Journal of Pharmaceutical & Biomedical Analysis
Vol. 7, No. 5, pp. 549–561, 1989
Printed in Great Britain

0731–7085/89 $3.00 + 0.00

Investigation of the relationship between melting-related parameters and *in vitro* drug release from vaginal suppositories

MICHAEL S. BERGREN, MICHELE M. BATTLE,* GORDON W. HALSTEAD† and DON L. THEIS

Control Research Laboratories, 7000 Portage Road, The Upjohn Company, Kalamazoo, MI 49001, USA

Abstract: The effect of temperature on drug release from meteneprost potassium vaginal suppositories was investigated using a dissolution test based on the USP I apparatus. Comparison of the dissolution results with the DSC melting behaviour revealed that drug release was extremely slow until melting of the suppository was essentially complete. The melting behaviour of the meteneprost potassium suppositories was also varied by preparing suppositories from bases with higher and broader melting ranges. The observed dissolution behaviour (at 37°C) confirmed that drug release increased as the melting temperature of a particular suppository decreased. Differential scanning calorimetry, viscosity and dilatometry methods were used to characterize the suppository melting process. The effects of suppository melting range, melt temperature and composition were investigated with respect to *in vitro* drug release. Methodology for the HPLC determination of meteneprost in suppositories and in dissolution media are also reported.

Keywords: *Meteneprost potassium; vaginal suppositories; suppository DSC; suppository dissolution testing; suppository melt viscosity.*

Comment: The work described here was completed prior to January 1986, at which time the development of meteneprost and its salts was terminated within The Upjohn Company. The authors believe that the work is generally relevant to the study of release of any water soluble drug from a lipid based suppository matrix where it is present as a solid dispersion.

Introduction

Vaginal suppositories containing meteneprost and its salts, particularly meteneprost potassium (9-deoxo-16,16-dimethyl-9-methylene PGE_2, potassium salt; Fig. 1), have been formulated in several suppository bases derived from glycerol esters of saturated fatty acids [1–3]. Clinical evaluation of these suppositories has revealed differences in the absorption of meteneprost which are formulation dependent. Studies in Rhesus monkeys have shown that drug absorption from lower melting meteneprost suppositories administered vaginally was more complete than absorption from suppositories formulated with a similar base exhibiting a higher melting range [4]. Recovery of radiolabelled meteneprost after vaginal administration of low and higher melting suppositories has

*Present address: Warner–Lambert Co., 2800 Plymouth Road, Ann Arbor, MI 48105, USA.
†To whom correspondence should be addressed.

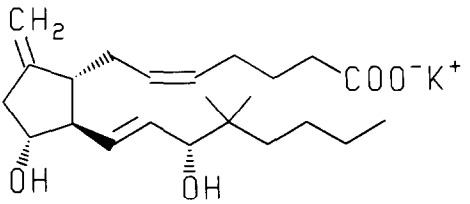

Figure 1
Structure of meteneprost potassium.

confirmed this result [5]. In a similar prostaglandin suppository, modifications affecting the melting behaviour of suppositories containing carboprost methyl (15-methyl-$PGF_{2\alpha}$, methyl ester) have also been shown to affect the release of drug [6, 7].

While it is clear that undesirable suppository melting behaviour has led to poor drug absorption in the clinic, the effect of melting behaviour on the intermediate step of drug release from the suppository has received less attention. The purpose of this study was to investigate the relationship between melting related parameters and *in vitro* drug release of meteneprost potassium from fatty suppository bases. Differential scanning calorimetry (DSC), viscometry and dilatometry were used to investigate and characterize the suppository melting process. The effects of suppository melting range, melt temperature and composition were investigated with respect to *in vitro* drug release. Methods for the high-performance liquid chromatography (HPLC) determination of meteneprost in suppositories and in dissolution media are also reported.

Experimental

Materials

Meteneprost potassium and the internal standard, flurbiprofen, were supplied by The Upjohn Company (Kalamazoo, MI, USA). Witepsol® suppository bases (E76, H15 and E85) were obtained from Dynamit-Nobel Chemicals (Triosdorf, FRG). The suppository base, Suppocire® AM, was purchased from Gattefossé, SFPA (Paris, France). All solvents used for HPLC were of distilled-in-glass quality (Burdick and Jackson, Muskegon, MI, USA). Colloidal silicon dioxide was obtained from Cabot Corporation (Boston, MA, USA; Cab-O-Sil). The remainder of the chemicals and solvents were obtained from standard commercial sources and were used as received.

Suppository preparation

In a typical small scale preparation, the suppository base (7.73 g) was melted in an oven at 56°C. After melting was complete, the suppository base was transferred to a temperature-controlled beaker at 45°C and 110 mg of meteneprost potassium was added. This mixture was homogenized until the drug was well dispersed; care was taken not to incorporate air. Colloidal silicon dioxide (160 mg) was added with further homogenization. The suppository melt was syringed into plastic suppository shells and allowed to cool at room temperature. In this manner, suppositories weighing approximately 800 mg, containing approximately 11 mg of meteneprost potassium and 2 wt% of colloidal silicon dioxide, were prepared using Witepsol® H15, E76, E85, and Suppocire® AM. Suppositories were also made using a mixture of one part of H15 and four parts of E76 as the suppository base. Larger quantities of meteneprost potassium suppositories formulated in Witepsol H15 were also obtained from clinical lots produced in house.

