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Comparison of recent techniques to characterize the crystallization behaviour of fatty suppository bases

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Abstract

The time course of crystallization of hard fat suppository bases has been studied by isothermal DSC, nuclear magnetic resonance spectroscopy, oscillation rheometry, and thermorheography.

The crystallization of hard fats was found to be a biphasic process, where the content of partial glycerides and the extent of supercooling determine the formation of crystal nuclei while the final solidification level depends upon the crystallization temperature.

The principles of different techniques and results are compared considering potential applications in process surveillance and quality control. The methods employed could also help to enhance pharmacopoeial specifications.

Keywords: DSC; Fat; NMR; Oscillation rheometry; Thermorheography

1. Introduction

1.1. Characterization of physicochemical properties of fats

The chemical properties of solid fats are tested extensively in modern pharmacopoeias [1–3], but little space is generally spent on their physical characteristics. However, detailed information concerning the melting and solidification behaviour

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of solid fats are indispensable for the control of production processes and the selection of suitable excipients. Since suppositories are to release active ingredients rapidly and completely, it may be necessary to consider the melting process in greater detail. The European Pharmacopoeia [4] describes a disintegration test for rectal and vaginal suppositories, which requires that they soften or disintegrate within 30 to 60 min in water at 37°C. The melting behaviour of suppository bases is characterized by an open tube melting point, but the practical relevance of this test with respect to stored specimens is decreased because samples are liquefied in the process of preparation. In order to determine melting temperature intervals and melting enthalpies of fats, waxes and related compounds, it has been suggested recently that storage-induced modifications should be eliminated by a standardized thermal pretreatment. Thus, samples are characterized by thermal analysis in a state which does not depend upon their history [5].

In addition, the solidification behaviour of fats and their preparations is of particular interest for manufacturing and physical stability reasons. A method for determining the solidification temperature has been given for some low-melting homogenous compounds in the European Pharmacopoeia [4], but is missing in the "hard fat" specifications. It is based upon the determination of the peak temperature occurring during solidification of the melt due to the heat of crystallization released and is thus similar to the Shukoff method [6] used by some manufacturers of triglycerides [7,8] to characterize their products. The solidification point is simple to determine but its value as a physical characteristic for the processing of suppository bases is limited (see Ref. [9]). Other methods for describing the kinetics of crystallization, which have been tested for their suitability for this purpose, are described below.

1.2. Current methods

An overview of the methods used in the present study to characterize the time course of crystallization of hard fat suppository bases is given in Table 1.

Isothermal differential scanning calorimetry (isothermal DSC)

In conventional DSC, the heat released or absorbed in structural transitions within the sample is measured by heating or cooling it at a predetermined rate (i.e. dynamically) over the temperature interval of interest [10]. An isothermal variant of

Table 1
Analytical techniques for characterization of hard fat crystallization processes

Sample	Method	Variable measured
At rest	Isothermal DSC	Heat flux/mV
	Nuclear magnetic resonance	Solid fat content/%m/m
Sheared	Oscillation rheometry	Storage and loss modulus
	Thermorheography	Temperature/K
		Torque/scale units

the method was first employed to characterize the crystallization of fats in food. Thus, Kawamura [11,12] studied the solidification of palm oil and rape seed oil. Later, Ziegleder [13,14] demonstrated in studies on cocoa fat that the method is suitable to describe its tendency to crystallize, which depends strongly upon its origin. Recently, the method has been used to assess the influence of additives upon the phase transition of cocoa [15] or the alteations occurring in chocolate layers on ice cream under various refrigeration conditions [16].

In isothermal DSC, a fully melted sample of hard fat is cooled rapidly to the crystallization temperature and after thermal equilibration the heat flux is measured isothermally as a function of time. After a sufficient number of nuclei have been formed during the nucleation time t_n, the heat released during crystal growth causes an exothermic deviation of the temperature signal. Its peak indicates the time at which the rate of solidification achieves its maximum. At this point the heating current required to compensate the exothermal heat flow of the sample is minimal. The area under the crystallization isotherm is a measure of the heat of solidification ΔH_s released.

Nuclear magnetic resonance (NMR) spectroscopy

NMR spectroscopy has been established recently in the analysis of triglycerides as a means of determining the solid fat content (SFC). For this purpose, pulsed low-resolution ^{1}H NMR spectrometers are used for preference [17]. This means that protons are detected but not discriminated with respect to their chemical bonding (e.g. $-\!\!\diagup\!\!\diagdown CH$, $\diagdown\!\!\diagup CH_2$, –OH groups), while their phase environment (crystal, viscous liquid, water) can be detected after excitation by high-frequency electromagnetic pulses.

