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SOFTENING OF SEMISYNTHETIC SUPPOSITORY BASES

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ABSTRACTS

The melting process of seventeen semisynthetic suppository bases has been evaluated by using a classical open capillary method together with differential scanning calorimetry and rheological analysis, in order to establish a physical mechanism for their premature softening. The presence in these materials of a mixture of different fat components with divergent melting points, as detected by the presented methods, satisfactorily explains this phenomenon.

INTRODUCTION

It is well known that some properties of suppositories, such as melting point, softening time, drug release, and even drug bioavailability, tend to change during storage[1,2]. These phenomena have been considered in connection with the polymorphism of suppository base[3,4].

In particular the hardening phenomena observed in suppositories prepared from semisynthetic triglycerides has been extensively studied[5-7], since it results in little or no suppository melting, and can cause local irritation, a defecatory reflex, or bowel obstruction. However, less attention has been focused on gradual softening of suppositories stored at room temperature, which represents a significant inconvenience for handling at industrial and user level.

The aim of the present work was to elucidate the aging and softening phenomena observed in suppositories prepared from semisynthetic suppository bases, by using differential scanning calorimetry studies and rheological analysis of fresh and aged fatty excipients.

EXPERIMENTAL

Materials

Seventeen semisynthetic, commercially available bases were chosen. Table I summarizes their physico-chemical properties as given by the suppliers.

Methods

The following studies were carried out in the samples of the products as received and after an ageing treatment (storage for 7 days at 41°C, followed by 7 days at 25°C).

a) Melting characteristics

The open capillary tube method was used. The semisynthetic base was melted at 50°C, introduced into an open capillary tube sufficient to fill a 1 cm column and stored at 14°C during

TABLE I

Physico-chemical characteristics of semisynthetic suppository bases (1)

Base	*Initial melting point (ºC)*	*Final melting point (ºC)*	*Physico-chemical characteristics (2)*			
			I.V.	*H.V.*	*S.V.*	*A.V.*
Estarinum B(3)	34	36	< 1	18-22	225-245	< 0.3
Estarinum B-fluid	34	36	< 1	ca. 15	225-245	< 0.3
Estarinum BLS	34	36	< 7	ca. 15	225-245	< 0.5
Estarinum B63	35.3	-	0,2	5.5-5.8	243	< 0.3
Estarinum C-fluid	36	38	< 1	ca. 15	225-245	< 0.3
Estarinum DA	40	42	< 2	53-57	210-230	< 1.0
Estarinum DLS	40	42	< 7	ca. 15	225-245	< 0.5
Estarinum D-fluid	40	42	< 1	ca. 15	225-245	< 0.3
Estarinum DEA	44	46	< 2	53-57	210-230	< 1.0
Estarinum E	34	36	< 3	≤ 5	220-230	< 1.0
Witepsol H32(4)	34	36	< 3	<3	240-250	< 0.2
Witepsol W 35	34	36	< 3	40-50	225-235	< 0.3
Witepsol W-S55	34	36	< 3	50-61	215-230	< 1.0
Supocire AM(5)	35	36.5	< 2	<6	225-245	< 0.2
Supocire AP	33	35	< 1	30-50	200-220	< 1.0
Supocire NC	38.5	40.5	< 2	<40	220-240	< 0.5
Supocire BS_2X	36	37.5	< 3	15-25	222-240	< 0.5

(1) From suppliers information
(2) I.V.: Iodine value; H.V.: Hydroxyl value; S.V.: Saponification value; A.V.: Acid value
(3) Glyco Ibérica, Barcelona (Spain)
(4) Dynamit Nobel Chemicals, Witlen (West Germany)
(5) Gattefose, Saint Priest (France)

twenty-four hours. The melting point was then measured in a water-bath with a heating rate of 1°C.min^{-1}. The temperature that caused clearing of the fatty base was noted.

