DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 2017
VOL. 43, NO. 4, 595–599
http://dx.doi.org/10.1080/03639045.2016.1274902

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RESEARCH ARTICLE

Elucidation of the variability in consistency of pharmacopoeia quality petrolatum

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ABSTRACT

The Pharmacopeia monograph for petrolatum poorly defines the material's physical properties. Indeed, differences between petrolatum grades can be substantial; yield stress varies between 65 and 280 Pa which can be compared with the consistency of respectively thin cream or thick ointment. This variation is not only due to differences in composition or refining process but also as a result of different processing; for example, thermal history influences petrolatum structure considerably. Slow cooling of petrolatum resulted in a yield stress of 26 Pa and fast cooling in 79 Pa. X-ray showed that crystallinity was 0.7% for the first cooling case and 1.5% for the second one. Crystallite size was estimated to be 20–50 nm. To investigate if this relatively small difference in crystallinity may induce the difference in consistency, 15 nm SiO_2 particles were added to petrolatum. Indeed, a small increase in SiO_2 concentration led to a major increase in yield stress. This was argued to be due to the small size of the particles, resulting in a large increase in absolute number of particles. The Pharmacopeia does not unambiguously define the pharmaceutical excipient petrolatum. As a consequence, the formulator has to take care of selecting the appropriate grade as well as to carefully control the processing of the material in order to achieve a consistent pharmaceutical product.

ARTICLE HISTORY
Received 3 October 2016
Revised 25 November 2016
Accepted 14 December 2016

KEYWORDS
Petrolatum; crystallinity; X-ray; yield stress; thermal history

Introduction

Petrolatum is one of the most commonly used ingredients in pharmaceutical and cosmetic ointments and creams. Despite the wide application of petrolatum, the Pharmacopeia monograph[1] for petrolatum or white soft paraffin describes it poorly. Only general identification tests are described and the physical characterization methods are drop melting point and consistency by a penetrometry test. Penetrometry is a method by which relatively large viscous deformations in materials can be observed. However since petrolatum is a viscoelastic material, meaning it combines both viscous and elastic characteristics, structural testing should also focus on its elastic properties. This can be studied in more detail using oscillatory stress testing[2]. Therefore, the Pharmacopeia monograph is not capable of describing differences between petrolatum grades in great detail and thus possibly a great variety of different petrolatum products comply with the Pharmacopeia monograph. Similar tests are described in the United States Pharmacopeia and Japanese Pharmacopeia.

The chemical composition of petrolatum can be described as a blend of three different components, two solid hydrocarbon waxes and a liquid hydrocarbon fraction[3]. The two waxes are described as paraffin and a microcrystalline wax consisting of an average of 26–30 and 41–50 carbon atoms respectively. Furthermore, paraffin waxes contain mainly straight chain alkanes, while microcrystalline waxes contain iso-alkanes and naphtene-containing alkanes[4]. The amounts and nature of these components may be different for various grades of petrolatum[5,6]. Sources of crude material, differences in refining steps and differences in blending after refining can all attribute to differences in nature of petrolatum raw materials[2].

Apart from chemical composition, it is known from other fields that thermal history and crystallinity can affect material structure. This is shown in studies on polyethylene glycol (PEG)[7] and medium chain polyhydroxyalkanoate[8]. Since petrolatum has been described as a gel structure[3], there may be parallels to polymer structure and behavior under different thermal conditions.

A method to study the properties of petrolatum is the assessment of the consistency. For example, the physical properties of several white petrolatum products of Japanese Pharmacopeia quality were studied and it was concluded that the spreading properties of the different petrolatum grades differed substantially. Physical properties were defined by the penetrating stress, shear stress, and yield stress[9]. Moreover brand and generic clobetasone butyrate ointments have been studied and it was concluded that different grades of petrolatum were used as indicated by a GC/MS method and it was suggested that these are the cause of different sensory properties[10]. Significant differences in rheological properties as a function of temperature were found for three different petrolatum grades[2]. However, an elucidation of the cause of the differences in consistency is lacking.