In a stationary magnetic field, the rotational axes of protons in a sample precess at a given frequency (the Larmor frequency) around the direction of the magnetic field. If the sample is irradiated with an electromagnetic pulse at a frequency corresponding to the precession frequency, the nuclei absorb energy and leave their equilibrium orientation, i.e. their axes are rotated away from the direction of the field vector (Fig. 1, Ref. [18]).

The spin–spin relaxation characterizes the decrease of transverse magnetization with time after a 90° impulse because the phase coherence of the rotational axes is gradually lost and eventually the signal vanishes. The corresponding time constant is called the transverse or spin–spin relaxation time T_2. Among the factors contributing to the desynchronization of precessing nuclei are molecular collisions together with intra- and intermolecular interactions. Therefore the spin–spin relaxation time depends upon the spatial order and distances of atoms in molecules [18]. Besides, the mobility of atoms is important and because transverse relaxation times are increased in low viscosity fluids the measurement of T_2 can be used to determine the SFC of partially crystallized fats. In solids, a typical value for T_2 is about 10 μs, while times higher by a factor of 10^4 are characteristic of liquids.

Because it is a fast method, NMR spectroscopy is used routinely in the food industry to determine the water content of various nutrients [19]. It is also used to

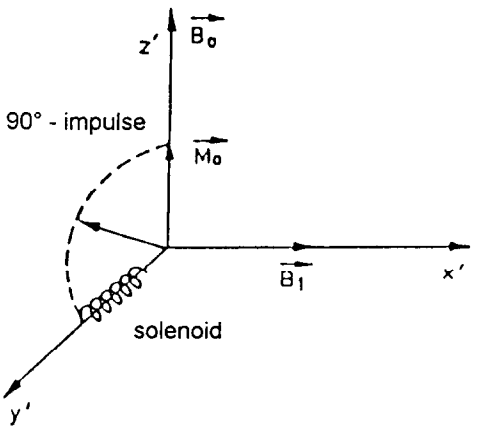

Fig. 1. Rotation of magnetization vector by a 90° impuse [18].

characterize milk fats [20–22], vegetable oils [23], cocoa fat [24] and chocolate [17] by means of their SFC. By measuring the same parameter as a function of both time and temperature, the technique can also be employed to study the hardening of fats upon storage [25,26]. In the field of pharmaceutics, Müller and Hassan [27] have recently studied the influence of drugs and excipients upon the SFC of glycerides by NMR spectroscopy.

Under isothermal conditions, the SFC increases sigmoidally with time, and the resulting curves yield information with respect to the nucleation time (t_n), the time of maximal solidification rate ($t_{s,max}$), and the final solidification level (S_∞).

Oscillation rheometry

Oscillation rheometry is applicable to both fluids and solids and can be used to determine both viscous and elastic components in the reversible deformation of viscoelastic substances. The method is also suitable for characterizing the time course of crystallization of triglyceride melts.

Usually, the solidification of fats is studied by first heating the samples to a temperature level that ensures a complete melt and cooling them to the crystallization temperature. At the initial temperature, they are completely liquid, so that viscous properties prevail. This state is hardly altered until the solidification starts and the volume fraction of solids increases as the number and size of crystals grow. The phase transition is also reflected by the rheological behaviour of the system as the elastic properties become prominent as solidification proceeds. The onset of crystallization can be detected by the jump of viscous and elastic components that accompany it.

These components are characterized numerically by the storage modulus G' and the loss modulus G''. The value of G' is a measure of the energy stored reversibly by the system and hence the elastic component, while G'' quantifies the energy that is transformed into heat and lost in viscous flow [28].

Oscillatory measurements can be carried out on a rotational viscometer if the mobile element, e.g. the external cylinder, is set in sinusoidal motion. The advantage compared to continuous shear experiments is that at low amplitudes the resting structure of the samples is not altered and the viscometer serves as a non-destructive probe (see, for example, Ref. [29]).

The angular rate of the external cylinder changes sinusoidally with time and imposes a strain gradient varying with frequency and amplitude upon the material in the shear gap. A stress signal with the same frequency can be measured at the internal cylinder, it has a lesser amplitude and its phase is shifted (see Ref. [28]).