b) Differential scanning calorimetry

The sample (ca. 10 mg) was sealed in an aluminium micropan and stored at 14°C during twenty-four hours. The micropan was then carefully bored, introduced into the analytical system (FP80, Mettler), and thermal scanning carried out at a rate of 1°C.min^{-1}, from 19°C to 45°C, in air.

c) Rheological properties

The supository base sample was melted at 80°C and stirred with a magnetic stirrer for 30 minutes. The temperature was then allowed to decrease to 38°C without stirring. A volume (10 mL) of the fluid was introduced into the cell (NVSt) of a Haake RV2 viscometer fitted with a M-500 head, previously thermostated (37°C), and a complete rheological analysis was carried out with rotor spinning velocities from 32 to 512.$\sqrt{2}$ min^{-1} (1st determination).

The sample in the viscometer cell vas cooled to 20°C for three hours, reheated to 37°C for twenty hours, and the rheological analysis was repeated (2nd determination). For the suppository bases with a melting point higher than 37°C, viscosity determinations were always measured at a temperature of two degrees centigrade above their melting point.

RESULTS AND DISCUSION

The results obtained are given in Tables II to IV.

TABLE II

Calorimetric and rheological characteristics of semisynthetic suppository bases (Hydroxyl value < 30, and melting range 33-36ºC)

Base	Melting point$^{(1)}$ (ºC)	Melting point$^{(2)}$ (ºC)	Differential Calorimetry$^{(1)}$ 1st endotherm (ºC)	Differential Calorimetry$^{(1)}$ 2nd endotherm (ºC)	Differential Calorimetry$^{(2)}$ 1st endotherm (ºC)	Differential Calorimetry$^{(2)}$ 2nd endotherm (ºC)
Estarinum B	34.4	34.7	30.0	35.0	33.0	37.0
Estarinum B-fluid	35.0	35.7	27.0	39.0	26.0	38.0
Estarinum BLS	34.8	34.8	27.0	37.0	30.0	37.0
Estarinum B63	35.3	36.0	-	35.5	-	37.5
Estarinum E	35.5	39.4	27.0	37.5	30.0	36.0
Witepsol H32	34.8	35.8	33.0	-	33.0	35.0
Supocire AM	35.6	36.2	29.7	38.5	-	37.5
Supocire BS$_2$X	35.1	35.3	26.5	38.5	22.3	36.0

	Viscosity$^{(1,3)}$ 1st Det. (mPa.s)	Viscosity$^{(1,3)}$ 2nd Det. (mPa.s)	Viscosity$^{(2,3)}$ 1st Det. (mPa.s)	Viscosity$^{(2,3)}$ 2nd Det. (mPa.s)	Hysteresis$^{(1,4)}$ 1st Det.	Hysteresis$^{(1,4)}$ 2nd Det.	Hysteresis$^{(2,4)}$ 1st Det.	Hysteresis$^{(2,4)}$ 2nd Det.
Estarinum	32.53	32.53	-	-	0	0	-	-
Estarinum D-fluid	38.14	103.21	-	-	0	11.20	-	-
Estarinum BLS	31.41	33.65	-	-	0	0	-	-
Estarinum B63	33.65	29.16	29.16	31.41	1.91	0.64	0	0.97
Estarinum E	41.50	35.90	-	-	8.77	4.88	-	-
Witepsol H32	29.16	22.43	-	-	0	0	-	-
Supocire AM	29.16	29.16	29.16	29.16	0	0	0	0
Supocire BS$_2$X	31.41	29.16	35.90	30.29	0	0	0	0

(1) Fresh sample
(2) Aged sample
(3) Ascendent ($n = 128$ min^{-1})
(4) Expresed as surface (cm^2) within the loop

TABLE III

Calorimetric and rheological characteristics of semisynthetic suppository bases. (Hydroxyl value > 30, and melting range 33-36ºC)

