

# Chemical and Physicochemical Characterization of Petrolatums Used in Eye Ointment Formulations

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**Abstract**—Petrolatums from different manufacturers were characterized by viscosity measurements, oil number and ratio of low to high mol. wt components (capillary gas chromatography). Viscosity measurements and oil numbers of original materials did not correlate with the viscosity of the processed material in eye ointments. The ratio of high carbon number components to the low carbon number components was a reliable predictor for the viscosity of the formulation.

Drugs in ophthalmic ointments are usually suspended in a petrolatum-based excipient. Commercial petrolatums are composed of solid and liquid saturated hydrocarbons (Barry & Grace 1971). The industrial preparation of petrolatum is a complex process. Due to the variability in crude oil resources and in product variability within one oil field, petrolatum manufacturers often need to add paraffin oil and microcrystalline waxes in order to meet product specifications.

Pharmaceutical manufacturers of eye ointments face a problem of structural breakdown and syneresis of ophthalmic ointments (Van den Pol 1960; Longworth & French 1969; De Rudder et al 1987). Pharmacopoeia specifications are unable to detect variability in composition of petrolatums in relation to the physical non-homogeneity of the ointment. This paper deals with the physicochemical and gas chromatographic characterization of petrolatums.

## Materials and Methods

Petrolatums originated from three different producers, referred to as producer A (Penreco, Pennzoil, PA), B (Protopet, Witco, NY) and C (Merk, DEA, Germany).

### Viscosity determinations and oil number determination

Before each experiment, petrolatum samples were melted at 75°C and subsequently cooled to room temperature. Fifteen hours after heating, viscosity determinations were performed with a Brookfield Synchro Lectric Viscosimeter (Brookfield Eng. Lab. Inc., Soughton, MA, HAT model equipped with a spindle T-E rotating at 2 rev min<sup>-1</sup>. All determinations were performed in triplicate at room temperature (20 ± 1°C).

**Oil number determination.** Three grams of petrolatum was evenly spread on a Whatman paper No 1 (12 cm × 6 cm) over a 5 cm × 6 cm area. The strips of paper were supported vertically at room temperature and the height of ascent oil was read after 24 h. The height of ascent expressed in mm, is defined as the oil number (De Rudder et al 1987). The determinations were carried out at 20 ± 1°C and at a relative humidity (r.h.) of 40%.

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### Working test

Fifteen hours before the experiments, blends were made by melting the different components at 75°C. After mixing the different components in the specified ratios the samples were allowed to cool to room temperature. For the working test a grease worker as described in ASTM D217 was used. The petrolatum was allowed to cool at different temperatures and the working test was performed by operating at a frequency of 1 stroke s<sup>-1</sup> for 1 min. After the working test was performed, viscosity and oil numbers were determined as described previously.

### Industrial production of eye ointment base

Industrial productions (70 kg) were performed with a petrolatum batch from producer C in a Fryma VME 120 mixer (Fryma Machinen AG, Rheinfelden, Switzerland). The petrolatum was melted at 75°C in the mixer and cooled to 28°C. During the cooling phase, mixing (500 rev min<sup>-1</sup>) and scraping (10 rev min<sup>-1</sup>) were performed to a temperature of 48°C. Scraping was continued to 38°C. Before each

Table 1. Viscosity and oil number of petrolatum blended with high viscosity oils and microcrystalline waxes originating from producer B. The blends were treated with the working test at different temperatures.

Material	Viscosity (mPa s)	Oil number (mm)
Petrolatum (pure)		
Not treated	740 000	44.2
Treated at		
30°C	522 857	44.9
40°C	845 714	39.6
50°C	943 333	41.6
Petrolatum/high viscous oil (85/15; w/w)		
Not treated	1 283 333	41.9
Treated at		
30°C	931 429	46.4
40°C	1 140 000	40.3
50°C	1 237 500	39.4
Petrolatum/high viscous oil/microcrystalline wax (70/92/1; w/w/w)		
Not treated	1 960 000	37.5
Treated at		
30°C	697 143	40.0
40°C	1 002 857	35.3
50°C	1 322 500	42.6

