DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(9-11), 1799-1806 (1987)

STRUCTURAL STABILITY OF OPHTHALMIC OINTMENTS CONTAINING SOFT PARAFFIN

D. De Rudder*, J.P. Remon* and P. Van Aerde**

* : Laboratory of Pharmaceutical Technology, State University of Gent, Harelbekestr. 72, B-9000 Gent, Belgium.

** : Alcon-Couvreur, Rijksweg 6, B-2670 Puurs, Belgium.

INTRODUCTION

Soft paraffin (vaseline, petrolatum) is widely used in the formulation of pharmaceuticals and cosmetics. Soft paraffin is a plastic mass consisting of a mixture of solid and liquid saturated hydrocarbons (normal, iso and ring paraffins). The crystalline network of solid hydrocarbons encloses the liquid phase and immobilizes this fraction through adsorption, capillary action and molecular interactions.(1)

Most of the drugs used in eye ointments are suspended in the excipient which contains mainly petrolatum. Several commercialized eye ointment formulations show structural breakdown and liquid separation (syneresis) leading to physical nonhomogeneity of the ointment.(2,3)

During production mixing is required to maintain homogeneity during the cooling phase of the manufacturing process.

In this study the influence of the mixing process and of the temperature treatment on a typical ointment base, is examined by oil number determination.
Basic characteristics of the petrolatum raw material such as "final" viscosity, melting enthalpy, X-ray diffraction and content of n-paraffins are correlated with oil numbers.

EXPERIMENTAL

Materials :

- All petrolatums and the lanolin oil used were of U.S.P. XXI grade.

Manufacturing methods :

- Composition of the ointment formulation : petrolatum/ lanolin oil (97/3, w/w).
- Laboratory scale production : formulations were prepared in a Hobart planetary mixer (2 kg batch size). After melting (70 °C), the mass was cooled to room temperature while stirring (100 r.p.m.).
- Industrial scale production : pilot batches (100 kg) were prepared in a Fryma VME 120 equipped with a homogeniser, a scraper and a stirrer. The homogeniser, used for drug dispersion, was not operated. The influence on the final consistence of the stirrer rate (1500, 1000 and 500 r.p.m.), of the scraper rate (10 and 2 r.p.m.) and of temperature treatment, was examined.

- Differential scanning calorimetry : several petrolatum samples and eye ointment formulations were submitted to a D.S.C. analysis using a Perkin Elmer D.S. calorimeter. Sample size was about 30 mg, the heating rate was 10 °C min^{-1} at a range of 5 mcal/°C^{-1}. The melting enthalpy was calculated for all samples.
- X-ray diffraction analysis : All samples analysed by D.S.C. were submitted to X-ray diffraction analysis using

a Philips X-Ray diffraction apparatus (Philips P.A. 25, equipped with a copper anticathode 25 mA, 40 KV.).

- Viscosity determination : "Final" viscosity was determined using a Haake RV 12 viscosimeter (N.V. spindle). The samples were heated to 55 °C in the cup, cooled to room temperature and the "final" viscosity was determined at room temperature (22 °C) after 24 hr.
  "Final" viscosity is defined as the minimum viscosity recorded at a constant shear of 2 r.p.m.
- Oil number determination : 3 gram vaseline or vaseline-lanoline oil blends were evenly spread on a Whatman paper n° 1 (12 cm x 6 cm) over 5 cm x 6 cm area. The strips of filter paper were supported vertically at room temperature and the height of ascent of oil measured after 24 h. The height of ascent expressed in mm is defined as the oil number. Oil numbers of experimental batches were determined within 24 h. after production.(4)
- Determination of n-paraffin content in petrolatum samples : the method described by Presting and Boenke (5) was used. The experiments were performed on 10 g of the samples.
- Production specifications : All batches were stirred and scraped until the temperature or 50°, 40° of 30°C has been reached.
  Beyond this temperature batches were cooled to room temperature with and without scrapers in motion.

RESULTS AND DISCUSSION

Influence of processing parameters on the oil number.

