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Methods of studying aging and stabilization of spray-congealed solid dispersions with carnauba wax. 1. Microcalorimetric investigation

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Abstract

Rapidly cooled materials are often unstable as a result of changes in their physical properties due to imperfect crystallization. In the process of spray-congealing, melted material is atomized into droplets which very quickly solidify. This increases the possibility of the material crystallizing in different metastable forms. In this study it is shown that isothermal microcalorimetry can be used to observe the change in the thermodynamic state of spray-congealed carnauba wax during storage. In order to accelerate the thermodynamic change in the spray-congealed wax, three annealing procedures have been developed and compared using isothermal microcalorimetry. By means of annealing, a spray-congealed product closer to a thermodynamically stable state has been achieved. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Microcalorimetry; Solid dispersion; Aging; Stabilization; Annealing; Spray-congealing

1. Introduction

Carnauba wax is an ester wax of vegetable origin, which is extracted from the leaves of the Brazilian carnauba palm (Hackett, 1969). The chemical compounds that constitute carnauba wax are mainly aliphatic esters, uncombined alcohols, ω-hydroxy esters, *p*-methoxycinnamic aliphatic diesters, and *p*-hydroxycinnamic aliphatic diesters composed of several chain lengths, in which C_{26} acids and C_{32} alcohols predominate (Vandenburg and Wilder, 1970; Tulloch, 1974; Valmalle and Karleskind, 1977). Although carnauba wax is a natural product, different types of it are known to have essentially the same composition (Vandenburg and Wilder, 1970), with a melting range of 82–85.5°C (Budavari et al., 1989), despite the wide distribution of compounds that make the wax a multicomponent system.

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Carnauba wax is one of the classic excipients used in pharmaceutical formulation work, e.g. as a glossing agent. It has also been suggested as a potential matrix material or even as a solvent for solid dispersions for sustained-release tablets (Dakkuri et al., 1978; Schroeder et al., 1978) or microspheres manufactured by coacervation (Madoule, 1981; Bodmeier et al., 1992; Giannola, 1995), spray-congealing (Mattsson et al., 1993; Madoule, 1996), or extrusion (Ghali et al., 1989; Miyagawa et al., 1996; Sato et al., 1997).

The concept of solid dispersion has been thoroughly investigated by numerous authors since it was first suggested as a means of increasing the dissolution properties of sparingly soluble sulfathiazole (Sekiguchi and Obi, 1961). Most authors have investigated the possibility of increasing the absorption of insoluble or sparingly soluble drugs by increasing the dissolution rate by dispersion in easily dissolvable matrix material such as polyethylene glycols, sugars, citric or succinic acid, polyvinylpyrrolidone, or urea (Kreuter, 1983; Corrigan, 1985; Ford, 1986). A number of authors have explored the possibility of retarding, sustaining, or prolonging the release of a drug substance or controlling the site of dissolution by dispersing drugs in, for example, polymethyl methacrylate, hydroxypropyl methylcellulose, ethylcellulose, etc. (El-Gindy et al., 1976; Oth and Moës, 1989; Dangprasirt and Ritthidej, 1995). Carnauba wax has also been suggested as a possible matrix material in the latter sense (De Luca et al., 1977; Schroeder et al., 1978; Miyagawa et al., 1996; Sato et al., 1997).

Three methods of manufacturing solid dispersions have been described (Chiou and Riegelman, 1971): the melting or fusion method, the solvent method, and the melting-solvent method. It has been observed that the cooling rate is of great importance for the technical properties of the product manufactured by the fusion method, such as the release of the incorporated active ingredients (Collett et al., 1976; Sjökvist Saers et al., 1993; Larhrib and Wells, 1997). Control of the cooling rate can be accomplished by using the unit operation of spray-congealing, where small droplets of melted material solidify very rapidly in cool air (Killeen, 1993). This solidification in air also enables the material to adopt its natural conformation without the risk of inheriting a conformation from a solid material in contact with the congealing wax (Klug and Alexander, 1974). The process is particularly suitable for large-scale production because it can be operated continuously (Kanig, 1964; Kreuscher et al., 1980). The fast and reproducible solidification in the process of spray-congealing is, however, a drawback due to the very rapid crystallization that takes place in the material. The possibility of introducing instability into the product, partially or totally, when the melt solidifies must be considered.

