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Research paper

Critical processing factors affecting rheological behavior of a wax based formulation

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Abstract

The use of a wax-based vehicle is one approach to stabilize a drug which is susceptible to hydrolysis and/or oxidation. The drug used in the study, as a microfine powder, is dispersed in the wax mixture and encapsulated in a soft gelatin capsule. To ensure reproducibility of drug content uniformity and encapsulability of the soft gelatin capsule dosage form, optimal viscosity and lot to lot uniformity of the viscosity of the suspension are required. The objective of the study was to identify the critical processing factors which could affect the rheological behavior of the wax based vehicle. Rheological behavior of the vehicle at temperatures ranging from 15 to 90°C was evaluated using a CSL Rheometer equipped with parallel plates and a shear rate sweep mode, unless otherwise specified. Viscosity vs. temperature profiles of the vehicle were determined using the same conditions at different cooling rates ranging from 1.3 to 20°C per min. Three distinct regions of phase transition of the wax mixture can be seen in the Arrhenius plot: (i) a sol region at temperatures above 50°C, (ii) a transition of gel to sol at temperatures ranging from 30 to 45°C, and (iii) a gel region at temperatures below 30°C. The vehicle in a sol region behaved as a Newtonian fluid, indicating minimal interactions between the hydrocarbon chains of the vehicle. The vehicle in a gel region behaved thixotropic in nature, as indicated by a hysteresis loop. The shear rate had a more pronounced effect on the area of thixotropy than the shear time. The cooling rate had a pronounced effect on the resultant viscosity. At the same applied shear rate, the vehicle which was cooled at a faster rate, may cause a recrystallization of the wax mixture in different crystalline forms, resulting in a higher viscosity than the vehicle cooled at a slower rate. This effect was more pronounced when the shear was applied at a lower rate. The results of this study indicate that shear rate and cooling rate are the critical processing factors in controlling the viscosity of the final product and must be well controlled in the manufacturing procedure.

Keywords: Wax-based; Rheological behaviour

1. Introduction

The use of a wax-based vehicle is one approach to stabilize a drug which is susceptible to hydrolysis and/or oxidation [1]. During the early stage of product development of an oxygen-sensitive compound utilizing a wax based formulation, it was observed that there were differences in the viscosities of some lots of the finished suspension [2]. The lots which resulted in a high viscosity suspension (>1000 cps) did not provide adequate flow and led to difficulty in soft gelatin encapsulation. The lots which resulted in a low viscosity suspension (<250 cps) exhibited a marginal drug content uniformity due to segregation of the drug during storage, prior to encapsulation and during the encapsulation process itself. The drug used in the study, a microfine powder, is dispersed in the wax mixture and encapsulated in a soft gelatin capsule. The manufacturing procedure is generally performed by melting purified beeswax, hydrogenated soybean oil and hydrogenated vegetable oil above their melting points, approximately 75°C, and mixing well until the mixture becomes liquid. The wax mixture is continuously homogenized and cooled to room temperature prior to the addition of the drug substance and other liquid excipients.

To ensure reproducibility of drug content uniformity and encapsulability, optimal viscosity and lot to lot uniformity of the viscosity of the suspension are required. The objective of this study was to identify the critical processing factors which could affect the rheological behavior and the resultant viscosities of the wax based vehicle.

2. Materials and methods

2.1. Materials

Hydrogenated soybean oil flakes (Welsch Holme &

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Clarke Co., Newark, NJ), hydrogenated vegetable oils (ADM Co., Decatur, IL), and purified yellow beeswax, NF (Strahl & Pitsch Inc., West Babylon, NY) were used for the preparation of the wax mixture in this study. These materials were used as received.

2.2. Preparation of the wax mixture

The hydrogenated soybean oil flakes, purified yellow beeswax and hydrogenated vegetable oils in a ratio of 1:1:4, respectively by weight were melted in a stainless steel jacketed vessel equilibrated at 75°C. The melted wax mixture was continuously mixed using a Lightnin® mixer at 500 rpm until it was cooled to room temperature. The mixture was kept at room temperature for 24 h prior to viscometry studies.