Fig. 1 shows the influence of processing parameters, performed on petrolatum 1-lanolin oil mixtures (97-3, w/w). The oil number is plotted versus the temperature at which stirring and/or scraping is stopped. The lowest oil number was obtained when both stirring and scraping were

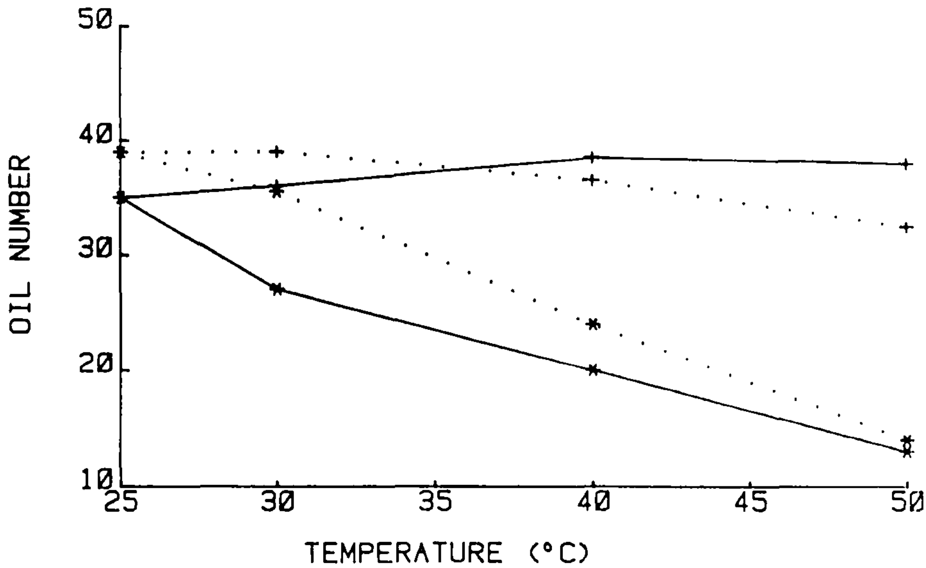

Figure 1

Oil numbers (of industrial batches) in function of temperature at which stirring and/or scraping is stopped. The scraper rotational speed was kept constant at 10 r.p.m. The value on the X-axis indicates the temperature when stirring was stopped (+) or when both stirring and scraping were stopped (•).

Two different speeds were selected for the stirrer : 500 r.p.m. (——); 1000 r.p.m. (···).

stopped at 50 °C. The oil number increased progressively as the mechanical shear was applied up to lower temperatures. All batches produced while scraping was continued until room temperature, showed a high oil number, independent of the temperature at which stirring was stopped.

It is obvious that scraping at lower temperatures, independent of stirring, has a dramatic influence on the oil number. Two levels of the scraper rotational speed were studied. The lower speed (2 r.p.m.) induced a distinct