Isothermal microcalorimetry is a highly sensitive method of comparing the thermodynamic state of differently treated samples of the same substance. The aim of this study was to evaluate whether isothermal microcalorimetry could be used to study the change in thermodynamic state of pure spray-congealed carnauba wax during storage. The accelerating influence of elevated storage temperatures has also been studied in order to explore the possibility of stabilizing the product by thermal treatment.

2. Materials and methods

2.1. Materials

Carnauba wax prime yellow powder, Imchem, Sweden, and carnauba wax prime yellow, in pieces, Malmsten & Bergwall AB, Sweden, used as supplied.

2.2. Spray-congealing

The spray-congealing unit (Drytec Ltd, UK) consists of a cylindrical section (diameter 1.95 m, height 1.90 m) with a conical base having a 65° angle. It is equipped with a rotating disc (diameter 200 mm) with 24 vanes (3 × 12 mm) placed in the top of the cylindrical section. The process parameters used were: speed of disc rotation 12 000 rpm, feed rate 0.5 kg/min, feed temperature 95–105°C, volume of cooling air 400 m^3/h (co-current), and air temperature 14–17°C.

Melted carnauba wax was charged to the rotating vaned disc. The hot melt immediately atomizes into small droplets, which solidify in the cool airstream as small spheres (median particle size: 80–110 µm).

2.3. Annealing

Samples from the freshly solidified material were stored for 2 days at elevated temperatures (40, 50, 60°C) in heating cabinets, followed by storage at room temperature before the microcalorimetric measurement.

2.4. Isothermal microcalorimetry

The microcalorimetric system used was the 2277-201 Thermal Activity Monitor (TAM), Thermometric AB, Sweden. A sample of about 500 mg was weighed into a 3-ml glass ampoule designed for use in the calorimeter and crimp-sealed with a rubber stopper with an aluminum overseal. An empty glass ampoule with a similar seal was used as reference. The analysis temperatures used were 25, 35, and 45°C. The analysis temperature was optimized to 45°C for the ensuing analyses. The calibration was performed electrically. The samples and references were equilibrated in the calorimeter for 15 min before being lowered into the measuring position. The measuring time was at least 24 h. During the analysis the rate of change of heat content (dq/dt) was recorded as a function of time. Exothermic reactions are presented as positive and endothermic reactions are presented as negative. Single analysis have been performed on all samples except for one sample, for which quadruple analyses were performed in order to estimate reproducibility.

3. Results

In Fig. 1 the results of the analysis performed at 25°C on both untreated and annealed samples are presented. The untreated sample shows an initial exothermic effect, which decreases and levels out after about 150 min at ≈ 0.5 µW. The curves for the treated samples all show alternating exothermic and endothermic effects close to 0. The endothermic and exothermic responses from the analysis of the treated samples which are located right at the beginning of the recording phase are too small to be distinguished with cer-