2.3. Viscometry and rheological studies

Viscosity versus temperature profiles of the wax mixture were performed using a CSL Rheometer (TA Instruments, New Castle, DE). Parallel plates with 2″ in diameter, 100 μm gap setting using a constant shear rate, as specified, were used in the study. The samples were equilibrated to 90 ± 0.1°C on a thermostatically controlled jacketed assembly in order to maintain the sample temperature. The samples were cooled to 15 ± 0.1°C at different rates ranging from 1.3 to 20°C/min by a circulating water bath.

Rheological behavior of the wax mixture was evaluated using the shear rate sweep mode by increasing the shear rate from 5 to 4500 s^{-1} and then reverting it to 5 s^{-1} over a 4-min time span at different temperatures (15–90°C), otherwise as specified.

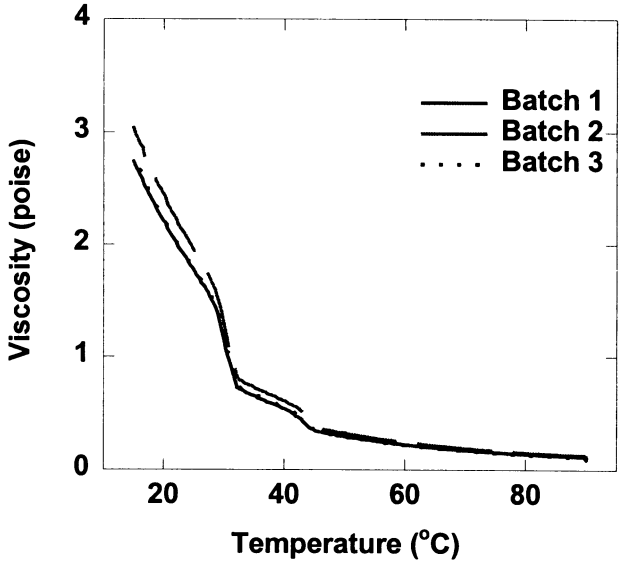

Fig. 1. Viscosity versus temperature profiles of the wax based vehicle prepared by different lots of the excipients.

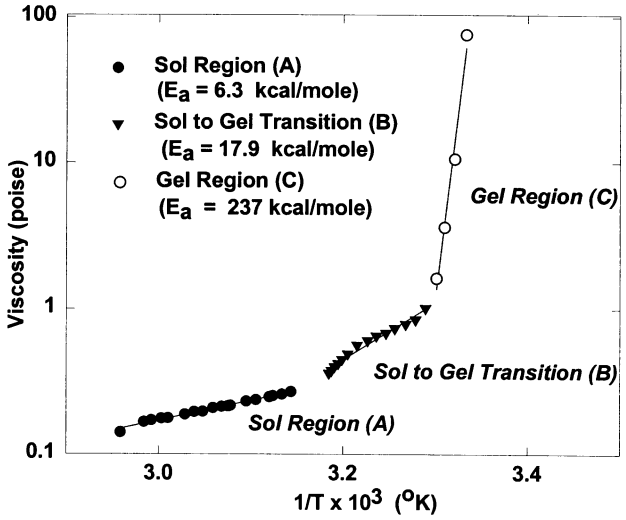

Fig. 2. Arrhenius plot of logarithm of the viscosity as a function of the reciprocal temperature of the wax based vehicle.

2.4. Differential scanning calorimetry (DSC)

2.4.1. Raw materials

Hydrogenated soybean oil flakes, hydrogenated vegetable oils and purified beeswax were analyzed by DSC using a Seiko Instrument SSC/5200 (Haake, Washingtonville, NY) at heat rate of 5°C/min with nitrogen flow rate of 50 ml/min. and a sample weight of approximate 5–10 mg in a closed pan.