Differences in consistency are relevant for the sensory properties of an ointment. It has been shown that rheological characterization yields a good indication for these sensory properties[11].

Apparently petrolatum products can exert significantly different rheological properties. This may impact both sensory properties of petrolatum containing products for patients but also the generic applicability of different Pharmacopeia quality petrolatum grades

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in manufacturing processes. However, it remains unclear what causes these significant differences. Consequently, a lack of a proper understanding of the physical characteristics of petrolatum exists. Because of this, pharmacists or formulation scientists working in pharmaceutical or cosmetic industry are not able to explain how and why Pharmacopeia quality petrolatum grades are different.

More understanding of this widely used pharmaceutical excipient is, therefore, crucial and thus our aim is to describe how Pharmacopeia quality petrolatum grades can differ and what factors determine their structure.

Materials and methods

Materials

All used materials are shown in Table 1. When Ph. Eur. quality is mentioned, this is with reference to the Pharmacopeia monographs of white soft paraffin (for petrolatum), hard paraffin (for petrolatum waxes), or liquid paraffin (for paraffin oils).

Batch production

Petrolatum Snowwhite N(r) was melted for 10 min at 80 °C on a water bath and subsequently filled in 100 ml PP containers. These were stored in a hot air cabinet that was slowly cooled down (approximately 0.1 °C/min) to room temperature, cooled down on a lab table at room temperature (approximately 0.4 °C/min), or cooled down in a freezer at −26 °C (approximately 5 °C/min) for 3 d. Afterwards, containers were stored at room temperature for 2 months prior to analysis.

An experimentally produced petrolatum was produced using 40 g microcrystalline wax concentrate HLA3129 and 60 g lytol oil. Both components were melted and mixed for 10 min at 80 °C on a water bath. Subsequently 50 g was poured in aluminum bags and either quickly cooled (approximately 5 °C/min) between ice plates for 10 min or slowly (approximately 0.125 °C/min) to room temperature for several hours.

Batches containing SiO_2 were produced by mixing in parts of the Aerosil(r) and molten petrolatum. This mixture was subsequently transferred to a 4M8-Trix homogenizer (ProCePt, Zelzate, Belgium) and mixed while cooling down to room temperature at 50 rpm for 30 min.

Rheological characterization

A stress-controlled rheometer (TA Instruments HR-2, New Castle, DE) equipped with a step-peltier stage (20 °C) and a 40 mm sand-blasted parallel plate (TA-instruments Cone plate geometry 40 mm) was used. Approximately 5 g of sample was placed on the peltier plate before slowly lowering the upper plate to the preset trimming gap of 1050 μm. After trimming of excessive sample, the geometry gap was set at 1000 μm. Before analysis samples were equilibrated for 3 min at 20 °C.

Yield stress was characterized using an oscillatory stress sweep where a logarithmic stress sweep at a frequency of 1 Hz was conducted within the range of 10–2000 Pa. The point of intersection with the G' and G" was defined as yield stress.

Viscosity of Kaydol(r) and Lytol(r) were estimated at 24.1 °C using a Brookfield DV3T rheometer (AMETEK Brookfield, Ochten, The Netherlands) with a Brookfield EZ-lock spindle set, spindle type 2 operated at 100 rpm.

Table 1. Overview of materials used in this study.

Ph. Eur. quality petrolatum grades	Snowwhite N(r)a, Snowwhite A4(r)a, Snowwhite T5(r)a, Fonoline H(r)a and Hansen and Rosenthal KG Pionier 3476(r)b
Ph. Eur. quality petrolatum waxes	Microcrystalline wax concentrate HLA3129a
Ph. Eur. quality paraffin oils	Kaydol(r)a and Lytol(r)a
Other components	Paraffin waxa, Microcrystalline waxa and Aerosil(r) 200 vv Pharmac

[a]Kindly donated by Sonneborn International, Amsterdam, The Netherlands.
[b]Hansen and Rosenthal KG, Hamburg, Germany.
[c]Evonik, Paris, France.