Chromatographic analyses

A modular HPLC chromatograph, consisting of a reciprocating piston pump equipped

with a pulse dampener (Model 110, Beckman Instruments, Berkeley, CA, USA), an autosampler (Model 8050, Varian Associates, Palo Alto, CA, USA), a UV detector equipped with a 214 nm wavelength kit (UVIII, Laboratory Data Control, Riviera Beach, FL, USA) and a recorder (Model XKR, Sargent Welch Co., Skokie, IL, USA) was used for all measurements. Data were collected and processed using an in-house digital computer system. The mobile phase was prepared as follows. Distilled water (570 ml) was added with stirring to 1.38 g of $NaH_2PO_4 \cdot H_2O$ followed by 430 ml of acetonitrile. The apparent pH was adjusted to 3.0 with concentrated phosphoric acid. The solution was filtered through a 5-μm filter before use. The separation was carried out on a 250 × 4.6 mm Zorbax® C_8 (DuPont, Wilmington, DE, USA) stainless steel column. The column temperature was ambient, the column pressure was approximately 1900 psi and the flow rate was 1.3 ml min^{-1}. Retention times of flurbiprofen and meteneprost were about 18 and 25 min, respectively.

Potency of the suppositories was determined by an internal standard method. The internal standard solution contained 3.5 g of K_2HPO_4 and 50.0 mg of flurbiprofen in 500 ml of mobile phase. The standard solution was prepared by accurately weighing about 10 mg of meteneprost potassium reference standard and dissolving it in exactly 10.0 ml of internal standard solution and approximately 10 ml of a diluent solution. The diluent solution consisted of 2.0 ml of 85% H_3PO_4 added to 250 ml of mobile phase. Samples were prepared by dissolving a suppository in 10 ml of hexane with sonication. The hexane solution was extracted with exactly 25.0 ml of internal standard solution for 5 min. The layers were separated by centrifugation, and 5 ml of the lower aqueous layer were added to 5 ml of the diluent solution described above. Aliquots (10-μl) of the standard and sample preparations were chromatographed using the conditions described.

The determination of meteneprost in dissolution media was accomplished by direct injection of 50-μl aliquots of the dissolution samples and standards using the same chromatographic system utilized for the potency assay. The column flow rate was increased to 2.0 ml min^{-1} yielding a retention time of approximately 19 min for meteneprost. The dissolution standards were prepared by accurately weighing approximately 2.4 mg of meteneprost potassium reference standard in 100 ml of 0.05 M phosphate buffer (pH 7.0).

In vitro *drug release*

The drug release test apparatus was a six-position dissolution apparatus (Vander-Kamp Model 600, Van-Kel Industries, Chatham, NJ, USA) with a variable temperature circulating water-bath (Model C-400, Techne, Cambridge, England). Conventional stainless-steel USP I baskets were used throughout. All release rate tests were conducted under sink conditions at 100 rpm in 500 ml of 0.05 M phosphate buffer (pH 7.0) contained in a 1000-ml dissolution flask at 37°C (except for the variable temperature studies). Suppositories of a single Witepsol® H15 lot were tested at various bath temperatures ranging from 32.0–38.1°C. Suppositories prepared from Witepsol® E76, H15, E85, H15/E76 mixture, and Suppocire® AM bases were tested at 37°C. Dissolution fluid (10 ml) was removed at each point (between 10–180 min) and filtered through a 0.22-μm membrane filter (Millipore® GS, Millipore Corporation, Bedford, MA, USA) prior to chromatographic analysis. The percent meteneprost potassium dissolved was calculated on the basis of the appropriate potency values.

Differential scanning calorimetry

A DuPont 910 DSC equipped with a Model 1090 thermal analyzer unit (DuPont Co., Wilmington, DE, USA) for data analysis and storage was used throughout these studies. Suppository samples (5–10 mg, accurately weighed) were sealed in aluminium pans, placed into the DSC cell, and the temperature was lowered to about −20°C with liquid nitrogen. Data were collected at 0.6 s/point over the temperature range of −10 to 60°C with a gradient of +2°C min^{-1} and a cell nitrogen purge rate of 50 cm^3 min^{-1}. The resulting data were plotted as heat flow (y-axis) versus temperature (x-axis). Baseline points were chosen such that the start and endpoints were at the same heat flow value (i.e. same y-value). Total peak area was determined as the integral of the signal over the time as determined by Simpson's Rule between the baseline points. The area was expressed in units of J g^{-1}. Percentages of the total area under the melting curves are referred to in the text in terms of percent melted. The instrument was calibrated with an indium calibration standard. In addition, temperature accuracy was also verified by demonstration that the melting transition onset of doubly-distilled water, as determined by the extrapolation to baseline of the leading edge of the melting endotherm, was within 1° of 0°C.