Both the damping and the phase shift can be used to characterize the viscous and elastic components of fats during crystallization. While this method has been applied to the crystallization kinetics of food fats [30], there are no experiences in the field of pharmaceutics.

Thermorheography

As early as 1975 Baenitz [31] introduced a method into food technology by which the solidification characteristics of chocolates and other fat-based preparations could be studied. The most important new feature of the procedure was that the whole course of crystallization of a steadily stirred melt could be described by only two parameters. This technique has been termed thermorheography.

In this instance, the melt is steadily stirred in a thermostatted cup. At the onset of crystallization, the solid fat fraction of the system starts to increase, while the remaining liquid components form the continuous phase in which the fatty crystals are dispersed. The liquid phase decreases by conversion to solids and the initially diluted suspension of crystals is converted intermediately to a semisolid paste and finally forms a compact solid.

In a thermorheographic apparatus the torque is recorded as a signal proportional to stress, which grows as crystallization proceeds. The slope of the torque profile characterizes the rate of solidification. In order to quantify this parameter, the solidification gradient g_s has been introduced, which corresponds to the slope of the linear segment of the profile.

If a melt is supercooled, crystallization does not begin instantaneously; it starts only after a sufficient number of nuclei have been formed. The time period up to the onset of noticeable crystallization has been called nucleation time t_n [32]. It can be derived from the torque profile by extrapolating both the initial horizontal section and the steeply ascending part of the curve and by projecting their intersection down to the time axis (Fig. 2).

In thermorheograms the onset of crystallization cannot only be identified by the steep increases of torque but also by a rise of temperature due to the release of the heat of solidification.

From the difference between the lowest and the highest temperature observed during crystallization, the extent of solidification can be assessed: the greater it is, the further the crystallization has proceeded. Both profiles yield complementary information and characterize the time course and the extent of crystallization.

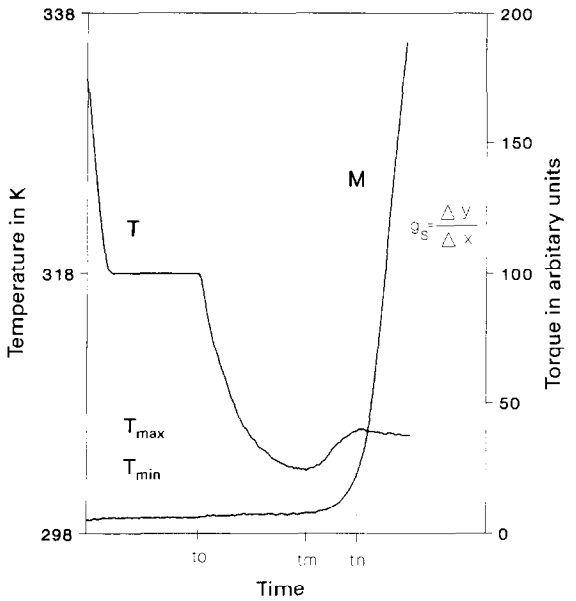

Fig. 2. Example of a thermorheogram.

2. Experimental

2.1. Methods

Isothermal differential scanning calorimetry

Apparatus. Thermoanalytical system TA 3000 (Mettler, D-Gießen); control and analysis unit TA processor TC 10 A and sample cell DSC 30 with standard sensor; aluminium pans with lid.

Operating conditions. Sample, Suppocire AT, 40–45 mg; reference, empty aluminium pan; flushing gas, nitrogen 50 ml min^{-1}; cooling, evaporating nitrogen, programmed (details see next paragraph); crystallization, temperature 299–303 K at 1 K intervals; calibration of temperature and heat flow by indium standard.

Procedure. Samples were sealed in pans, melted at 338 K, kept at this temperature for 15 min and subsequently cooled to 318 K within 10 min (cooling rate, 2 K min^{-1}). After a period of 15 min they were cooled to the crystallization temperature at maximal rate. After establishment of the target temperature, the exothermic heat flow profile was recorded.

NMR spectroscopy

Apparatus. Minispec PC 120 (Bruker, D-Karlsruhe) consisting of sample head with permanent magnet, control- and evaluation unit with application software EDM 110 A; refrigeration thermostat F3-C (Haake, D-Karlsruhe). The sample head was cooled using protein-free Frigen^{R} Inert (Hoechst, D-Frankfurt). Heating block AL 20 (Gebr. Liebisch, D-Brackwede); recirculating thermostat F10-HC (Julabo D-Selbach/Schwarzwald); sample tubes, diameter 10 mm and length 150 mm (Bruker, D-Karlsruhe).