X-ray diffractometry

Room temperature XRD measurements were carried out on a Bruker-AXS D8 Advance powder X-ray diffractometer, in Bragg–Brentano mode, equipped with automatic divergence slit and a PSD Våntec-1 detector. The radiation used was Cobalt $K\alpha_{1,2}$, $\lambda = 1.79026$ Å, operated at 30 kV. A range of 5–60 2θ was studied. Crystallite size was calculated using the Scherrer equation (Equation (1)) by using a K-value of 0.89 and calculating the β value by measuring half the maximum intensity of the crystalline peak and subtracting the instrumental line broadening. Crystallinity was determined using the ratio between background and peak area, calculated with the XRD analysis program DiffracEVA (Bruker, The Netherlands).

$$\text{Scherrer}: \tau = \frac{K\lambda}{\beta cos\theta} \quad (1)$$

Results and discussion

Rheological differences between grades of petrolatum

For a number of different grades of Ph. Eur. quality petrolatum yield stress was measured. The results are shown in Figure 1.

As can be clearly seen in Figure 1, the Pharmacopeia quality petrolatum grades differ significantly in rheological properties. The most easily spreadable petrolatum (Fonoline H(r)) has an average yield stress of 65 Pa and the stiffest petrolatum (Snowwhite N(r)) a yield stress of 280 Pa, which can be considered a profound difference since these result in different sensory sensations. These are

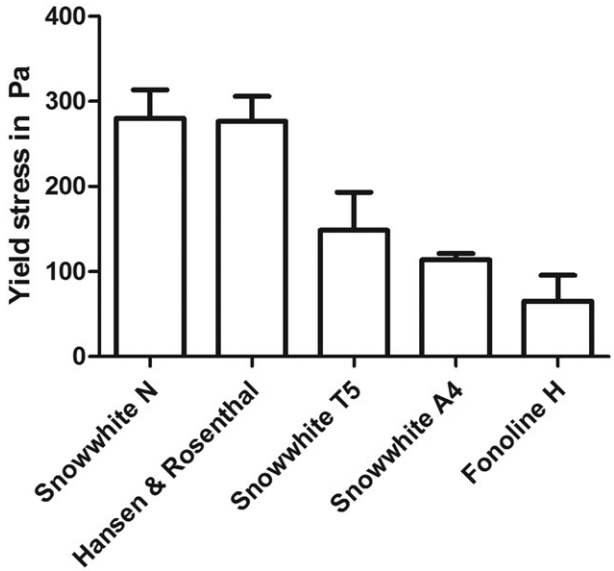

Figure 1. Differences in yield stress in Pascal at 20 °C for different Ph. Eur. quality petrolatum grades, 95% confidence interval is shown in bars.

Table 2. Influence of thermal history on yield stress of petrolatum snowwhite N® shown for four different cooling and storing conditions. After thermal treatment samples were stored for two months at room temperature.

Thermal history	Yield stress at 20 °C (in Pa)
Bulk sample from warehouse	280
Cooled in hot stove cooled with approximately 0.1 °C/min	341
Cooled on lab table cooled with approximately 0.4 °C/min	463
Stored at −26 °C for three days and heated to room temperature afterwards	661

comparable to those of a thin cream (65 Pa) and an ointment (280 Pa). Obviously, Pharmacopeia criteria are not sufficient to select petrolatum with consistent rheological properties. This complicates the choice for the appropriate grade of petrolatum in pharmaceutical or cosmetic manufacturing when there is a need to provide the patient with a constant sensory feel when applying the product.

For petrolatum Snowwhite N(r), the influence of thermal history has also been tested, results are shown in Table 2.

It can be clearly observed that due to differences in thermal history even within a single grade of petrolatum significant differences in consistency exist (ranging from 280 to 661 Pa). These differences are still present after storing the samples for 2 months at room temperature. Surprisingly, the influence of thermal history has not been described for petrolatum before. Clearly not only chemical composition but also thermal history influences petrolatum structure significantly. This consequently implicates that even if one grade of petrolatum is used in manufacturing of a pharmaceutical product, batch-to-batch variety may still be significant depending on thermal history.