2.4.2. Wax mixture

Four samples of the wax mixture prepared from the rheological studies using different cooling rates of 1.3°C/min and 15°C/min along with different shear rates of 500 s^{-1} and 4500 s^{-1} were analyzed by DSC using a Seiko Instrument SSC/5200 at heat rate of 10°C/min with nitrogen flow

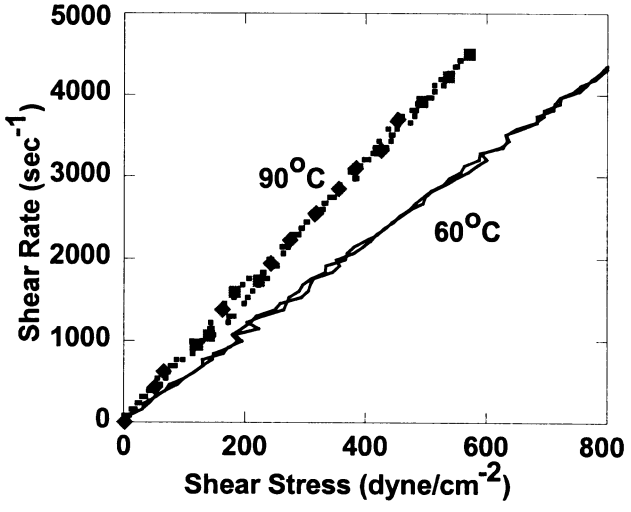

Fig. 3. Shear stress versus shear rate profiles of the wax based vehicle at 60–90°C, indicating a newtonian behavior.

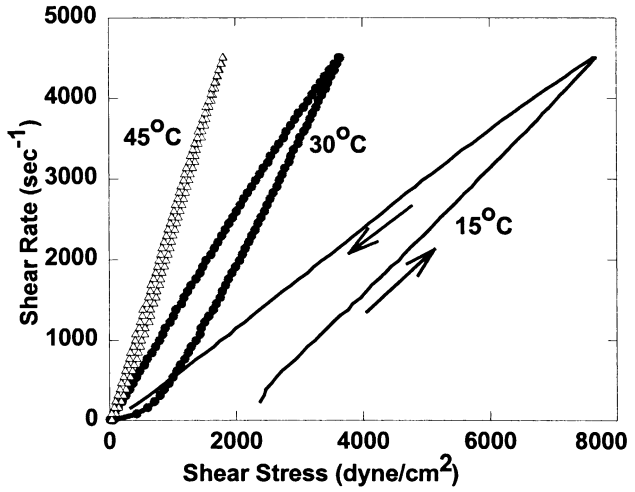

Fig. 4. Shear stress versus shear rate profiles of the wax based vehicle at 15–45°C, indicating a thixotropic behavior.

rate of 40 ml/min and a sample weight of approximate 5–8 mg in a closed pan.

3. Results and discussion

3.1. Viscometry and rheological studies

Viscosity versus temperature profiles of three samples of the wax based vehicle prepared from different lots of the raw materials using a constant shear rate of 4500 s^{-1} and a cooling rate of 7.5°C/min exhibited essentially identical profiles as shown in Fig. 1. An apparent viscosity (η) is defined using the Arrhenius relationship [3]:

$$\eta = Be^{-Ea/RT} \quad (1)$$

where E_a is the activation energy of flow, R is the gas constant, T is the absolute temperature and B is a constant of integration. The activation energy of flow can be calculated from the slope (E_a/R) of the line described by Eq. 2:

$$ln[\eta] = \frac{-E_a}{RT} + ln[B] \quad (2)$$

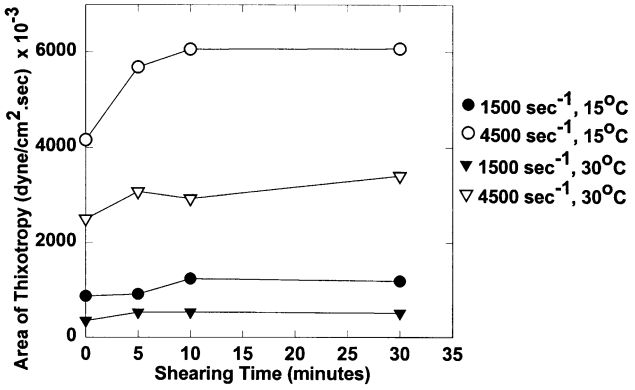

Fig. 5. Effect of shear rate on the area of thixotropy of the wax based vehicle at different temperatures.