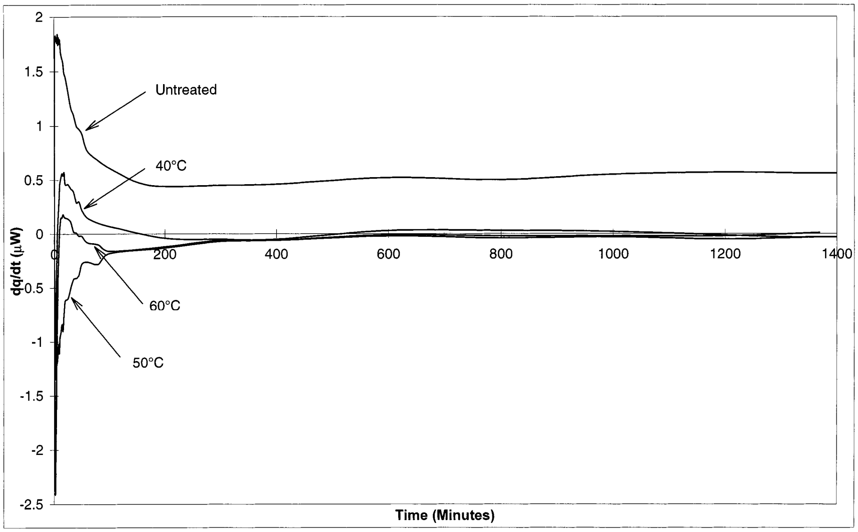

Fig. 1. Microcalorimetric investigation of spray-congealed carnauba wax annealed for 2 days at 40, 50, or 60°C, stored for 5 days at room temperature, and measured at 25°C, compared to an untreated sample of the same age.

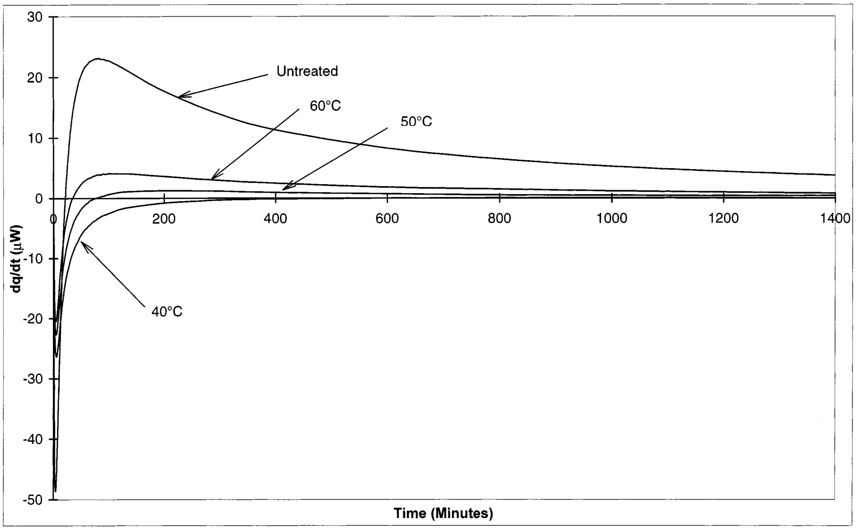

Fig. 2. Microcalorimetric investigation of spray-congealed carnauba wax annealed for 2 days at 40, 50, or 60°C, stored for 5 days at room temperature, and measured at 35°C, compared to an untreated sample of the same age.

tainty from possible disturbing effects, such as friction when the ampoules are lowered into the measuring position. The output values recorded when the response becomes stable are too small to be reliably distinguished from 0. The effect resulting from the untreated sample is also small, although in contrast to the annealed samples it is consistent over 21 h of the 24-h analysis presented.

Fig. 2 shows the results of the analysis performed at 35°C. All the samples initially show endothermic reactions, which change to exothermic. The endothermic reaction is fastest for the untreated sample, followed by the samples annealed at 40, 50, and 60°C, respectively. The exothermic reaction dominates the response of the untreated sample after only about half an hour of analysis, followed by the sample treated at 60°C, which shows an exothermic reaction after about 40 min of analysis. The samples annealed at 50 and 40°C then follow, with exothermic reactions predominating from 1.5 and 6 h, respectively. After 24 h of analysis only minor exothermic reactions persist for the treated samples, the largest being for the 60°C sample followed by the 50°C sample and the 40°C sample, while the unannealed sample still shows an effect of about 4 µW.

The results of the analysis performed at 45°C are presented in Fig. 3. The untreated sample shows a large exothermic effect in contrast to the treated sample, which after an initial endothermic effect of different sizes only shows minor exothermic effects. The exothermic reaction is dominant after only a few minutes, after about half an hour and after about 2 h, respectively, for the annealed samples. The exothermic effects after 24 h of analysis for the treated samples are larger than during analysis at 35°C, indicating faster reaction rates, but occur in the same order, i.e. 60, 50, and 40°C.