Base	*Melting point(1) (ºC)*	*Melting point(2) (ºC)*	*Differential Calorimetry(1) 1st endotherm (ºC)*	*Differential Calorimetry(1) 2nd endotherm (ºC)*	*Differential Calorimetry(2) 1st endotherm (ºC)*	*Differential Calorimetry(2) 2nd endotherm (ºC)*
Witepsol 35	34.2	34.4	28.0	38.0	32.0	38.0
Witepsol S55	35.5	36.8	29.0	38.0	33.0	39.0
Supocire AP	34.1	37.8	-	37.5	22.5	33.5

	Viscosity(1,3) 1st Det. (mPa.s)	*Viscosity(1,3) 2nd Det. (mPa.s)*	*Viscosity(2,3) 1st Det. (mPa.s)*	*Viscosity(2,3) 2nd Det. (mPa.s)*	*Hysteresis(1,4) 1st Det.*	*Hysteresis(1,4) 2nd Det.*	*Hysteresis(2,4) 1st Det.*	*Hysteresis(2,4) 2nd Det.*
Witepsol 35	53.85	53.85	-	-	8.96	5.48	-	-
Witepsol S55	67.31	59.45	-	-	13.56	13.39	-	-
Supocire AP	31.41	32.53	31.41	35.90	0	0	0.79	0

Same foot notes as Table II

TABLE IV

Calorimetric and rheological characteristics of semisynthetic suppository bases. (High melting point excipients)

Base	*Melting point(1) (ºC)*	*Melting point(2) (ºC)*	*Differential Calorimetry(1) 1st endotherm (ºC)*	*Differential Calorimetry(1) 2nd endotherm (ºC)*	*Differential Calorimetry(2) 1st endotherm (ºC)*	*Differential Calorimetry(2) 2nd endotherm (ºC)*
Estarinum C-fluid	38.0	38.0	25.0	38.0	25.0	38.0
Estarinum D-fluid	39.8	40.1	24.0	41.0	25.0	40.0
Estarinum DA	39.6	39.2	36.0	-	34.0	42.0
Estarinum DEA	41.0	41.0	24.0	40.0	33.5	40.0
Estarinum DLS	40.0	39.8	24.0	41.0	25.0	40.0
Supocire NC	38.2	33.8	26.0	40.5	36.5	42.0

	Viscosity(1,3) 1st Det. (mPa.s)	*Viscosity(1,3) 2nd Det. (mPa.s)*	*Viscosity(2,3) 1st Det. (mPa.s)*	*Viscosity(2,3) 2nd Det. (mPa.s)*	*Hysteresis(1,4) 1st Det.*	*Hysteresis(1,4) 2nd Det.*	*Hysteresis(2,4) 1st Det.*	*Hysteresis(2,4) 2nd Det.*
Estarinum C-fluid	35.90	62.82	-	-	0	3.54	-	-
Estarinum D-fluid	35.90	103.21	-	-	0	4.10	-	-
Estarinum DA	34.77	77.40	-	-	0	13.84	-	-
Estarinum DEA	47.11	141.35	-	-	48.3	10.54	-	-
Estarinum DLS	35.90	103.21	-	-	0	4.10	-	-
Supocire NC	30.29	30.29	31.41	43.75	0	0	0	5.31

Same keys as Table II

a) Melting characteristics: The method described above for this test was a simulation of the melting processes which occur during the manufacture and utilization of suppositories.

The observed melting point values (mean of five determinations) for all the fresh bases were in good agreement with the suppliers specifications, although the Estarinum D group gave slightly lower values. In particular, the batch of Estarinum DEA type examined had a melting point 3°C lower than expected.