Viscosity measurements

Apparent suppository melt viscosities were determined using a Brookfield cone and plate viscometer (Model LVTDCP, Brookfield Engineering Laboratories, Inc., Stoughton, MA, USA) equipped with a thermostatted sample cup. The term "apparent viscosity" refers to the fact that colloidal silicon dioxide and meteneprost potassium, both solids, were suspended in the melts. The viscometer was equipped with a CP-52 spindle (cone angle, 3.0°; cone radius, 1.2 cm) and was capable of operating over a shear rate range of 0.6–120 s^{-1} with a full scale torque of 673.7 dyn cm. Sample suppositories were melted at 50°C on a heating block and were syringed (0.5 ml) into the thermostatted part of the viscometer. Sufficient time was allowed for a stable reading to be obtained.

Dilatometry

The volumetric dilatation of Witepsol® H15 suppository base was measured with a 10-ml glass capillary dilatometer (Kontes, Cat. No. K329100, Vineland, NJ, USA). The instrument correction was estimated by filling the dilatometer with 10.0 ml of de-aerated water and measuring the dilatation at 5° intervals between 0–50°C. Temperature equilibration was achieved by immersion of the dilatometer up to the zero mark in a thermostatted bath (Lauda RCS-6, Brinkman Instruments, Westbury, NY, USA) and volumes were recorded after stable readings had been maintained for at least 5 min. The correction for glass expansion was found to be unnecessary when the total volume expansion was compared to the predicted values based on the temperature dependence of the density of water. The maximum volumetric error over this range was <0.005 ml.

Samples of Witepsol® H15 suppository base were prepared by de-aerating the commercial product at 45°C under vacuum (<5 mmHg). The melt was allowed to solidify and age for about 3 weeks prior to the dilatometric study. A portion of the suppository base was weighed (approximately 3.35 g total), and placed in the dilatometer. Sufficient de-aerated water was added as a sealing liquid (approximately 6.8 ml) to provide the remainder of fill volume. The volume change was monitored at 5°C intervals over the range 0–50°C as described above. Stable equilibrium was generally

achieved in 20 min or less. Measurement times longer than a few hours were avoided to prevent artificial volume reductions associated with the hardening (phase changes) of the suppository base. A sample of the same suppository base was analysed by the DSC procedure described above to provide a basis for comparison with the dilatometry data.

Results and Discussion

The melting behaviour of meteneprost potassium vaginal suppositories was varied by preparing 800 mg suppositories containing approximately 11 mg of drug, 16 mg (2 wt%) of colloidal silicon dioxide (CSD) and 773 mg of Witepsol® H15, E76, E85, H15/E76 (1:4) or Suppocire® AM. The drug content of these suppositories was monitored using a reversed-phase HPLC assay. Sample suppositories were dissolved in hexane followed by extraction of the drug into an aqueous acetonitrile solution buffered at about pH 7.6. The pH of the separated aqueous phase was adjusted to about pH 3.0 to be consistent with the pH of the mobile phase. Typical chromatography is shown in Fig. 2.

The mean recovery of meteneprost from spiked placebo (800 mg Witepsol® H15 with 2% CSD) was 100.0 ± 0.3% (n = 9) over a meteneprost potassium range of 2.76–42.3 mg/suppository. Least-squares analyses of the data yielded a correlation coefficient of 1.000 with a line described by amount found (mg) = 0.9997 amount added (mg) + 0.005. The intercept was not significantly different from zero. The mean recovery of drug from suppositories formulated with Witepsol® E76, E85, H15/E76 (1:4) or Suppocire® AM was 99.2 ± 0.2% at the 11 mg meteneprost potassium/suppository

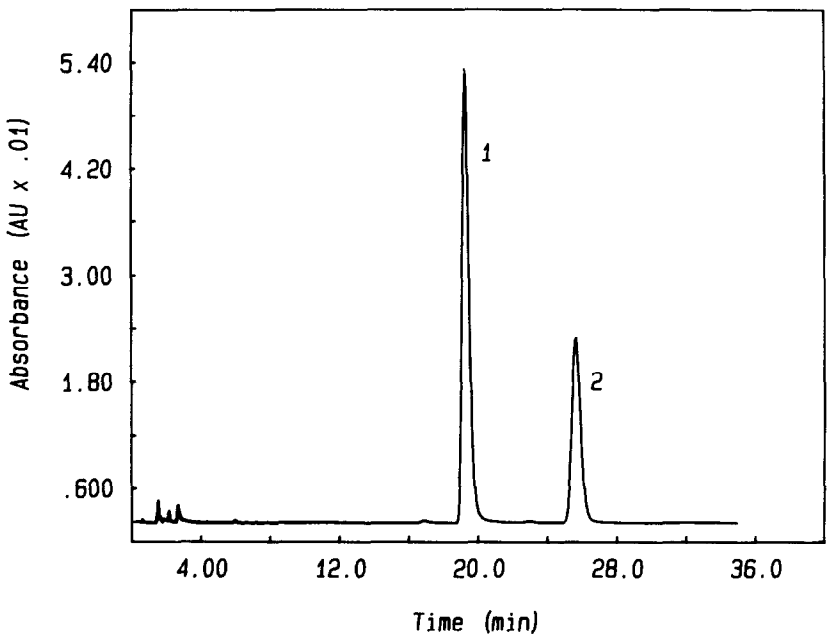

Figure 2
Chromatogram of a typical Witepsol® H15 based suppository sample preparation containing flurbiprofen (internal standard, peak 1) and meteneprost (peak 2). Conditions are those described in the Experimental section.

spiking level. On the basis of the recovery studies, the extraction efficiency was maintained even at acidities near pH 7.0 presumably due to the high acetonitrile content of the aqueous phase. No chromatographic interference was observed from the various suppository bases using the potency chromatography conditions. A typical assay precision for 10 H15 suppositories was a RSD of 1.2%.