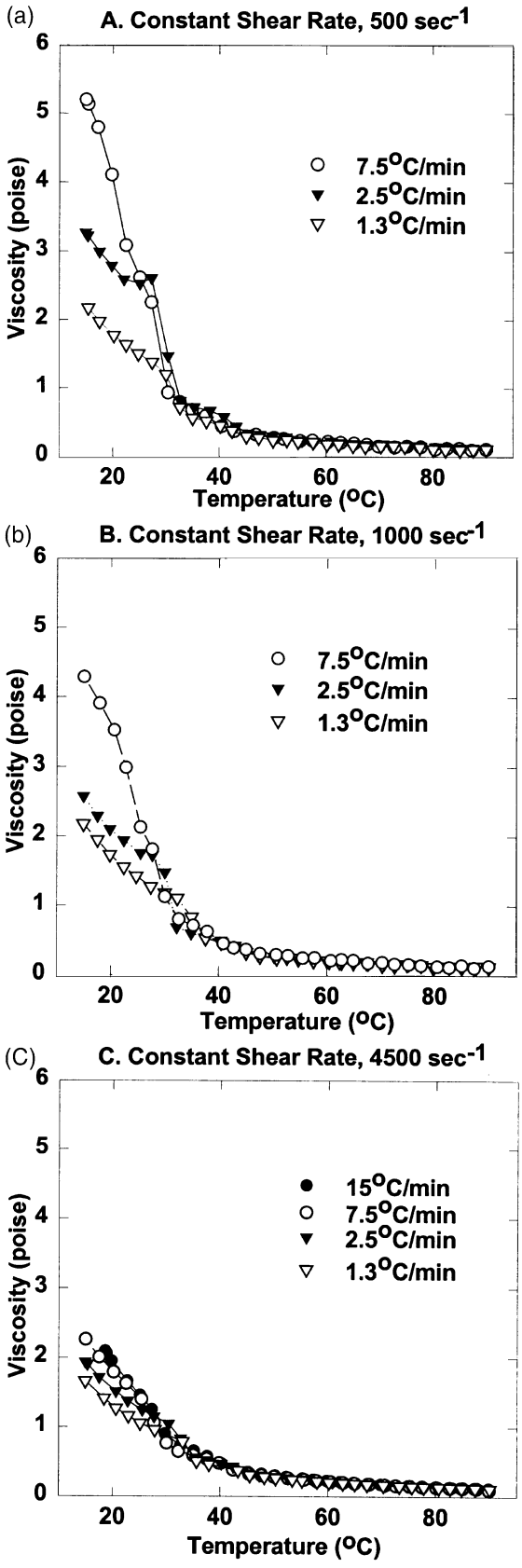

Fig. 6. Effect of cooling rate on the viscosity versus temperature profiles of the wax based vehicle at different shear rates.

Table 1
Effect of total time of cooling on the viscosity of the wax mixture[a]

Cooling condition	Cooling time (min)	Viscosity[b] (cps)
Fast	21	1000
Slow	103	415

[a] Homogenized for 5 min prior to cooling step, mixed with the anchor mixer at 44 rpm during cooling and intermittently, every 5 min, homogenized at 3500 rpm by jogging the homogenizer.
[b] Brookfield coaxial viscosimeter, spindle #SC4-15, 100 rpm at 25°C.

At a shear stress of 700 dynes/cm^2 with a constant cooling rate of 20°C/min, three distinct regions of the phase transition of the wax mixture were clearly seen in the Arrhenius plot of the logarithm of viscosity versus reciprocal temperature (Fig. 2). At temperatures above 50°C (Region A), the mixture exhibited a liquid-like behavior, as indicated by a low activation energy of flow ($E_a = 6.3$ kcal/mole). At temperatures ranging from 30 to 45°C (Region B), the transition of gel to sol or sol to gel occurs and the activation energy of flow was increased to 17.9 kcal/mole. At temperatures below 30°C (Region C), the mixture exhibited a gel-like behavior, as indicated by a significant increase in the activation energy of flow ($E_a = 237$ kcal/mole). Large values of E_a indicate that the viscosity drastically increases with decreasing temperature.