Operating conditions. Field strength of permanent magnet B_0 0.47 Tesla; working frequency f 20 MHz; lag time 9 μs; sampling times $T_1 = 11$ μs, $T_2 = 70$ μs; trigger time t_z 2 s; correction factor F 1, 3307. The correction factor F was determined before measurements using calibrator substances with known content of solids.

Operating procedure. Solid fats were melted in a heating cabinet at 338 K. Aliquots were transferred to the sample tubes to a filling level of 4 cm. Tubes were closed using plastic caps. Samples were kept at 338 K in a heating block for 15 min and then for 30 min at 318 K in a water bath.

The sample heat was adapted to crystallization temperature. Insertion of the sample tube started the experiment. The increase of solid fat content was recorded under computer control.

Oscillation rheometry

Apparatus. Rheometer system Rheolab MC 20 (Physica, D-Stuttgart) with universal measuring device UM and liquid recirculating thermostat viscotherm VT 10; software package Rheologic OS 200-Stress-TF for control of oscillation experiment.

Operating conditions. Double gap measuring system MS-Z1 (Physica, D-Stuttgart); cooling temperatures 298, 301, 304 K; stress 35 Pa; frequency 1 Hz; variable strain amplitude (measured).

Operating procedure. A sample volume sufficient to fill the double gap between cup and rotor completely was poured into the measuring device. After thermal equilibration at 318 K, the temperature was kept constant for 15 min and then switched to the cooling temperature. This was the beginning of the experiment and the start of rotor oscillations. Both the temperature profile and the phase shift angle were recorded continuously. From the phase shift angle, storage and loss moduli together with the loss factor were computed.

Thermorheography

Apparatus. Rheosyst 5000 (Coesfeld Meßtechnik, D-Dortmund) with components controller, measuring drive and TRG stand; heating cabinet FST 420 (Heraeus,

D-Hanau); thermostat F4-M and cryostat F3-Q (Haake, D-Karlsruhe); compact cooling thermostat RMS-RM6 (Lauda, D-Lauda-Königshofen); computer for data acquisition IBM PS/2 Model 50 (IBM, Greenock, UK); Data acquisition card Model DT 2905 (Stemmer PC Systeme, D-Puchheim).

Operating conditions. Range of measurements for crystallization studies, 0–16.2 N cm (MB 3); stirrer, oblique-surface rotor; stirring rate, 128 min^{-1}; crystallization temperatures, 293–303 K at 2 K intervals. The data acquisition card had four voltage input channels, which could be amplified by a common factor. Because torque and temperature were measured simultaneously, the output voltages of the sensors had to be adjusted as follows: temperature was measured at a level of 10 mV K^{-1} corresponding to a voltage of 1 V at 373 K, while the analogue output of the torque sensor yielded a maximum voltage of 10 V. The latter was therefore attenuated to one tenth before both were amplified by a factor of four.

Operating procedure. The sample was put into the measuring cup thermostatted at 333 K after having been melted in a heating cabinet at 338 K. After introduction of the preheated rotor and closing the cup with a heated lid, the drive was lowered so that the rotor coupling could be engaged. Finally, the drive assembly was moved downward to the measuring position. The sample volume was sufficient for complete immersion of the rotor in this position and the fixed stirring rate ensured homogenous mixing of the sample. The temperature was measured by a sensor located in the centre of the sample. After equilibration for 10 min at 333 K, the thermal control jacket was switched to a second thermostat, cooled rapidly to 318 K and kept at that level for another 15 min. In a second step, the thermal jacket was brought down to the crystallization temperature by switching to a cryostat at the beginning of the crystallization experiment. Both sample temperature and torque were measured continuously and recorded under computer control.

2.2. Materials

The influence of temperature upon the time course of crystallization has been studied using the suppository bases Suppocire AT (Gattesfossé, F-Saint-Priest; Lot 9375), Witepsol H5 (Hüls AG, D-Witten; Lot 077) and Witepsol W 35 (Hüls AG, D-Witten; Lot 392).

3. Results

3.1. Isothermal DSC

Crystallization isotherms are shown in Fig. 3. They indicate that the onset of crystallization is delayed with increasing temperature. Similarly, the peaks characterizing the maximal solidification rates are shifted to longer times at higher temperatures.