In vitro drug release from the suppositories was monitored using chromatographic conditions derived from those used for the potency assay. The concentration of meteneprost in dissolution samples was determined by direct injection of drug containing dissolution media. Typical chromatography for a dissolution sample is shown in Fig. 3. The mean recovery of the drug from spiked placebos (2% CSD in Witepsol® H15) in 0.05 M phosphate (pH 7) dissolution media was 98.1 ± 1.8% over a range of 25–150% of theory (100% = 10 mg of meteneprost/suppository). Least-squares analyses of the data yielded a correlation coefficient of 0.9998 with a line described by amount found (mg) = 0.9588 amount added (mg) + 0.1451. The results indicate a combined filter/placebo bias of approximately 2% over this concentration range for the dissolution assay. No chromatographic interference was observed for dissolution samples of the various suppositories described above. Dissolution results in terms of "percent dissolved" were calculated on the basis of the results of the potency assay for each type of suppository.

The effect of temperature on drug release from Witepsol® H15 was evaluated using an *in vitro* dissolution test based on the USP I basket apparatus. The temperature of the dissolution bath was varied between 32–38°C in approximately 1° intervals. The results of these variable temperature runs are shown in Fig. 4. Comparison of the dissolution

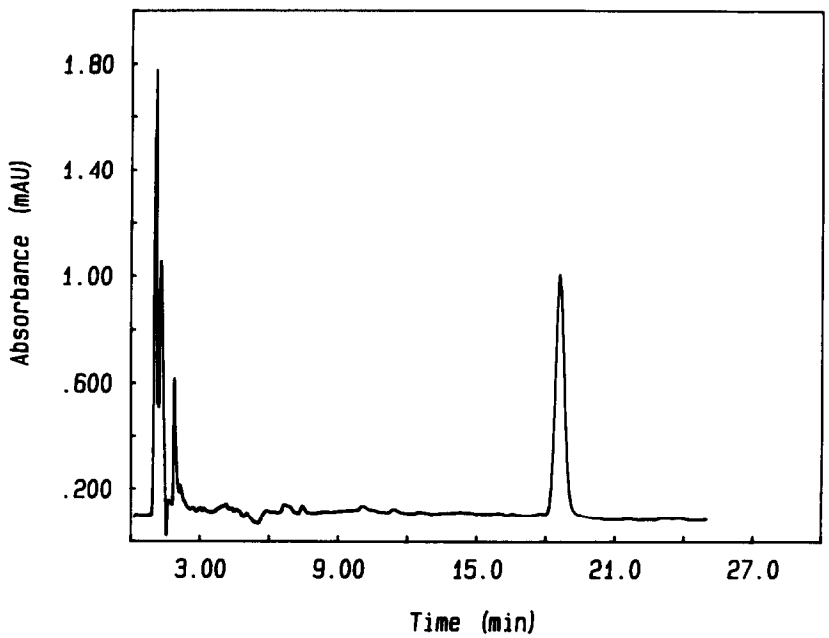

Figure 3
Chromatogram of a typical suppository dissolution sample containing meteneprost. Conditions are those described in the Experimental section.

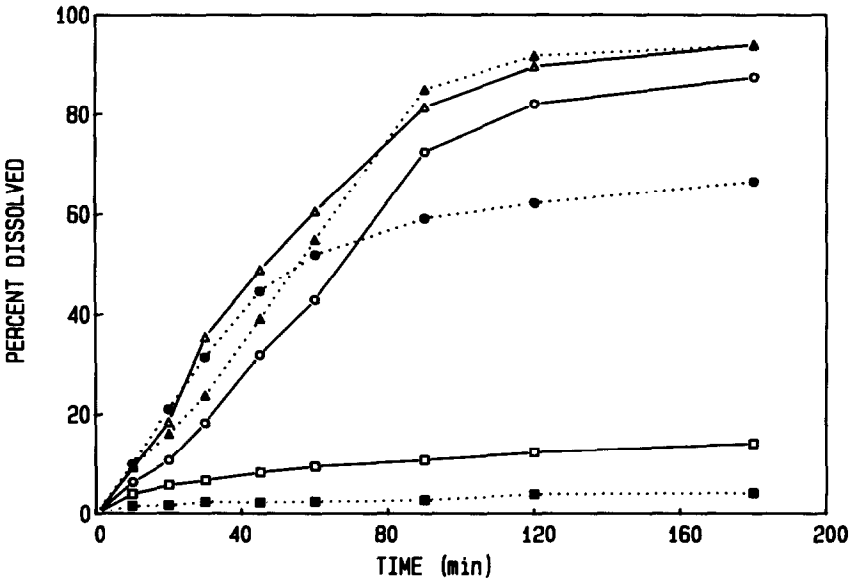

Figure 4
Dissolution profiles for Witepsol® H15 suppositories over the temperature range 30–40°C: ■, 32.8°C; □, 34.5°C; ●, 35.2°C; ○, 36.0°C; ▲, 37.0°C; and △, 38.1°C.