Increased temperature accelerates the reaction rates, and consequently the largest differences between samples were detected at an analysis temperature of 45°C, which was therefore chosen as the temperature for further analysis. Temperatures higher than 45°C have not been tested in order not to interfere with the phase transition in the range 57–66°C. (Basson and Reynhardt, 1988). The choice of this analysis temperature does not permit stability predictions regarding room temperature, but does allow comparisons with a standard. A sample of the raw material at least 5 years old has been used as comparative sample, on the assumption that it is close to a

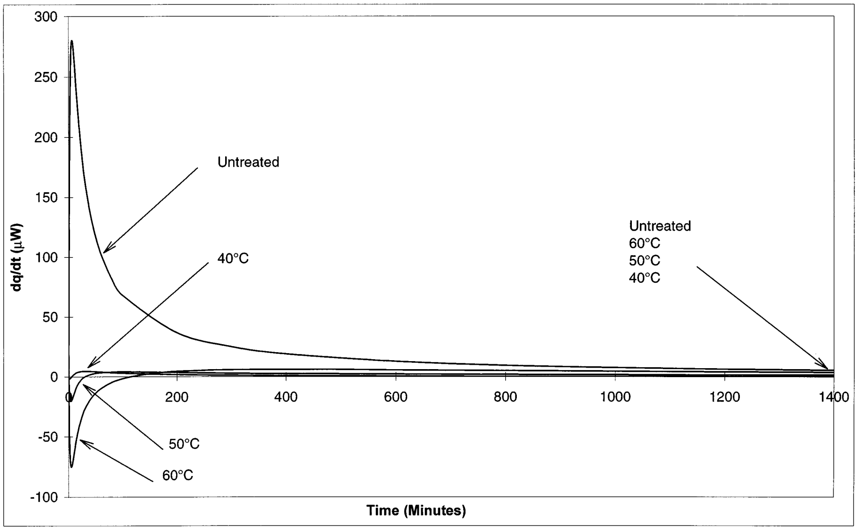

Fig. 3. Microcalorimetric investigation of spray-congealed carnauba wax annealed for 2 days at 40, 50, or 60°C, stored for 5 days at room temperature, and measured at 45°C, compared to an untreated sample of the same age.

thermodynamic stable state. Its performance during analysis at 45°C has in this case been chosen as measure of stability.

The reproducibility of the microcalorimetric analysis at 45°C is demonstrated in Fig. 4, where four equivalent experiments are compared. The figure demonstrates the investigation of the spray-congealed carnauba wax after storage at room temperature for 6 months. The result shows small differences between the curves. The shift from an endothermic to exothermic reaction takes place for all channels in the course of 2 min, the maximum value being between 45 and 51 μW. All channels show their maximum value after 47 min.

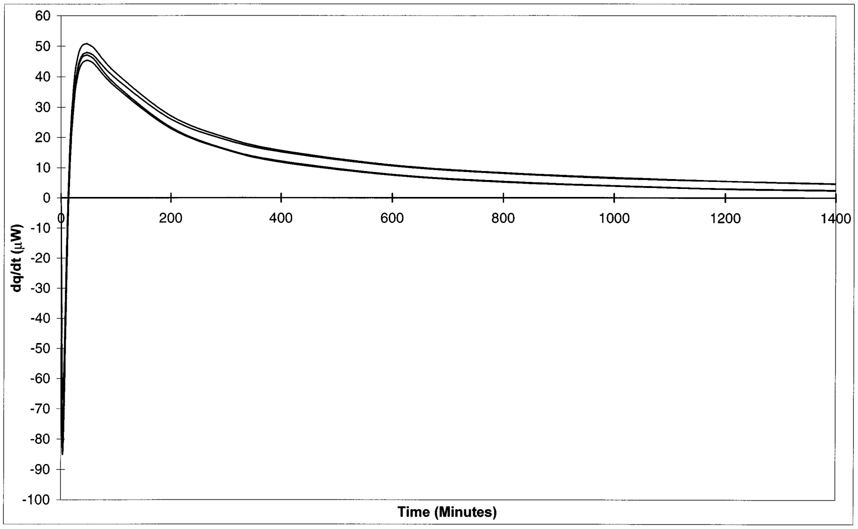

Fig. 4. Microcalorimetric investigation at 45°C of four equivalent samples of spray-congealed carnauba wax after storage at room temperature for 6 months.