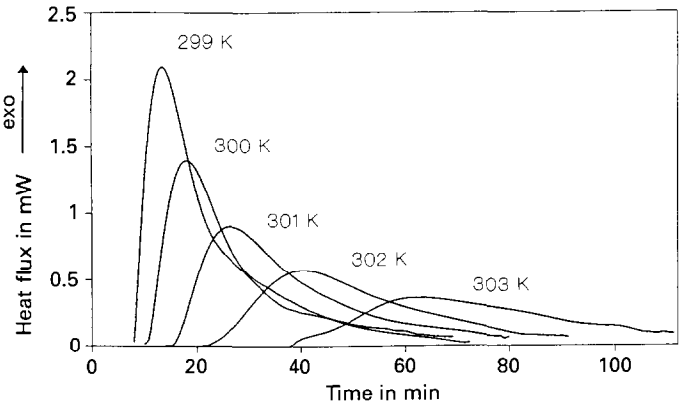

Fig. 3. DSC isotherms for Suppocire AT at various crystallization temperatures.

The initial impression that the maxima in Fig. 3 are located on an exponential function is confirmed in Fig. 4, where a semilogarithmic plot of $t_{s,max}$ against the crystallization temperature yields a straight line. The same type of relationship holds for the dependency of the nucleation time upon crystallization temperature, where the line is shifted towards lower temperatures. The slope indicates that a temperature decrease of about 1.5 K reduces the nucleation time of Suppocire AT by approximately one half (Fig. 4).

The total heat of crystallization obtained from the areas under the solidification curves is also given in Fig. 4 as a function of the crystallization temperatures

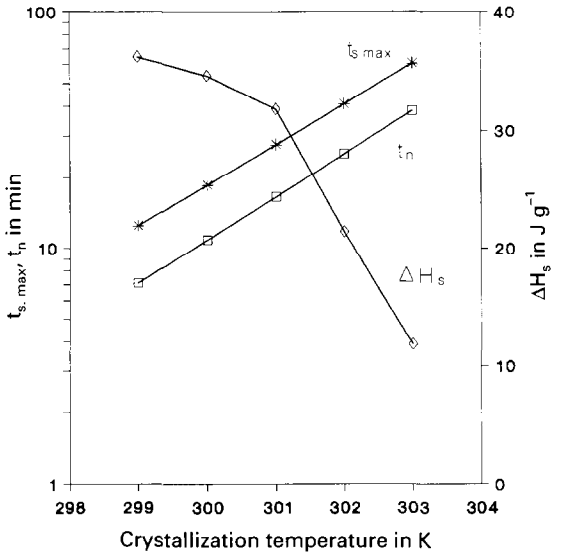

Fig. 4. Crystallization parameters for Suppocire AT obtained by isothermal DSC. $t_{s,max}$, Time of maximal solidification rate; t_n, nucleation time; ΔH_s, heat of solidification released.

Table 2
Final solidification levels of Suppocier AT as a function of crystallization temperature measured by isothermal DSC and NMR spectrocopy

Crystallization temperature/K	Final solidification level S_f	
	Isothermal DSC	NMR
298	–	48.9
299	36.6	–
300	35.2	36.8
301	32.1	
302	21.6	22.2
303	11.9	–
304		6.1

studied. The integral heat is diminished at higher temperatures. If little heat of crystallization is released, the solidification level is low. In order to quantify the extent of solidification of Suppocire AT, the melting enthalpy ΔH_s of a stored sample was measured using the same apparatus and found to be 99 J g^{-1}. A sample stored for more than 12 months can be assumed to be completely solidified. Considering that the same quantity of heat is released in the crystallization as consumed upon melting, the solidification levels depicted in Table 2, which were obtained at different crystallization temperatures, can be assumed to represent the final solidification levels. It may be difficult to determine fractional areas under the DSC curves and the quotient is only valid if crystallization is measured up to its apparent preliminary endpoint. If the experiment is terminated before completion, and the integration stops too early, there is a risk of underestimating ΔH_s, particularly since the return of the signal to the baseline is difficult to verify.

For the sake of comparison, solidification levels obtained by NMR after 60 min are given in Table 2.

3.2. NMR spectroscopy

The results obtained with Suppocire AT under isothermal conditions by NMR for observation intervals of 60 min at temperatures between 278 and 304 K are displayed in Fig. 5.