Influence of thermal history on crystallinity and structure

Since petrolatum is a saturated solution of different alkane chain lengths[3], alkane solubility will depend on temperature. At lower temperature, the solubility of longer chain alkanes will be lower and thus these will solidify and potentially crystallize. Therefore, crystallinity will be depended on thermal history. Two experimentally produced petrolatum samples with a different thermal history were characterized using X-ray diffractometry and results are shown in Figure 2 and Table 3.

A small difference in amount of crystalline material was found between slowly and rapidly cooled petrolatum (0.7% and 1.5%, respectively). To determine crystallite size, it is conventional to use polarized light microscopy or confocal laser scanning microscopy. However, it appeared that the observed crystallite size is greatly depended on sample preparation and the part of the sample that is observed using these techniques. Interestingly, crystallite size can also be determined using X-ray. It is a convenient method for determining the mean size of nanosized crystallites and sample preparation is not as destructive as for microscopy. Furthermore, a larger quantity of sample can be observed and these samples are, therefore, more representative for the material. Crystallite size can be analyzed by determining the peak width of the crystalline peaks and calculating the crystallite size using the Scherrer equation[12].

For the experimentally produced petrolatum, crystallite size was determined by X-ray diffractometry. Crystallite size was around 30 nm and peaks were at the same position suggesting the same crystal type. The resolution of the X-ray diffractometer was insufficient to estimate crystallite size accurately for this small crystallite size; therefore, only a certainty range of crystallite sizes can be provided of 20–50 nm.

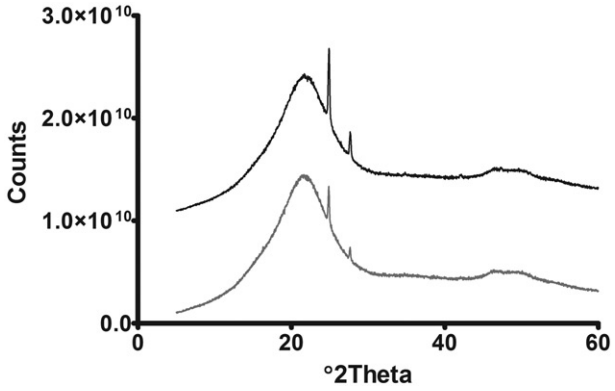

Figure 2. X-ray data of experimentally produced petrolatum with different thermal history, forcefully cooled petrolatum shown in black and slowly cooled petrolatum shown in dark gray. The black line has been moved upwards with an increment of $1x10^{10}$ counts to observe the differences.

Table 3. Influence of thermal history on the yield stress and crystallinity of experimentally produced petrolatum.

Thermal history	Yield stress at 20 °C (in Pa)	Crystallinity in %
0.1 °C/min to room temperature	25.5 ± 0.8	0.7
5 °C/min to 0 °C and then to room temperature	78.6 ± 3.1	1.5

For the samples, no clear influence of cooling rate on crystallite size was observed, while this influence has been described for other products such as milk fat, lard and canola oil[13,14]. Here, it was shown that faster cooling results in smaller crystals. For petrolatum, however, the crystallite size was similar for both samples. This may be due to the fact that petrolatum is a chemically different product compared to milk fat and canola oil and may, therefore, crystallise differently. Furthermore, crystal size for milk fat and canola oil was determined using polarized light microscopy, which can observe crystals of micrometer size and not nanometer size. This technique exerts high stresses to samples during preparation as well[4].

Apart from the difference in crystalline mass, also a profound difference in yield stress was found (Table 3): the 0.7% crystalline petrolatum exhibited a yield stress of 25 Pa at 20 °C compared with 79 Pa for the 1.5% crystalline material. Apparently, thermal history has a major impact on petrolatum structure. This has also been reported in the literature for polymers[7,8] and food products such as milk fat and lard, palm oil, and canola oil[13–16].