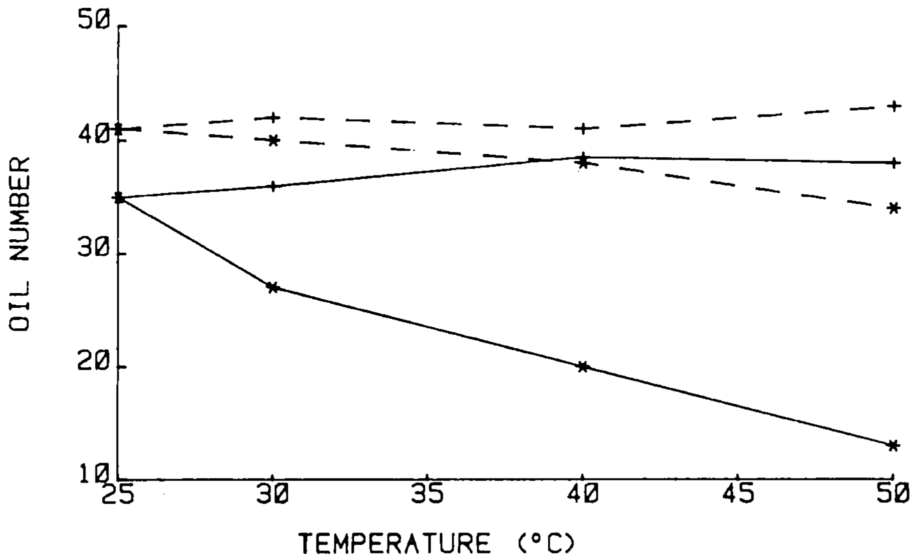

Figure 2

Oil numbers (of industrial batches) in function of temperature at which stirring and/or scraping is stopped. The stirrer rotational speed was kept at 500 r.p.m. The value on the X-axis indicates the temperature when stirring was stopped (+) or when both stirring and scraping were stopped (•).

Two different speeds were selected for the scraper : 10 r.p.m. (——); 2 r.p.m. (– – –).

higher oil number than the higher one (10 r.p.m.) (Fig. 2). Batches with an oil number over 25 showed visual syneresis after one week. Oil number values obtained from laboratory scale experiments were similar to those of the industrial batch productions indicating that scaling had no influence on the oil number.

Because shear induced syneresis could be attributed to a difference in the microcrystalline structure of the petrolatum, D.S.C. and X-ray analysis were performed on two

Table 1. Melting enthalpy and oil number for petrolatum-lanoline oil blends

	Melting enthalpy $(mcal/g^{-1})$	Oil number (mm)
Petrol.1-lan.oil blend (97/3) (Batch A)	910	20
Petrol.1-lan.oil blend (97/3) (Batch B)	981	40
Petrol.2-lan.oil blend (97/3)	1317	19

samples : an industrial batch with a low (A) and one with a high oil number (B). As can be seen from Table 1, the melting enthalpy of batch A is approximately equal to batch B.

This could indicate that the extent of microcrystalline structure formed during cooling is independent of the oil number and that chemical composition of the ointment rather than processing parameters may influence the bleeding tendency. These findings were confirmed by X-ray diffraction analysis. The low oil number of batch A increased with time and reached the level of batch B after 5 weeks.

Table 2 shows the relation between " final" viscosity, oil number and n-paraffin content of commercial grade petrolatums.

A low oil number is related to a high "final" viscosity, a high n-paraffin content and a high melting enthalpy.

Table 2. Oil number, "final" viscosity and amount of n-paraffin for pure petrolatums

	Oil number (mm)	Melting enthalpy (mcal/g)	Final viscosity (mPa.s)	Amount n-paraffin (g w/w)
Petrolatum 1	15	750	350	16.8
Petrolatum 2	5	1225	10,653	40.6
Petrolatum 3	0	1509	9870	46,1

As can be seen from Table 1, petrolatum 1, with a relative high oil number of 15, yielded a petrolatum-lanolin blend with a very high oil number of 40 while petrolatum 2 with an oil number of 5 produced an ointment with an oil number of only 19.
This may confirm that the chemical composition (content of n-paraffin) is the main factor influencing the physical stability of eye ointments on petrolatum basis.

CONCLUSION

Mechanical shear has a deleterious effect on the physical stability of petrolatum. The oil number determination may be a useful tool for the optimization of a production process and the prediction of physical stability of petrolatum ointments. Problems related to the syneresis of these ointments are basically dependent on the "quality" of the petrolatum raw material.
Experimental production prooved that with an oil number of pure petrolatum up to a value of 5, no problems of syneresis are encountered, even after application of mechanical shear. D.S.C and "final" viscosity may give supplementary information for the selection of an appropriate petrolatum.

REFERENCES

1. B.W. Barry and A.J. Grace, Journal of Texture Studies, 2, 259 (1971).
2. R. Cheng-Chyi Fu and D.M. Lidgate, J. Pharm. sci., 74 290 (1985).
3. A.R. Longworth and J.D. French, J. Pharm. Pharmacol., 21, Suppl. 1S-5S (1969).
4. H.J. Van der Pol, Pharm. Weekbl. 9, 3 (1960).
5. W. Presting and R. Boenke, Die Pharmazie, 9, 562 (1954).