This graph confirms the observation that crystallization begins earlier with more pronounced supercooling and that the solid fat fraction increases earlier at lower crystallization temperatures.

Additionally, the SFC curves indicate that crystallization is a biphasic process, with a transition from the shoulder observed at 298 and 300 K to an extended plateau at 302 to 304 K. This initial rise of the solid fat fraction is caused by the chemical composition of the base. The hydroxyl value of Suppocire AT ranges from 25 to 35, with a preferred value of 32, which is obtained by adding monoglycerides (approx. 2%) and diglycerides (approx. 20% [33]). The partial glycerides crystallize

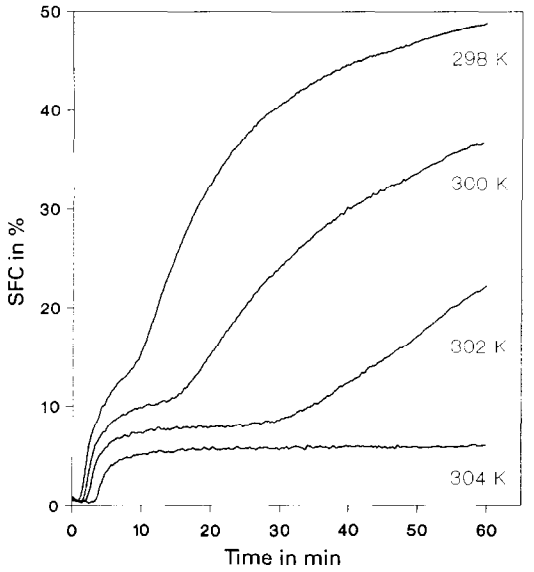

Fig. 5. Solid fat content of Suppocire AT at various crystallization temperatures.

first under the conditions studied because their melting points are higher than those of triglycerides containing the same fatty acids.

The height of the shoulder and of the plateau level decrease at higher temperatures because the extent of supercooling is reduced. The crystallization of the bulk of triglycerides is initiated on the surface of partial glyceride nuclei. In NMR studies, the intermediate plateau levels off at higher temperatures before the second phase begins because in contrast to TRG experiments the sample is at rest and not sheared. Therefore, the melt containing crystals is not mixed and secondary nucleation cannot take place. The quantity of solids after 1 h is in good agreement with results obtained by isothermal DSC (Table 2).

Differences between similar suppository bases can also be quantified by isothermal NMR as shown in Fig. 6. Whereas a biphasic fractionated crystallization is evident for both Suppocire AT and Witepsol W 35, which have a higher content of partial glycerides, the curve for Witepsol H5 is simply sigmoidal. This base has a low hydroxyl value and a narrow distribution of fatty acid chain lengths (80% C_{12} and C_{14}). Compared to the other two bases, the onset of crystallization is clearly delayed, but it proceeds rapidly within 20 min and a final level of more than 80% is achieved. Depending upon the composition of mono-, di- and triglycerides and the fatty acid spectrum, the solidification levels of various suppository bases can be quite different.

The solidification level is an important characteristic of the cooling phase if suppositories are manufactured on a large scale. After casting, they pass through a cooling tunnel in order to solidify rapidly because hardness is important for the subsequent operations of packing and shipping. For this purpose, a large fraction

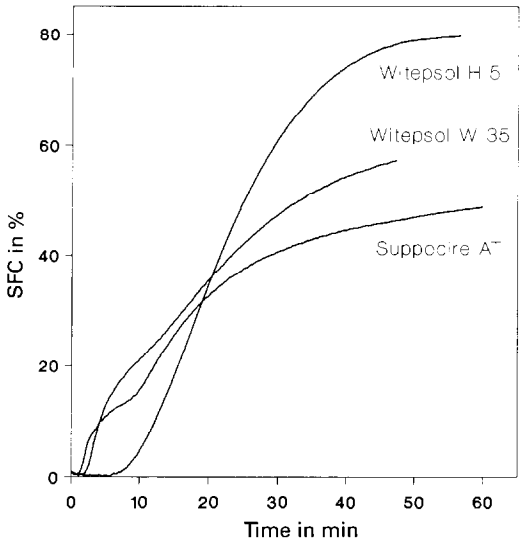

Fig. 6. Solid fat content of different hard fats at 298 K.

of the fatty matrix has to be converted to the solid state. Isothermal NMR spectroscopy can be used to optimize both the temperature in and the passage time through the cooling tunnel for specific formulations, in order to achieve the final SFC level required.