Generally, on aged samples, significant increases in the melting point values were not observed and for this reason increments in the disintegration time of the suppositories molded with these excipients would not be expected. Divergent values of Δ t° (difference between melting point after 41°C storage and the initial value) were only detected for Estarinum E, Supocire AP and NC samples (Δ t° values of +3.9°C, +3.7°C and -4,4°C, respectively). In the first two products these differences probably correspond to the energy absorption required to transform the initial metastable form to a stable one[3,8,9], and in the case of Supocire NC the difference in melting point is probably related to the rapid microcrystallization after the first melting, giving a fat excipient with a softening temperature lower than required, even prior to the pharmaceutical formulation. This is particularly inconvenient for a suppository vehicle to be used in compounding high amounts of active ingredients soluble in the excipient (eg. essential oils) that produce a large decrease of the melting point.

b) Differential scanning calorimetry: Accuracy in melting-range determinations was attained by utilizing a heating rate of $1°C.min^{-1}$. The poor heat transfer characteristics of fats[10] prevent the use of faster speeds due to the lag time in the return to thermal equilibrium. Speeds of $5°C.min^{-1}$ and higher eliminated or shifted the sharp peaks observed at $1°C.min^{-1}$.

In an experiment where changes in the peak positions of 1°C were being sought and metastable transformations were not, this choice was mandatory since slower heating rates yielded sharper endo- or exotherms, and located an equilibrium transformation temperature more accurately[11].

A small group of bases (Tables II-IV) exhibited a single melting endotherm, but the majority of the fresh excipients studied showed two and even more endotherms (three peaks in bases E, W35 and WS55). In this second group the temperature of the last endotherm tended to coincide with the melting point value determined in an open capillary tube.

However, the melting point tempoerature distribution for the different components of each base in this group is bi- or multimodal, involving a premature softening of the excipient at the temperature of the first endotherm, several degrees before the expected value. These differences can rise to 17°C (DLS base).

c) Rheology: It is well known[12,13] that a direct viscosity determination at 37°C of these excipients produces very similar rheograms, close to newtonian or slightly dilatant, independently of the excipient analyzed. The viscosity values (1st determination) obtained in this work confirm this observation, being compressed within an interval of 29.16-67.31 mPa.s.

The rheological differences between the fat suppository bases can be valuated by a modification of the method of Möes[14] in which a second viscosity measurement (2nd determination) is carried out after cooling and storage at room temperature of a premelted sample. The objetive was to reproduce the excipient melting encountered in the pharmaceutical formulation, moulding and cooling procedures, and "in vivo" liquification with subsequent bioavailability of the active principles.

c.1. Suppository bases with H.V. <30, and melting range 33º-36ºC (Table I): Excluding the bases B-fluid and E, this group give low viscosity values due to their complete liquification at 37°C, yielding a set of newtonian rheograms with practically overlapping of τ (Pa) vs D (s^{-1}) curves for both (first and second) determinations.

The highest viscosity measured on the first determination for the B-fluid and E bases can be explained by the temperatures (39°C and 37.5°C) of the second endotherms in the initial calorimetric analysis. Both bases are incompletely liquified at the standard temperature for rheology (37°C), and shows that single melting point determination is not enough to represent the real behaviour of this kind of bases.

The remarkable viscosity increase found on the second determination for the B-fluid base is related to its high melting point. Certainly the value obtained by the open capillary technique is insufficient to justify this difference. Nevertheless in the second determination of the rheogram a clear hysteresis can be observed reflecting a pseudoplastic behaviour which causes thixotropy. An analogous situation was detected on C-fluid base.

The second viscosity determination of base E was lower than the first one. This unexpected decrease when the base E was known to tend to higher melting values on storage is due to the lesser hardening properties of β stable forms of palmitic and stearic glycerides, which form during crystallization structures with lower density than β′ones. The base E has been shown to have important pseudoplastic properties (see hysteresis) but to be critically sensitive to melting and ageing procedures as Fig. 1 shows, where the change in the first endotherm probably corresponds to the intermediate amorphous to crystalline shift.