profiles reveals a rapid increase in drug release at temperatures above 35°C. Visual examination of the contents remaining in the stainless steel baskets after the 3-h runs revealed that the suppositories had retained their characteristic physical shape at 32°C (not shown in Fig. 4 due to <2% drug dissolution in 3 h), 32.8 and 34.5°C. Visually, the suppositories appeared to be melted in the remaining higher temperature runs. It is clear from the 32 and the 32.8°C runs that erosion of the suppository or dissolution of the lipid matrix had a minimal effect on drug release for these suppositories.

A typical DSC curve for the H15 based suppository is shown in Fig. 5. Examination of the melting behaviour (Fig. 5) indicates that although melting began below 30°C, the suppository was not substantially melted (i.e. >90%) until 35°C. Complete melting was observed for these suppositories at approximately 37°C and this corresponds to nearly complete drug release at the 2- and 3-h time points during the 37.0 and 38.1°C dissolution runs (Fig. 4).

While it is not surprising that drug release from the suppository increases with increased suppository melting, it is apparent that drug release from the suppository is very slow until the suppository base is nearly *completely* melted (see Experimental for an explanation of percent melted). This fact is more readily discerned from a plot of dissolution (percent meteneprost dissolved) against temperature (Fig. 6). As the suppository melts, a gradual increase in dissolution rate is observed until melting is nearly complete. At this point (approximately 35°C), drug release increases dramatically. In the dissolution experiment, this point visually corresponds to the suppository losing its characteristic shape and forming a molten pool at the top of the dissolution basket. At temperatures where this did not occur (where the original shape was retained but the surface was mottled or chalky in appearance) drug release was invariably extremely low. The steepness of the curve in Fig. 6 demonstrates that the relationship of

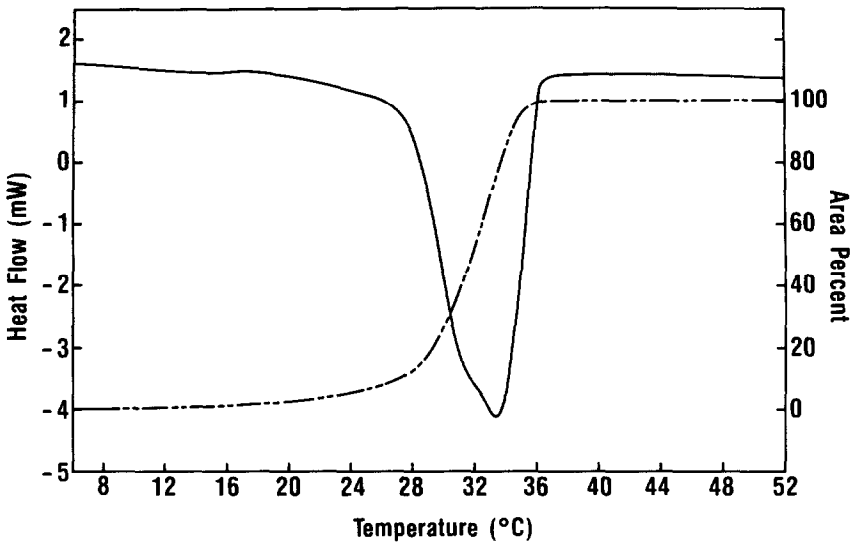

Figure 5
Typical DSC melting curve for a Witepsol® H15 based suppository. Suppository composition and instrumental conditions are given in the Experimental section.

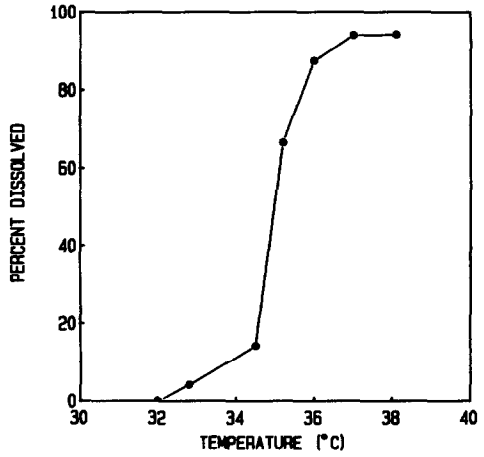

Figure 6
Graph of percent dissolved in 3 h against temperature for Witepsol® H15 based meteneprost suppositories.

suppository melting to drug release (*in vitro*) is essentially an all-or-nothing proposition: complete melting is necessary for satisfactory drug release to occur.