3.3. Oscillation rheometry

Measurements were carried out under controlled stress, so that the sample is permanently subjected to a constant force τ. The corresponding strain γ, which changed during the course of crystallization processes, was recorded. The storage modulus G', the loss modulus G'', and the loss factor $\tan \delta = G''/G'$ were computed for all times from the ratio of τ and γ. At the onset of crystallization, both moduli and the loss factor change almost instantaneously by several orders of magnitude; therefore the ordinate was scaled logarithmically.

Specific properties of a rheogram will be discussed taking the experiment on Suppocire AT at 304°C as an example, which is depicted in Fig. 7.

It is particularly suited for closer inspection because the process of crystallization takes more than 15 min under these conditions and is not completed within a few seconds as in other cases.

Initially, only two dependent variables can be distinguished because the loss factor, given by the quotient of G'' and G' remains constant at the upper edge of the graph. This indicates that $G'' \gg G'$ and hence the sample is in the completely liquid state. During the first half hour, the G'' curve rises slightly because the viscosity of the melt is also temperature dependent and increases while the sample is cooled. After 33 min the final temperature is attained, but crystallization does not start yet so that G'' remains constant. After 50 min G'' starts to rise indicating a

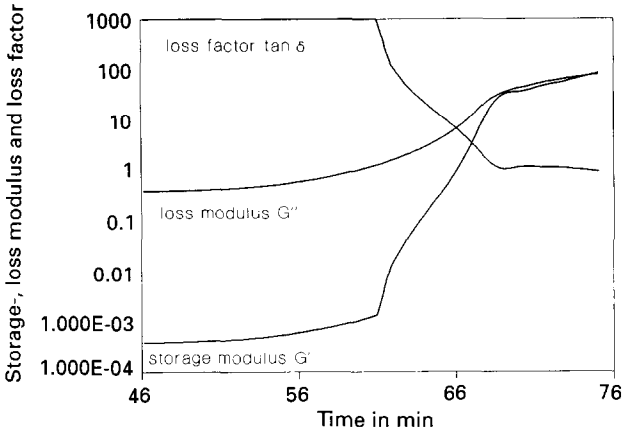

Fig. 7. Oscillation rheometric parameters of Suppocire AT at 304 K.

change of rheological properties due to the onset of nucleation. However, the loss factor tan δ is still at the upper edge of the graph, which means that the ratio of viscous and elastic components is still greater than 1000:1. The first change of the storage modulus is recorded after 67 min, a value of $G' > 10^{-1}$ corresponds to a volume fraction of crystals of about 6%.

From this time on, the solid fraction increases continuously and the quotient of G'' and G' enters the measurable range. During the initial phase of crystallization, the loss factor decreases rapidly, but after the 69th minute, the values of storage and loss modules are nearly equal so that tan δ remains constant. During this interval half of the volume of the hard fat base is solid and half liquid.

Fig. 8 shows the results of analogous experiments with Suppocire AT at 298, 301 and 304 K, which indicate that differences in the initial phase of crystallization are

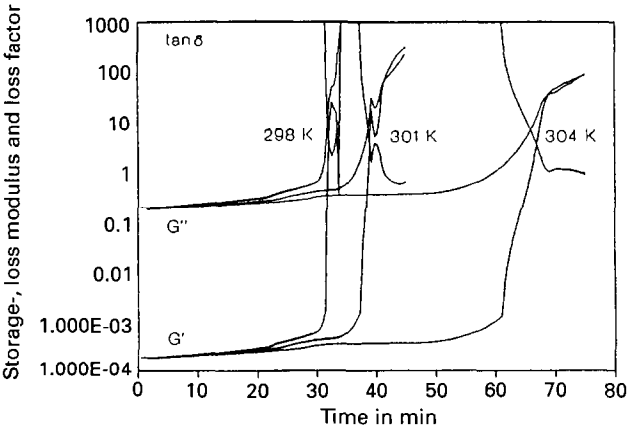

Fig. 8. Differences of oscillation rheometric parameters of Suppocire AT at three crystallization temperatures.

much higher at lower temperatures; however, the dependent variables change much more rapidly. At a high rate of solidification, a significant quantity of heat of crystallization is released in a short time. Because of the high viscosity and low thermal conductivity of the melt, heat generated cannot be taken up immediately by the cooling surfaces of the sample container. The resulting short transient temperature increase can cause fractions of already solidified fat to melt again so that the storage modulus can decrease temporarily although crystallization proceeds (see 298 K results in Fig. 8).