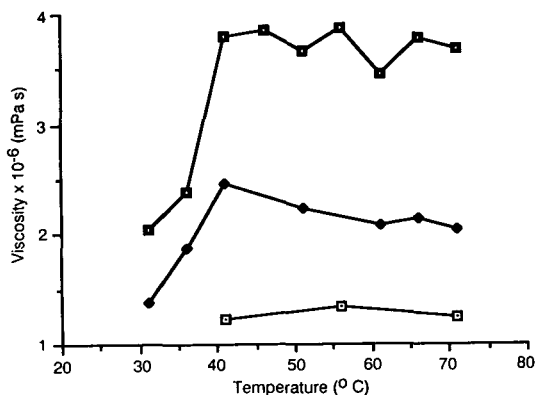


FIG. 1. Viscosity of three different petrolatum batches (producer C) after treatment at different temperatures with the grease worker.

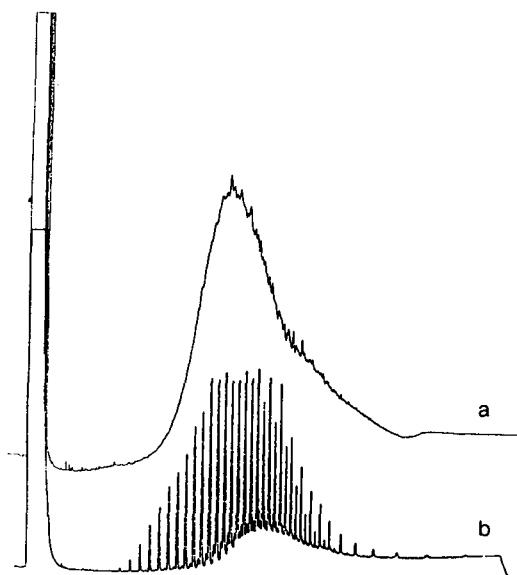


FIG. 2. Gas chromatographic profile of a liquid paraffin fraction (a) and of the microcrystalline waxes (b).

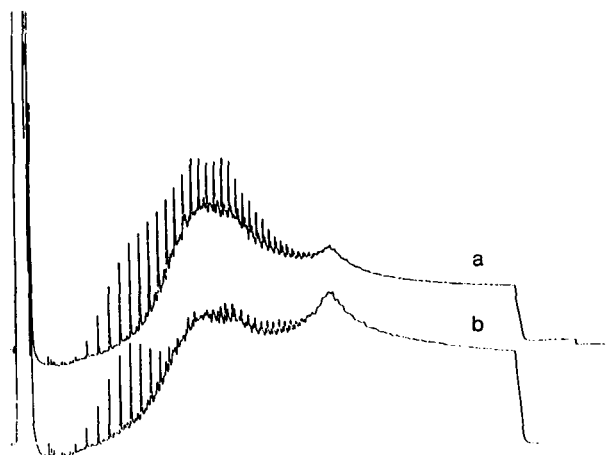


FIG. 3. Gas chromatographic profile of petrolatum (a) from manufacturer A and of the synthesis fraction (b).

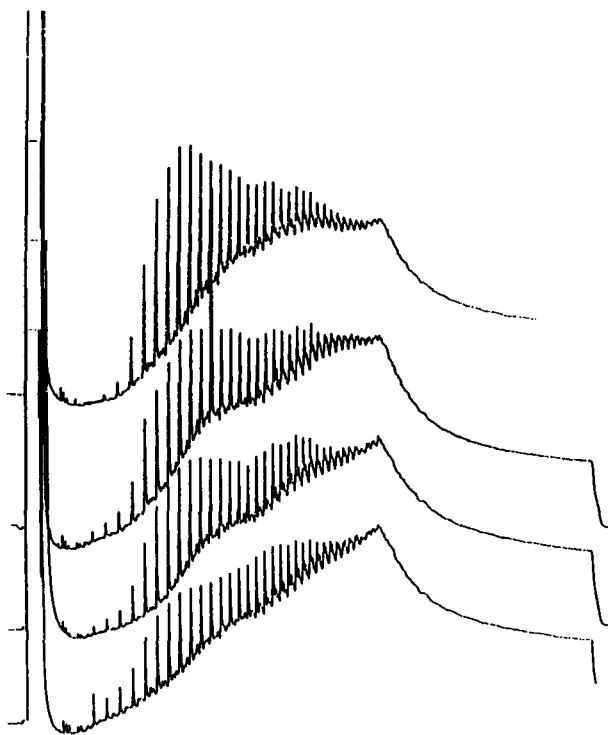


FIG. 4. Gas chromatographic profile of four separate batches from manufacturer B.