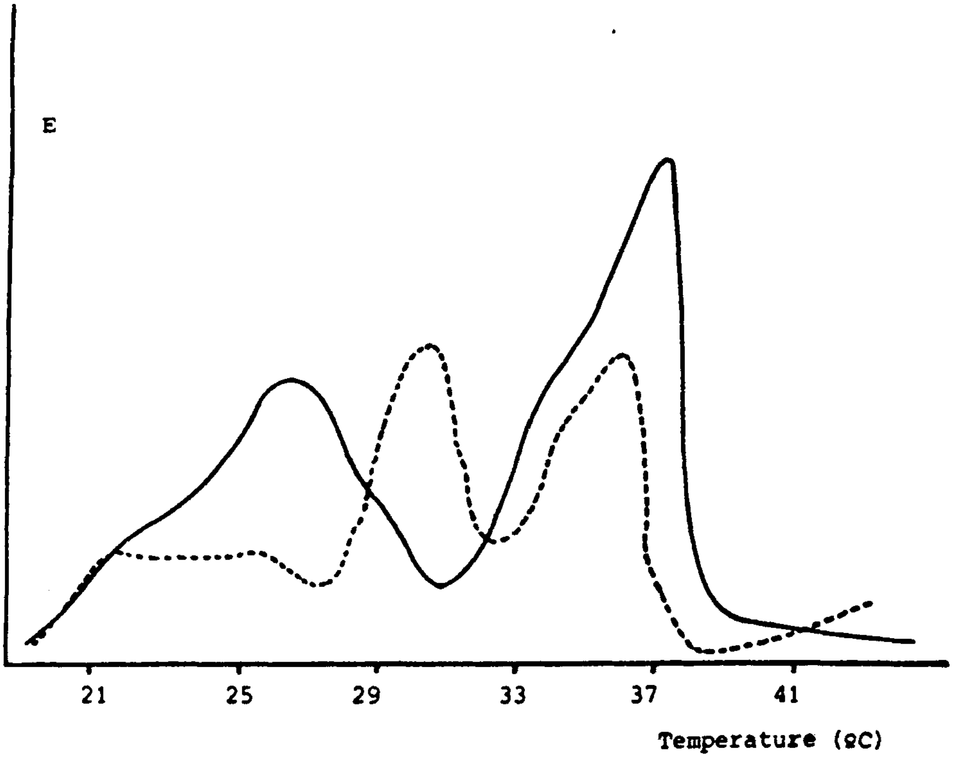

Fig. 1.- Differential scanning calorimetry for base E.

— Fresh sample
... Aged sample

c.2. Suppository bases with H.V. >30, and melting range 33º-36ºC (Table I): This group contains the excipients (Witepsol 35 and S55) with strong pseudoplastic properties, which were initially more viscous at 37°C. The thixotropy of Supocire AP is negligible.

c.3. Suppository bases of high melting point (Table I): With the exception of Supocire NC, a significant increase in viscosity on the second determination with a clear thixotropic behaviour can be detected for all of these bases.

Supocire NC is an excipient with a medium crystallization rate recommended for use when compounding large amounts of active ingredients soluble in the base, and causing a considerable decrease in melting point. However, the absence of increments of viscosity in the second determination, and null hysteresis, indicates that there will be a slow thixotropic recovery of solid consistency after the first melting.

CONCLUSIONS

The above results indicate that the majority of the suppository bases studied are thermodynamically stable excipients (with the exception of the batch of base E). However, the manufacture of a base with a predetermined melting point, by blending appropiate amounts of esters, fatty alcohols, etc., can produce a finished material with a multimodal melting profile. This can cause a softening of the mass several degrees below the expected melting temperature, which is an obvious source of inconvenience during the industrial production and user handling of the suppositories, specially when they contain lipophilic drugs dissolved or even suspended in the excipient. The use of fat excipients with a single or narrower melting profile, is therefore advisable.

The calorimetric and rheological data presented clearly show that the physical behaviour of a suppository base is only partially represented by its melting point, and a more suitable characterization can be obtained by including data from differential scanning calorimetry and viscosity determinations on fresh, and short-term aged samples. These three tests also allow control of interbatch variations for a determined suppository base, as consequence of insufficient transesterification during the synthesis which could give a non-statistical distribution of the fatty acids on glycerine.

The results of this study in no way reflect the quality of any base tested, or on the ability of any of the manufacturers to supply a range of bases suitable for individual needs.

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