During the next study, temperature was maintained constant at 37°C and the melting behaviour of the meteneprost potassium suppositories was varied. This was accomplished by preparing suppositories identical to those tested in the variable temperature study, except that fatty suppository bases with a broad spectrum of melting ranges were substituted. The results for area percent melted of the suppositories formulated with Witepsol® E76, E85, H15/E76 (1:4) and Suppocire® AM are summarized in Table 1. In this manner, meteneprost potassium suppositories melting (at the 90 area percent level) between 34–43°C were obtained. Dissolution profiles for these suppositories at 37°C are given in Fig. 7. In general, the observed dissolution behaviour

Table 1
Temperatures (°C) at which the various percentages of the total area under the DSC curve occurred

Base	Area percent melted* 75%	90%	100%
H15	33.2	34.2	36.6
E76	35.1	36.2	38.5
E85	40.5	42.8	46.6
H15/E76	34.2	35.6	37.8
AM	33.8	35.6	39.0

*Percent melted in the text refers to percentages of the total area under the melting curve.

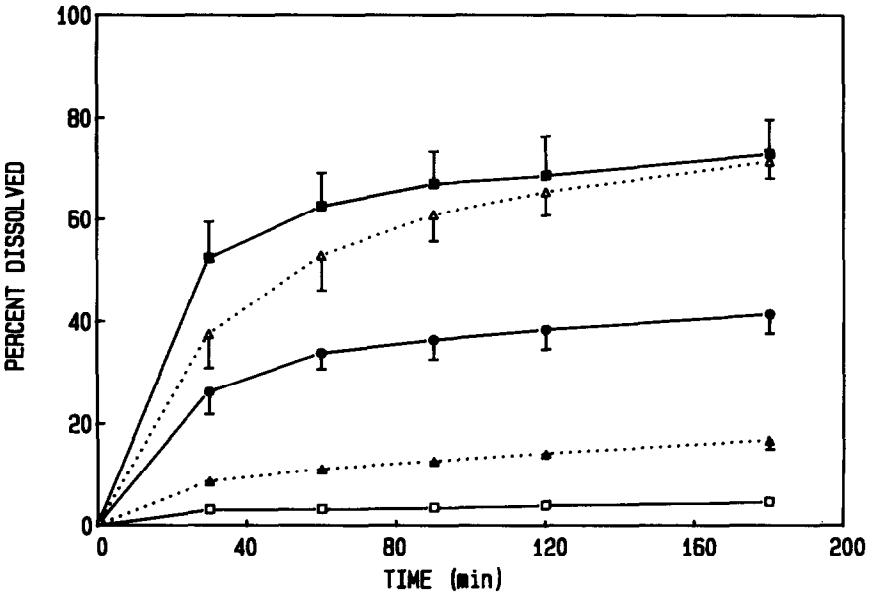

Figure 7
Meteneprost potassium suppository dissolution profiles at 37°C; 1 SD is shown. ■, H15; △, H15/E76 (1:4); ●, AM; ▲, E76; and □, E85.

confirms that lower melting corresponds to greater drug release. Examination of the melting behaviour in Table 1 for the various suppositories indicates that both E85 and E76 will not be completely melted at 37°C and consequently drug release should be minimal (Fig. 7). Suppositories formulated with H15 and H15/E76 (1:4) are nearly completely melted (>90 area percent) and exhibit good drug release characteristics. Suppositories containing AM base represent an intermediate case melting over a broader temperature range than the corresponding H15-based suppository.

Several workers have proposed models for the release of drug from fatty suppository melts [8, 9] and the mechanism is usually broken down into three steps. Since meteneprost potassium is only slightly soluble in molten H15 base, the first step is mass transport of drug particles by sedimentation within the suppository melt. After transport to the lipid/aqueous interface, the drug particles are first wetted by the aqueous phase

and dissolution of the drug follows in the final step. If transport of the drug particles to the interface is assumed to be rate limiting and dissolution is assumed to be much faster than this transport rate, mass transport for lipid insoluble drugs can be described by equation (1) [8]:

$$\phi = C \cdot S_b \cdot V_s, \tag{1}$$

where ϕ = mass flow of particles, C = concentration of particles in the suspension, S_b = interfacial area and V_s = the sedimentation rate. From equation (1), the mass flow in the lipid phase (constant interfacial area) is proportional to drug particle concentration and the sedimentation rate. The sedimentation rate (V_s) is in turn proportional to the square of the particle size and is inversely proportional to the viscosity of the suppository melt [10]. Within the framework of this model, if drug release from the suppositories in Fig. 7 is transport limited, then drug release would be dependent on the viscosity of the suppository melt. However, the release of drug from the suppositories may be more complex than that described by equation (1) because of possible effects of the colloidal silicon dioxide as primary particles (10 nm) or as aggregates. It is unlikely that drug release is dissolution rate limited since the aqueous water solubility of meteneprost potassium is >50 mg ml^{-1}.