sampling in the temperature range from 68 to 38°C, vacuum was applied to avoid air being mixed into the ointment base. Petrolatum samples were taken for viscosity determinations at the following temperatures of the petrolatum mass: 68, 58, 56, 50, 46, 38, 36, 33 and 28°C. Using a silicone tube, the petrolatum was transferred to the hopper of an IWK TU 100 (IWK Verpackungstechnik GmbH, Statensee, Germany) filling line for eye ointment tubes. In this hopper a mixing arm rotating at 10 rev min<sup>-1</sup> kept the petrolatum in motion. Further samples were taken at the end of the silicone tube, in the hopper, at the filling needle and from filled tubes.

#### Gas chromatographic analysis

A Perkin-Elmer 8320 Capillary Gas Chromatograph (Perkin-Elmer, Norwalk, USA) equipped with an on-column injection and an OV-1 column (10 m × 0.32 mm) with a 0.1 μm film thickness and a flame ionization detector was used. Temperature programming was as follows: initial temperature 100°C increasing to 300°C at a rate of 15°C min<sup>-1</sup> followed by an isothermal period of 10 min at 300°C. Samples were dissolved in xylene at a concentration of 2 mg mL<sup>-1</sup> and 1 μL was injected. Quantification of the paraffin oil was performed using a standard oil (Vestan A 180) with a 400 Da mol. wt. Quantification of the microcrystalline waxes was performed using two standards: 1-heptadecene (for the lower mol. wt carbons up to C<sub>24</sub>) and squalane (for carbons > C<sub>24</sub>). The ratio in peak heights for the high carbon distribution (C<sub>26</sub>–C<sub>38</sub>) vs the heights for the low carbon distributions (C<sub>17</sub>–C<sub>25</sub>) were calculated.

Table 2. Viscosity and ratio of high hydrocarbon distribution (C26-C36) vs low hydrocarbon distribution (C17-C25) for 8 different petrolatum batches from producer C.

Batch number	Viscosity (mPa s)	Ratio (high vs low hydrocarbon distribution)
1	1 100 000	19.90
2	772 000	2.54
3	650 000	2.30
4	550 000	1.32
5	520 000	1.36
6	500 000	1.35
7	420 000	1.13
8	1010 000	4.08

### Results and Discussion

De Rudder et al (1987) have reported on the deleterious effect of mechanical shear on the physical stability of petrolatum and have stressed the importance of the quality of raw materials. The same authors suggested that with a maximal oil number of 5, no problem of oil syneresis should be seen. The routine use of oil number determination as a quality control tool proved to be inadequate, since for several petrolatum batches syneresis occurred even if the number was lower than 5. Besides, small variations in ambient temperature and r.h. showed a dramatic influence on the oil number value. For one batch of petrolatum B the oil number increased from  $3.8 \pm 0.3$  (at  $21^\circ\text{C}$ ) to  $16.8 \pm 1.1$  (at  $28^\circ\text{C}$ ). For the same petrolatum the influence of r.h. (at the same temperature of  $28^\circ\text{C}$ ) on the oil number was as follows: the

