (15). Their results also confirm the presence of multiple phases in sebum. Their samples were also mixtures of solids and liquids at body temperature. They showed that as the percentage of the unsaturated portion increased, the viscosity of the sample decreased. We showed that as the unsaturated portion increased, the saturated portion's melting temperature decreased, which in turn may contribute to the decreased viscosity.

SUMMARY

The present research showed that:
1. Sebum is not one phase but may exist in multiple phases at skin temperature (32°C).
2. Two transitions are at very low temperatures, Mp-1 and Mp-2. These are attributed to the unsaturated portion of sebum, generally, Mp-1 to the unsaturated triglycerides and fatty acids and Mp-2 to the unsaturated wax ester. At skin temperature, these compounds are liquid.
3. Two transitions occur at higher temperatures, Mp-3 due to saturated wax esters and

Mp-4 due to saturated fatty acids plus triglycerides (DSC could not always differentiate these peaks). At skin temperature, these components are solid.
4. As the amount of saturated species increases, more of the solid phase is present in sebum relative to the liquid phase.

Changes made to the constituents of sebum-carbon chain length, saturation, and replacement of triglycerides with fatty acids, as happens in acne, affect Mp-3 and Mp-4 in the following way (these are the most relevant transitions to skin):

1. Increasing carbon chain length raises the Mp-3 and Mp-4 transition temperatures quite dramatically, i.e., 25 to 30 degrees above skin temperature, and so there is little chance of liquification of these solids at skin temperature.
2. Increasing the amount of saturated constituents raises the Mp-3 and Mp-4 transition temperature 10 to 15 degrees, and so there is little chance of these components melting these at skin temperature.
3. Increasing the proportion of triglycerides increases the Mp-4 transition temperature, which would be expected.

The most important finding from this research is that sebum exists in multiple phases—liquids and solids—and that the degree of saturation controls the relative amounts of these phases. Whether the presence of an excessive amount of the solid phase of sebum in the follicle plays a role in the pathogenesis of acne still remains to be investigated. The literature reports indicate that comedonal plugs are enriched saturated species (10). Additionally, it is also known that lipids from skin of acne patients are deficient in polyunsaturated fatty acids such as linoleic and sebaleic acids (14). Both of these reports support the possibility that the sebum of acne patients is out of balance with regard to the relative amount of the solid versus the liquid phases. The presence of excessive amounts of the solid phase would render it difficult for the liquid phase to dissolve the solid phase, and could plausibly lead to altered sebum flow and blockage of the pilosebaceous duct as is known to occur in acne patients. In any case, our results suggest that there is a solid component in sebum at skin temperatures irrespective of its composition.

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