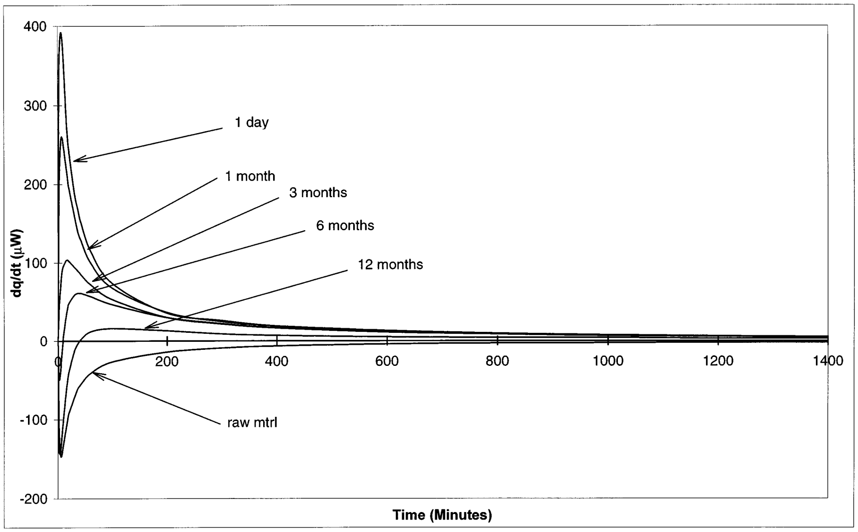

Fig. 5. Microcalorimetric investigations at 45°C of spray-congealed carnauba wax after storage at room temperature, compared to the raw material.

After 1400 min the differences between the channels are less than 2.5 µW.

Fig. 5 demonstrates the change in a spray-congealed material during storage at room temperature in comparison to the raw material. The measurements in the graphs were made at 45°C. Liberation of heat during measurement of the relatively freshly prepared material is observed, which decreases during storage and gradually changes in the direction of an initial endothermic reaction similar to the form of the graph of the raw material. The thermodynamic state of the spray-congealed carnauba wax obviously changes during storage in the direction of that of the standard. This change can also be seen in Fig. 1 as a continuous exothermic process which releases 2.5 µW.

Figs. 6–8 give examples of experiments with annealed materials and a measuring temperature of 45°C. The spray-congealed material was annealed for 2 days at 40, 50, or 60°C and then stored at room temperature preceding the measurement. The diagrams show that the state of the material has changed during the annealing process and continues to change after the annealing procedure is terminated. The exothermic reactions are significantly smaller than for an untreated sample of the same age. The reduction of the exothermic contribution is obviously very slow, but it is accelerated by the annealing procedure, which can be seen when comparing Figs. 5–8. The endothermic part of the graph also changes and becomes more and more significant.

For each annealing temperature, the results show a significantly reduced and delayed exothermic contribution, which decreases with storage time. The initial endothermic heat flow increases with storage time. No exothermic contribution is shown by samples annealed at 50 and 60°C and stored for 12 and 6 months, respectively.

4. Discussion

The principle behind isothermal microcalorimetry is based on the fact that almost all physical and chemical processes are accompanied by heat changes, the heat flow to or from a sample being recorded versus time and compared to the heat flow to or from a reference (Buckton and Beezer, 1991; Angberg, 1992; Briggner et al., 1994). The reaction rate is at all times proportional to the effect (dq/dt) and the integral of the curve is equal to the heat (Q) absorbed or evolved by the