The rheogram shown in Fig. 3 indicated that the wax-based vehicle at temperatures above 60°C behaved as a Newtonian fluid, which all interactions are such that no structure is contributed to the liquid [4]. There was no effect of shear on the viscosity of the mixture, as indicated by the superimposable up and down curves on the rheogram. Shear stress and shear rate are directly proportional, a single viscometric point can characterize the liquid rheology. Increasing temperature decreases the viscosity as shown in Fig. 3 because it reduces intramolecular forces of attraction. In contrast, at lower temperatures, particularly below 45°C, the wax mixture became thixotropic in nature, as indicated by the hysteresis loops (Fig. 4). This indicates a breakdown of structure (shear thinning) that could not reform immediately when the stress was removed or reduced. If recovery occurs rapidly, the ascending and descending shear stress/shear rate rheograms will be essentially superimposable [4]. If the structure does not immediately recover, the descending rheogram will have lower stress values at each shear rate than the ascending as shown in Fig. 4. The presence of thixotropy is indicative of shear and time-dependent structural changes within the suspension.

The effect of shear rate on the area of thixotropy of the wax based vehicle at 15 and 30°C is presented in Fig. 5. The results indicate that the shear rate had a more pronounced effect on the area of thixotropy than the shear time (or peak hold time). The effect of cooling rate of the wax based vehicle was also investigated. The cooling rates ranging from 1.3 to 15°C/min had a pronounced effect on the resultant viscosity of the product, particularly when low shear rates, i.e. 500 s^{-1} and 1000 s^{-1}, were applied, as shown in Fig. 6A,B, respectively. The vehicle which was cooled at a faster rate exhibited a higher viscosity than the vehicle cooled at a slower rate. This effect appears to be minimized when higher shear rate (i.e. 4500 s^{-1}) was applied as shown in Fig. 6C. These data suggest that the shear rate and cooling rate had a pronounced effect on the rheological behavior and the resultant viscosities of the wax based vehicle. These results were corroborated by viscosity measurements made on this same wax based vehicle prepared on a production scale and cooled at different rates as presented in Table 1.

3.2. Differential scanning calorimetry (DSC)

3.2.1. Raw materials

The DSC data of the raw materials from two different lots are presented in Table 2. The results indicate that the raw materials used in the study exhibited lot to lot consistency with regard to their melting points and heat of fusions. The viscosity versus temperature profiles of three samples of the wax based vehicle prepared from different lots of the raw materials using a constant shear rate of 4500 s^{-1} and a cooling rate of 7.5°C/min exhibited essentially identical profiles as previously shown in Fig. 1. The DSC data, along with the comparable viscosity versus temperature profiles of the wax based vehicle prepared from different lots of the raw materials, confirm that the raw materials used in the manufacture of the product should not contribute to the differences in the resultant viscosities of the finished suspensions.

3.2.2. Wax mixture

DSC thermograms of the four samples of the wax mixture, which were prepared from the viscometry studies using different cooling rates (1.3 and 15°C/min) along with different shear rates (500 and 4500 s^{-1}), are shown in Fig. 7.

Table 2
DSC data of raw materials used in the preparation of the wax base vehicle

Excipients	Lot#	Onset of peak (°C)	End of peak (°C)	Melting point (°C)	ΔΔH (mJ/mg)
Hydrogenated soybean oil flakes	940046	56.9	75.0	69.1	189.8
	940047	54.9	75.1	68.8	193.9
Hydrogenated vegetable oils	940060	33.7	53.0	47.0	21.0
	940062	28.0	50.7	47.1	20.0
Purified yellow beeswax	930050	50.9	67.6	62.2	57.2
	930051	51.1	67.4	62.1	58.5