highest oil number ( $24.2 \pm 1.0$ ) was observed when the lowest r.h. was used (25%) and at 40% r.h. the oil number fell to  $14.6 \pm 0.5$ . Similar findings were observed for the other batches from the same supplier and for batches from the two other suppliers. The influence of the r.h. on the migration of the petrolatum could be explained by the affinity of the hydrophobic petrolatum for the paper. For a lower ambient r.h., fewer water molecules were absorbed by the paper resulting in a higher affinity of the petrolatum for the paper and in higher oil numbers. The producers of petrolatum add high viscous paraffin oils and microcrystalline waxes at the end of the production process in order to obtain the required viscosity. In a first attempt to solve the problem of syneresis, the influence of the addition of high viscosity oil and waxes on viscosity and oil number was examined. Those determinations were done after the mixtures were treated at different temperature using the working test. Table 1 shows the viscosity and oil number data on mixtures prepared from petrolatum, high viscosity oils and microcrystalline waxes, all originating from producer B. The data confirm that the working test (mechanical shear) has an influence on the viscosity and on the oil number, especially when the working test was performed at temperatures below  $40^\circ\text{C}$ . Fig. 1 shows an example of the variability in viscosity of three batches of petrolatums from producer C. For all three batches, the working test has no major influence on the viscosity at temperatures between  $70$  and  $40^\circ\text{C}$ . For two out of the three batches a dramatic influence below  $40^\circ\text{C}$  can be seen. No correlation was found between viscosity, oil number and submission to working test. So physicochemical tests proved

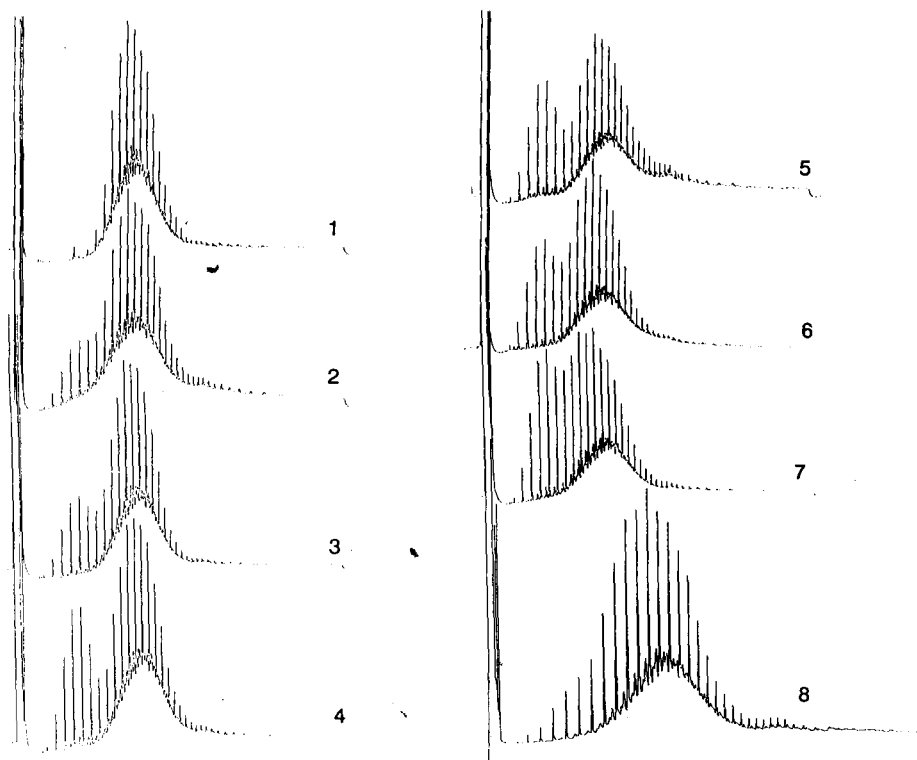


FIG. 5. Gas chromatographic profile for eight separate batches from manufacturer C. The numbers refer to the batch numbers (Table 2).

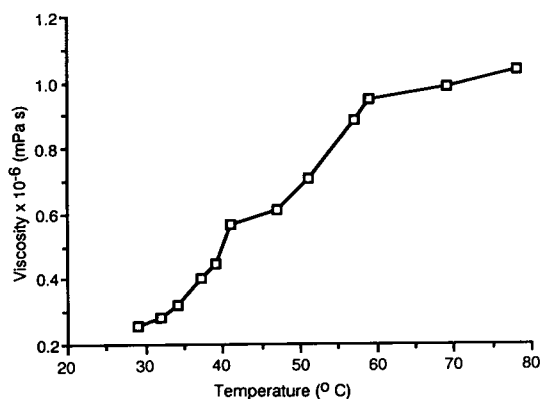


FIG. 6. Viscosity data of a petrolatum base processed in an industrial mixer and cooled with two different mixing and scraping programmes. Viscosity of the mass during petrolatum transfer and filling are also indicated. Mixing rate  $500 \text{ rev min}^{-1}$  + scraping rate  $10 \text{ rev min}^{-1}$  (mixing stopped at  $38^\circ\text{C}$ ).

to be inefficient for defining parameters that are helpful in the prediction of petrolatum behaviour during and after industrial production.