The viscosity results for the meteneprost potassium suppositories are given in Table 2. Since the E76 and E85 suppositories are not completely melted at 37°C these measurements were taken at the temperatures in Table 1 representing 100 area percent melted. At 37°C, the AM based suppository is the least viscous followed by the H15 and H15/E76 (1:4) based suppositories, respectively. On the basis of the viscosity results (Table 2), the differences in the observed *in vitro* drug release (Fig. 7) between the AM, H15 and H15/E76 (1:4) based suppositories cannot be explained in terms of differences in mass transport of drug particles by sedimentation. The same meteneprost potassium

Table 2
Viscosity measurements of meteneprost potassium suppository melts

Sample	Shear rate (s^{-1})	Viscosity (mPas)	Temperature (°C)
Placebo*	120	74.2	37.0
H15 + 2% CSD	120	72.4	37.1
H15 base*	120	35.0	37.2
H15	120	82.1	37.0
	60	86.9	37.0
	24	96.1	37.0
AM	120	67.8	37.3
	60	70.4	37.1
	24	79.1	37.1
H15/E76 (1:4)	120	95.5	37.0
	60	104	37.0
	24	111	36.8
E76	120	84.7	39.0
	60	92.0	39.0
	24	110	39.0
E85	120	60.8	46.2

*Placebo suppositories were prepared as described in the Experimental without 11 mg of meteneprost potassium. H15 base refers to Witepsol® H15 without drug or 2% CSD.

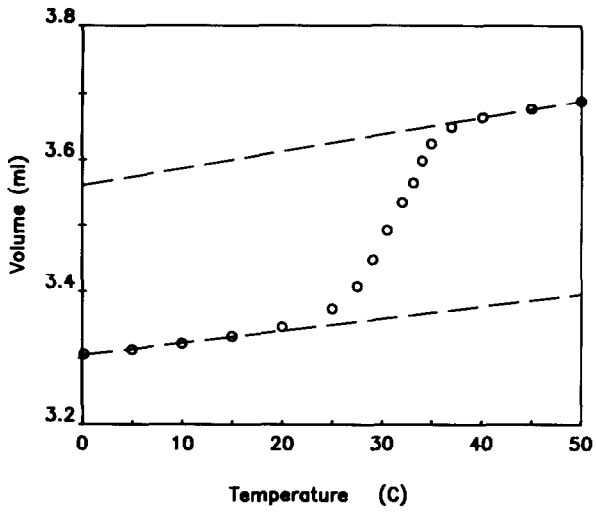

Figure 8
Dilatometric profile of Witepsol® H15 suppository base. Circles are experimental data points. Dashed lines correspond to the limiting low and high temperature thermal expansions of the solid and melt, respectively.

bulk drug lot was used to prepare all of the suppositories and particle size is assumed to be constant in these samples. The viscosity results for H15 base and H15 + 2% CSD placebo are in good agreement with the results of other investigators [10]. The addition of 2% CSD approximately doubles the observed viscosity for H15 based suppositories and addition of meteneprost potassium further increases the observed viscosity. Previous workers have also reported the slight non-Newtonian pseudoplastic behaviour indicated by the results for the suppository melts in Table 2 [10].

The percentage of liquid triglycerides in the suppositories at various temperatures has been estimated by determining the percentage of the total area under the DSC melt profile below a particular temperature. Other methods can be used to obtain comparable results. In particular, dilatometry measurements on Witepsol® H15 suppository base samples were undertaken to provide complementary data on the melting process. An experimental volume against temperature profile is shown in Fig. 8. The straight line extrapolations of the low temperature solid and the high temperature liquid thermal expansions are also indicated. These extrapolations can be used to estimate the liquid/solid ratios graphically as described in ref. 11. The results of such an analysis are shown in Fig. 9, where a comparison is made to the integrated DSC melt profile.

The correspondence between the dilatometric measurements and the DSC cumulative melt profile (Fig. 9) further establishes the appropriateness of the DSC method for determination of melt fraction. This close correspondence is not necessarily maintained for alternate choices of the DSC experimental parameters. It is important to remember that DSC is a dynamic technique, as opposed to a quasi-equilibrium technique, and results obtained by DSC will only replicate those obtained by equilibrium methods in the limit of low scan rates, small sample sizes, and good thermal contact between the sample and its container. Since slow scan rates and small sample sizes result in reduced response, an appropriate compromise must be achieved at which a sufficient signal is obtained with an absence of thermal lag. Our choice of parameters reflects this compromise. It should be noted that equilibrium in this case refers to time periods in the order of hours, since

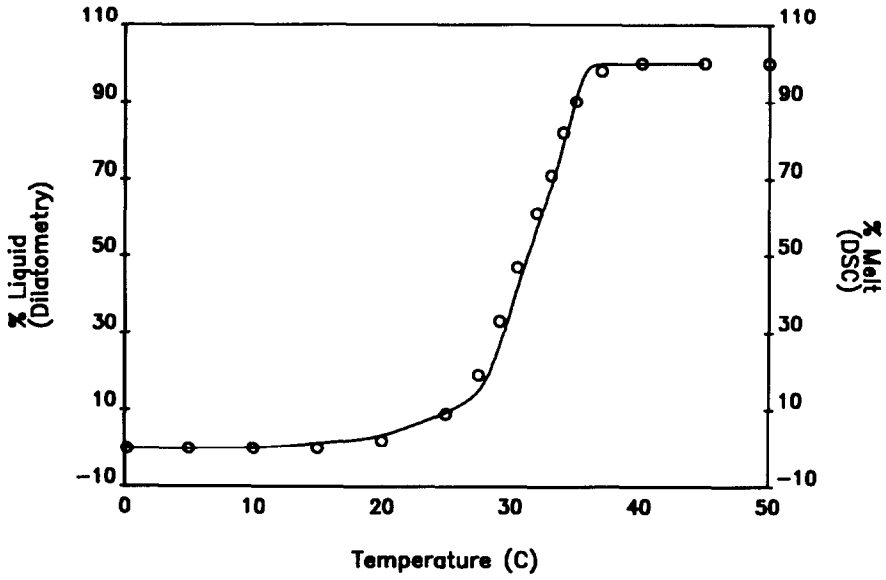

Figure 9
Comparison of percent liquid by dilatometry (O) and percent melted by DSC (−) for the same sample of Witepsol® H15 suppository base.

longer time periods (e.g. in the order of weeks or months) will result in possible changes in phase compositions and degree of crystallinity.