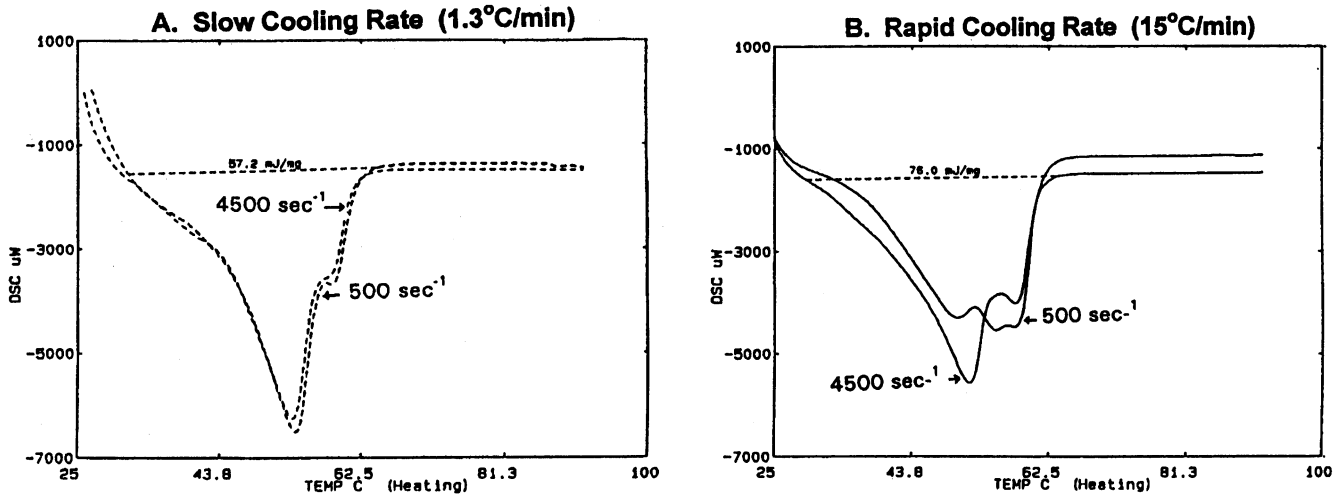

Fig. 7. DSC thermograms of the wax mixture prepared by different cooling rates and shear rates.

The slow cooling rate (1.3°C/min) exhibited comparable endotherms for both shear rates as shown in Fig. 7A. In contract, the faster cooling rate (15°C/min) exhibited different endotherm characteristics between low and high shear rates applied as shown in Fig. 7B. The wax mixture used in the study contains the purified beeswax, hydrogenated soybean oil flakes and hydrogenated vegetable oils. The beeswax itself consists of esters of straight-chain monohydric alcohols with even-numbered carbon chain from C_{24}–C_{36} esterified with straight-chain acids also having even numbers of C atoms up to C_{36}. Soybean oil consists of triglycerides of oleic acid 26%, of linoleic acid 49%, of linolenic acid 11%. Hydrogenated vegetable oils are mixture of triglycerides of fatty acids. Therefore, different cooling rates applied in this wax based vehicle may result in different phase transitions and polymorphic transitions of triglycerides and fatty alcohol components present in the wax mixture, which may have a pronounced effect on the resultant viscosities of the finished suspension. The effect of the cooling rate on the DSC characteristics of the wax-gelled ointment base was reported by Timmins et al. [5]. The temperature control during the heating and cooling phases of molten hard fats were also shown by Loth et al. [6] to have considerable consequences to the crystallization kinetics and to their crystal structures.

4. Conclusions

To achieve reproducibility of drug content uniformity and encapsulability of a wax based formulation into a soft gelatin capsule dosage form, optimal viscosity and lot to lot uniformity of the viscosity of the finished suspension must be ensured. Rheological behavior of the wax mixture is temperature-dependent. A transition temperature from a Newtonian behavior to a thixotropic nature was observed at approximately 45°C. The results of this study indicate that the shear rate and cooling rate are the critical processing factors in controlling the resultant viscosity of the wax based vehicle and must be well controlled in the manufacturing procedure. Rheometer and DSC were found to be very useful tools for characterization of process-induced variations in a wax based vehicle.

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