Capillary gas chromatographic (GC) characterization of different petrolatums was undertaken. Fig. 2 shows the profile of the liquid paraffin fraction (a) and of the microcrystalline waxes (b). Fig. 3 gives the GC profile of a petrolatum from manufacturer A (a) and of the syneresis fraction (b), indicating that this latter fraction contained the liquid paraffin fraction and the low mol. wt microcrystalline waxes. Petrolatum from producer A showed an excellent viscosity for eye ointment production ( $347\,000 \text{ mPa s}$ ) but an unacceptable degree of syneresis. The GC pattern of the four batches from producer B are characterized by a high amount of high mol. wt carbon waxes and paraffin oil in comparison with petrolatum A (Fig. 4). This explains the high viscosities of petrolatum B ranging from  $800\,000 \text{ mPa s}$  for batch 4 to  $1\,107\,000 \text{ mPa s}$  for batch 2 in relation to the petrolatum from producer A. These petrolatums showed no syneresis but their viscosity was too high to be used as an eye ointment base. The liquid paraffin fraction in the petrolatum from producer B was different in comparison with petrolatum A although the mol. wt range was similar. Producer C supplied several consecutive batches of petrolatums. Table 2 indicates the viscosity and the ratio of high hydrocarbon distribution (C26–C38) vs low hydrocarbon distribution (C17–C25) for 8 different batches of supplier C. The GC profiles of these petrolatums are completely different from petrolatum A and B. The liquid paraffin fraction has a mol. wt of about 400 as compared with Vestan 180 and is identical for all batches. Two different microcrystalline wax distributions are seen in the chromatograms (Fig. 5). The batch numbers 3 to 7

showed acceptable viscosity for an eye ointment base. The differences in viscosities were due to variations in ratio of high vs low carbon number hydrocarbons. In the case of batch 1 the low mol. wt microcrystalline waxes were missing while the highest viscosity was observed. For batch 7 the highest concentration of low mol. wt microcrystalline waxes correlated with the petrolatum of lowest viscosity (Table 2).

Fig. 6 shows the viscosity data of an ointment base from supplier C as a function of the mixing process during the cooling phase of industrial production of eye ointment. Mixing was stopped at  $38^\circ\text{C}$  as it was previously shown that shear had a deleterious effect on the structure of petrolatum if applied below  $40^\circ\text{C}$ . Applying a positive pressure in the mixing vessel to enable transfer of the eye ointment via the silicone tubing to the hopper on the filling line (2 transfers were performed) did not affect the viscosity, neither did the continuous motion (at  $10 \text{ rev min}^{-1}$ ) in the hopper. Viscosity measurements on the sample collected at the filling needle or from the ointment tubes were no different from those of the samples taken at the end of the silicone tubing or from the hopper after 2 h of mixing at  $28^\circ\text{C}$ . All viscosities were between  $120\,000$ – $230\,000$  and  $160\,000$ – $270\,000 \text{ mPa s}$  after first (4 samples) and second transfer (5 samples), respectively.

In our opinion it should be useful to specify in pharmacopoeias and in commercial leaflets from petrolatum manufacturers the viscosity ranges for petrolatums used in eye ointments. However, these viscosities should not be measured at  $100^\circ\text{C}$  (as can be found in manufacturers' leaflets) but rather at room temperature, since this value gives a better indication of the viscosity of the ointment as it will be used by the patient.

It can be concluded that capillary gas chromatography is a useful tool to optimize the composition of petrolatums resulting in a precisely defined product, reducing to a large extent the batch variability of petrolatums for the industrial production of eye ointments.

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