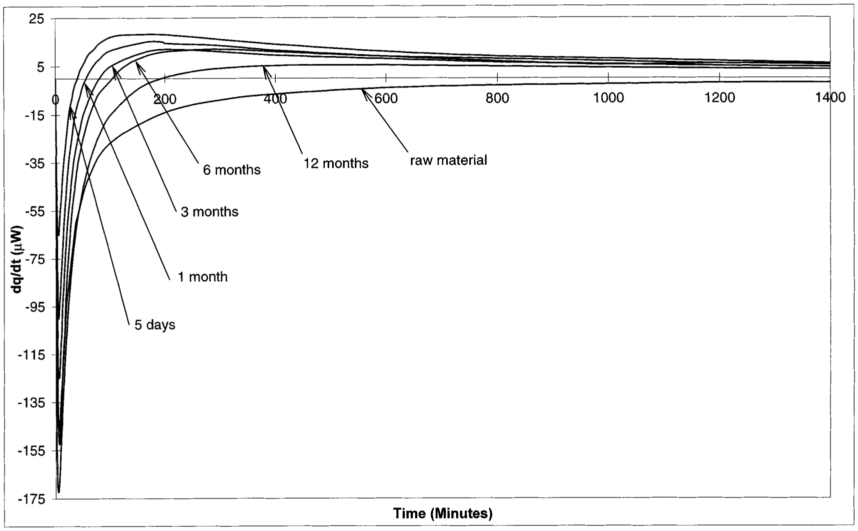

Fig. 6. Microcalorimetric investigations at 45°C of spray-congealed carnauba wax annealed at 40°C for 2 days and stored at room temperature preceding the measurements, compared to the raw material.

system. The sum of the highest reaction rates is described by peaks in the graph.

Isothermal microcalorimetry has several advantages (Buckton and Beezer, 1991). In the course of a few hours of analysis a reaction with a half-life of 17 years can be detected, which means that the result of a stability study lasting several years can be predicted in less than 24 h. However, the technique unfortunately has drawbacks, e.g. the unrecorded equilibration time preceding the measurement, when important processes may be occurring undetected, as well as the fact that all processes taking place in the sample are measured, which may make the response difficult to

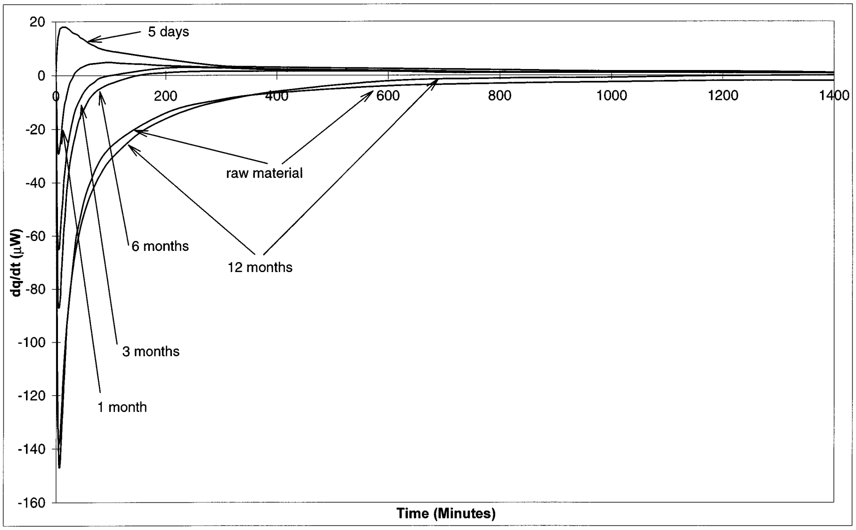

Fig. 7. Microcalorimetric investigation at 45°C of spray-congealed carnauba wax annealed at 50°C for 2 days and stored at room temperature preceding the measurements, compared to the raw material.