3.4. Thermorheography

Torque profiles obtained with Suppocire AT at various temperatures are shown in Fig. 9. Depending upon the degree of supercooling, the curves differ with respect to nucleation time and solidification gradient. It is evident that nucleation times increase with increasing external temperature and that the solidification rate, which manifests itself in the more gentle slopes of the terminal sections, decreases correspondingly.

A prominent feature of the solidification profiles shown is a shoulder, which is pronounced at low crystallization temperatures, shifted toward lower torques as the degree of supercooling decreases and finally disappears at 303 K. This phenomenon was also observed on NMR. It is due to the elevated content of partial glycerides, which tend to form intermolecular hydrogen bonds between glycerol free hydroxyl groups and fatty acid carbonyls. For lauric mono- and diglycerides, melting points between 323 and 333 K have been observed [34]. With respect to partial glycerides, the degree of supercooling is therefore much more pro-

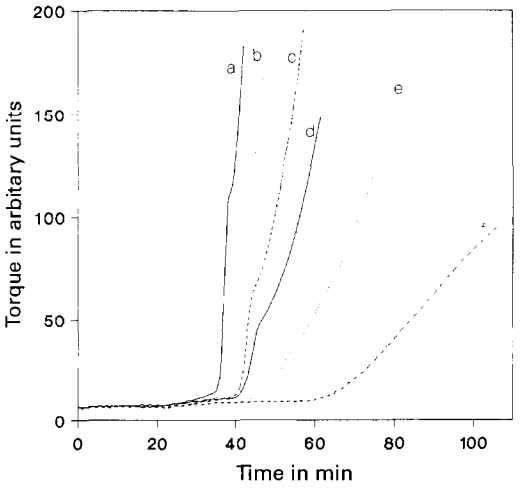

Fig. 9. Torque profiles of Suppocire AT as a function of crystallization temperature. Key: a, 293 K; b, 295 K; c, 297 K; d, 299 K; e, 301 K; f, 303 K.

nounced than for the triglycerides constituting the bulk of the mixture. Under the thermal conditions studied, it appears that partial glycerides solidify first and form crystal nuclei, which grow by accretion of triglycerides. The phenomenon of biphasic crystallization was observed in all suppository bases with elevated hydroxyl values.

4. Discussion

The results of our study indicate that isothermal DSC, NMR spectroscopy, oscillation rheometry and thermorheography are suited to characterize various aspects of the time course of crystallization of suppository bases.

While all methods can be used to study the effect of temperature on nucleation time, only those in which the sample is not sheared yield information concerning the solidification level. If NMR is used, the SFC can be observed directly as a function of time, whereas from isothermal DSC data it has to be calculated as the ratio of two areas. Because the latter procedure is prone to error, and considering the simpler operation, NMR spectroscopy offers distinct advantages in determining the extent of solidification.

This parameter is of interest for the optimization of temperatures and residence times of suppositories in the cooling tunnel. Since DSC apparatuses and NMR spectrometers have become standard analytical equipment, they should also be used to improve production processes.

The methods, in which the melt is subject to shear, are suited to study the crystallization behaviour of suppository bases under conditions closer to those prevailing in the manufacturing operation. The principles of oscillation rheometry and thermorheography have been discussed above. If similarity to production conditions is important, the latter is advantageous because both sample container and stirrer resemble devices used in corresponding large scale industrial operations.

The shape of the stirrer precludes the measurement of absolute viscosities, but absolute values are not required if only changes of resistance are of interest, which indicate the onset and progress of crystallization. For this purpose, apparent viscosities and arbitrarily scaled torques are sufficient.

While the non-shear methods are valuable for the optimization of cooling conditions, which affect the terminal part of the solidification process, techniques in which samples are subjected to a strain allow the rheological behaviour of the melt under dynamic conditions to be studied, which correspond to the situation immediately before and during the moulding process.

Because it has been found that several apparatuses can be used to characterize the solidification behaviour of fatty suppository bases, it is suggested that an update of present pharmacopoeial requirements for hard fat by a test of solidification properties be considered. In the laboratory, a thermorheographic technique using a rotational viscometer could be used. Since this would have to be a conventional method, for which exact conditions have to be specified, the experiments reported could serve as a starting point.

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