It has been demonstrated that meteneprost potassium vaginal suppositories must be substantially melted (i.e. >90 area percent from DSC) for significant *in vitro* release of drug to occur. Variable temperature dissolution profiles have shown that, at temperatures where the suppositories are not completely liquid, erosion or dissolution of the lipid matrix had minimal effect on drug release from these suppositories. In meteneprost vaginal suppositories formulated with lipid bases possessing a variety of melting ranges, satisfactory drug release was observed only in those suppositories which are nearly completely melted on the basis of their DSC melting curves. Suppositories whose melting curves extended beyond 37°C exhibited a lower extent of dissolution and a slower dissolution rate. Viscosity of the suppository melts was found to be less critical in terms of good meteneprost release when compared with complete melting at temperatures ≤37°C. Suppositories with a smaller melting range exhibited better drug release characteristics as long as complete melting had occurred. This factor may explain the slower release observed for AM based suppositories when compared to the more viscous (in the melt) H15 or H15/E76 (1:4) based suppositories.

The *in vitro* drug release results reported in this study are in substantial agreement with published *in vivo* results for vaginal drug absorption from meteneprost containing suppositories. Wickrema Sinha *et al.* have found in human female subjects that 77 ± 3% of the radiolabelled dose was recovered unabsorbed from Witepsol® E76 based meteneprost suppositories compared with 54 ± 20% recovered unabsorbed from Witepsol® H15/E76 (1:4) meteneprost suppositories [5]. Maximum plasma concentrations were reported to be 6.3–7.3 ng ml^{-1} at 12–18 h and 10.3–21.8 ng ml^{-1} at 6–8 h after administration of E76 and H15/E76 based suppositories, respectively [5]. In studies in female Rhesus monkeys, vaginal administration of the adamantanamine salt of

meteneprost resulted in peak plasma levels of 10–20 and 1–8 ng ml^{-1} using lower melting H15 based suppositories and higher melting E76 based suppositories, respectively [4]. In both studies, the *in vivo* drug absorption results correlate in rank order with the *in vitro* drug release observed for the E76 based suppositories when compared with the H15 and H15/E76 based suppositories. For this type of lipid based vaginal suppository, complete suppository melting would appear to be the critical factor controlling drug release and subsequent vaginal absorption. DSC has been found to be a suitable technique for the characterization of the suppository melting process and hence was useful as a predictor of optimal drug release in these lipid based meteneprost potassium vaginal suppositories. In a quality control environment, it would be desirable to utilize DSC area percent measurements to ensure good *in vitro* drug release for this type of suppository formulation.

References

[1] M. Borten, L. A. DiLeo and E. A. Friedman, *Am. J. Obstet. Gynec.* **150**, 561–565 (1984).
[2] C. Somell and A. Olund, *Contraception* **33**, 189–194 (1986).
[3] S. E. Eder, M. Chatterjee and C. Salvio, *Prostaglandins* **32**, 19–23 (1986).
[4] F. A. Kimball, J. C. Cornette, G. L. Bundy and K. T. Kirton, *Prostaglandins* **20**, 559–569 (1980).
[5] A. J. Wickrema Sinha, S. B. Reele, S. R. Shaw and B. A. Thornburgh, Abstracts of Papers, 43rd International Congress of Pharmaceutical Sciences, Montreux, Switzerland; Abstract 214, p. 310 (1983).
[6] A. C. Ganguli, K. Green and M. Bygdeman, *Prostaglandins* **14** 779–784 (1977).
[7] M. Bygdeman, A. Ganguli, K. Kinoshita, V. Lundstrom, K. Green and S. Bergstrom, *Contraception* **15**, 129–141 (1977).
[8] A. J. M. Schoonen, F. Moolenaar and T. Huizinga, *Int. J. Pharm.* **4**, 141–152 (1979).
[9] J. J. Rutten-Kingma, C. J. deBlaey and J. Polder, *Int. J. Pharm.* **3**, 179–186 (1979).
[10] J. J. Tukker, W. T. P. M. vanVught and C. J. deBlaey, *Acta Pharm. Tech.* **29**, 187–194 (1983); and references therein.
[11] J. Hannewijk, A. J. Haighton and P. W. Hendrikse, in *Analysis and Characterization of Oils, Fats and Fat Products*, (H. A. Boekenoogen, Ed.), pp. 119–182. Interscience, New York (1964).

[*Received for review 30 November 1987*]