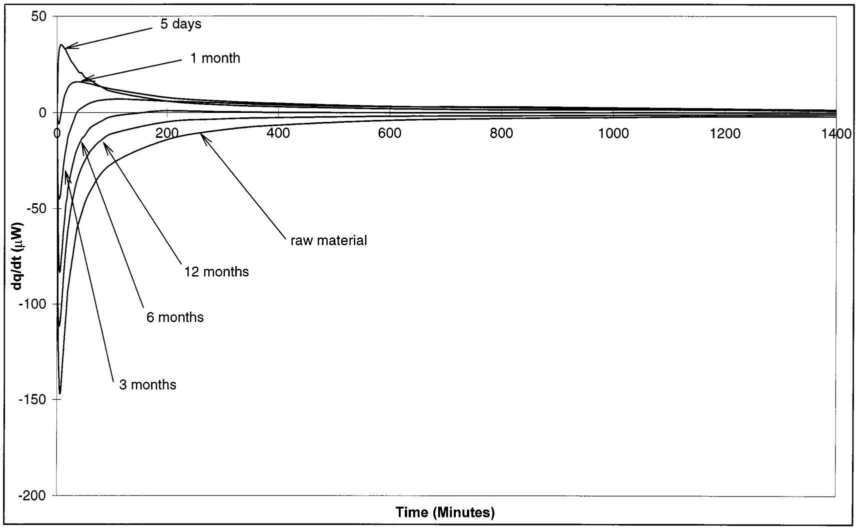

Fig. 8. Microcalorimetric investigations at 45°C of spray-congealed carnauba wax annealed at 60°C for 2 days and stored at room temperature preceding the measurements, compared to the raw material.

interpret if several processes are ongoing simultaneously. It has, however, been successfully used in the pharmaceutical field to study changes of crystallinity due to water uptake (Angberg et al., 1991) or induced crystal changes during the processing of powders (Briggner et al., 1994), to assess the degree of disorder in both lactose (Sebhatu et al., 1994) and hydrophobic powders (Ahmed et al., 1996), and to study the oxidation of phosphatidylcholine (Singh et al., 1996).

The results obtained in the microcalorimetric analysis show a performance dependent on age and temperature history connected to analysis temperature. The complex combination of exothermic and endothermic reactions and the switch from one to the other is probably just a matter of reactions with opposite signs taking place at the same time and recording their total.

A higher analysis temperature allows all reactions to proceed at a higher speed, and consequently the maximum response (heat per time, dq/dt) is greater, even though the integral (total heat, Q) may be the same. It is not meaningful, however, to calculate the integral in this particular case since part of the reactions take place during the unrecorded tempering phase that opens the analysis. Recording during this phase is not recommended because large disturbances are introduced into the system when the sample and reference (differing in temperature from the microcalorimeter) are immersed. Endothermic reactions can be expected when there is a difference between the storage and the measuring temperature. However, this change is already complete during the 15 min equilibrium time preceding the measurements and does not influence the shape of the graph.

The peaks in the graphs after 3–5 min of recording are not true peaks but a reflection of the inertia of the system. This should be interpreted as a continuous process which started during the unrecorded tempering phase.

When carnauba wax is allowed to solidify in the spray-congealing process, it is quenched from about 90°C to close to room temperature in a fraction of a second. It is most likely not possible for all of the molecules to adopt a stable configuration before the material is solid and some crystal defects can be expected, as with any process using rapid cooling. The graphs recorded at 25°C show that an exothermic reaction is ongoing in the untreated sample throughout the analysis, indicating a possible aging/stabilizing process. No evidence of a continuous process going on in the treated samples has been found in this analysis at 25°C. At analysis temperatures of 35 and 45°C the exothermic contribution for the unannealed sample is even greater. Analyses at 45°C of untreated samples stored different periods at room temperature reveal that changes are taking place during storage. The recorded graphs gradually approach the shape of the graph of the 5-year-old raw material, i.e. the standard. The exothermic reaction decreases in size and the endothermic reaction increases. These findings prove that an exothermic reaction taking place in the untreated spray-congealed carnauba wax during storage very slowly changes the quenched material towards the thermodynamic state of the raw material.

An untreated sample analyzed at 45°C continues to show an exothermic reaction after 2 days of analysis (data not shown), indicating that a stable state has not yet occurred. Samples annealed at temperatures close to this analyzing temperature will also most likely not have attained a completely thermodynamic stable state but a state close to it. (It must be remembered that analyzing at a temperature above the storage temperature is also an annealing process.)

During the 2 days of annealing, the temperature increase will probably have allowed increased mobility in the solid crystal lattice and fusion of material in high-energy states as well as low-melting crystalline components. Basson and Reynhardt (1988) reported the amount of liquid in carnauba wax to be a few percent at 40 and 50°C, increasing to $\approx 35\%$ at 60°C. The increased mobility caused by the temperature rise gives the carnauba wax molecules an opportunity to rearrange themselves in a more advantageous configuration seen as an exothermic reaction. The rearrangement process most likely decreases the mobility when disordered material is allowed to adopt an ordered configuration, leading to a slowdown in the speed of the rearrangement process, seen in the graphs as a gradual lowering of the exothermic reaction for the untreated samples. When the annealing process is finished and the temperature is suddenly lowered to room temperature, the molecules lose their increased mobility and melted components are once again at risk of adopting an unstable configuration.

The initial endothermic reactions for all samples when analyzed at 35°C probably already took place during the unrecorded tempering phase when the analysis is performed at 45°C. The endothermic reactions for the treated samples may represent fusion of low-melting crystalline components or a structural change in the crystal lattice which carnauba wax is reported to undergo when heated (Basson and Reynhardt, 1988).

The result of analyzing four samples of the same origin at 45°C in all four channels of the TAM shows little difference between the curves. The difference between the time and size of the maximum endothermic response as well as the time and the size of maximum exothermic reaction is less for the four samples than for other analyzed samples. The difference between the curves after the maximum exothermic reaction is in some cases of the same size as for annealed samples of successive age. However, by studying analysis of samples stored for longer periods of time as well, conclusions can be drawn. Also, the response after the maximum exothermic reaction corresponds to a diminishing amount of reacting sample which approaches 0 and consequently the absolute difference to 0, as well as difference between samples, becomes naturally less.

Treatment of spray-congealed carnauba wax samples at 40, 50 and 60°C for 2 days is a powerful means of reducing the exothermic contribution to a size comparable to an untreated sample stored for 3–6 months. However, the exothermic reaction is not eliminated and the samples continue to change during storage, as seen by the results from analysis of stored annealed samples at 45°C, although no evidence of change has been verified in the analysis at 25°C.

The resulting graphs from the microcalorimetric analysis of spray-congealed carnauba wax are complicated reflections of the samples' thermal history. When the annealing process, introduced to stabilize wax quenched from 95 to 105°C, is terminated, the material is once again quenched from this particular temperature to room temperature and then exposed to the analysis which can be regarded as a second annealing. When analysis is performed at a temperature lower than the first annealing temperature, i.e. 35°C, the crystalline parts which formed during the preceding annealing and the amorphous parts which formed when the annealing suddenly stopped and which melt below the analyzing temperature will fuse, giving rise to an endothermic response. An exothermic contribution to the response is formed by crystallizing fused or solid amorphous parts. The graphs for the treated samples consequently show rapid endothermic reactions followed by exothermic reactions. The largest exothermic reaction for the annealed samples was thus recorded for the 60°C sample, while the 40°C sample shows the least reaction, with the 50°C sample in between.

Analyzing at an intermediate temperature like 45°C gives a complicated response. Analyzing of the sample annealed at 40°C involves an additional annealing, with a release of exothermic energy which is larger than for the samples annealed at higher temperature. For the samples annealed at 50 and 60°C, the principal result is the same as for analyzing at 35°C.

The result after the annealing process is thus not uniform but dependent on the annealing temperature. Different equilibrium states seem to prevail at different temperatures.

The results of further investigations, e.g. DSC and X-ray, will be reported in a later publication.

5. Conclusions

Spray-congealed carnauba wax exists in an unstable state and slowly ages during storage towards a stable state. By means of an annealing procedure whereby the carnauba wax spheres are treated at elevated temperature, the speed of the stabilization process can be accelerated. However, the material does not reach a fully stable state after the annealing procedure but a thermodynamic state closer to the stable state and continues to change during storage. The analyses have indicated that carnauba wax has different stable states at each temperature.

These investigations have shown that it is possible to observe the aging and the effect of annealing on the stabilization of spray-congealed carnauba wax by isothermal microcalorimetry. The stabilization process is delayed at room temperature but can be significantly accelerated by an annealing procedure at temperatures as low as 40–60°C.

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