Linking crystallinity to structure

Because of the significant influence of thermal history on petrolatum yield stress, it was hypothesized that a minor difference in crystallinity can influence yield stress significantly. To study this, the addition of particles with a size comparable with the observed crystallites was tested. SiO_2 particles with a primary particle size of 15 nm (Aerosil(r) 200 VV Pharma, Thane, India) were added to petrolatum Snowwhite N(r).

Results are shown in Figure 3. It can be clearly seen that above approximately 0.9% of silica particles a significant increase in yield stress of petrolatum occurs. Obviously, a relatively small amount of small particles can have a significant effect on yield stress of petrolatum. From this perspective, it is not unlikely that a difference of 0.8% in crystallinity between the two tested samples may have a profound effect on petrolatum structure.

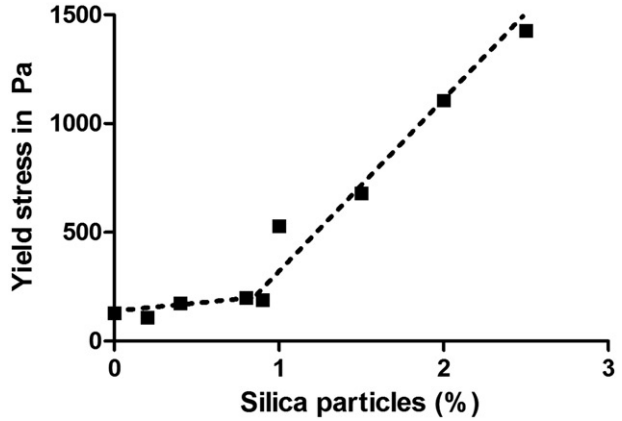

Figure 3. Influence of amount of SiO2 particles (m/m) added to petrolatum Snowwhite N(r) on yield stress at 20 °C.

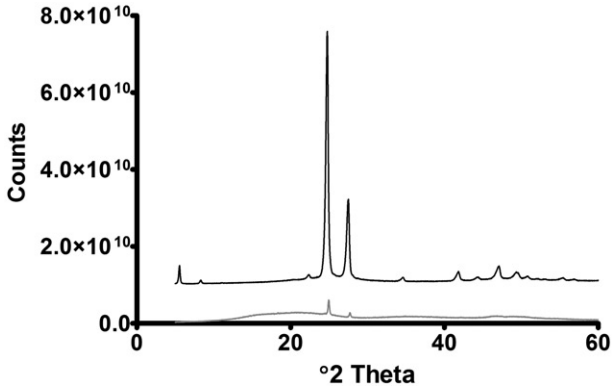

Figure 4. X-ray data of petrolatum waxes, paraffin wax in black, and microcrystalline wax shown in gray. The black line has been moved upwards with an increment of 1×10^8 counts to observe the differences.

The steep increase in yield stress after the addition of a certain amount of particles suggests a threshold value. A similar phenomenon has been studied extensively for polymer composites where the influence of particulate filler size was evaluated. It was shown that a particle size-dependent influence of polymer composite reinforcement exists. Small particles reinforce the polymer composite to a larger extent than larger particles. Furthermore, it was shown that particle size influences polymer composite reinforcement but also that the influence of amount of material added was non-linear suggesting a threshold value[17].

Since a small increase in crystalline mass of petrolatum crystals will account for a large increase in number of petrolatum crystallites, it can be expected that this increase in number of particles can have a profound influence on petrolatum rheological properties. This is in line with the literature on polyhydroxyalkanoates where a higher amount of particles results in a harder structure[8].

Characteristics of petrolatum components

To study what components in petrolatum are responsible for its crystallinity, X-ray analysis on paraffin wax and microcrystalline wax was conducted. Results are shown in Figure 4 and show clear peaks in the paraffin wax diffractogram, but not in that of the microcrystalline wax. From this, it can be concluded that paraffin wax is the component responsible for crystallinity in petrolatum. Possibly, this is due to the fact that paraffin wax consists of straight chain alkane branches which can potentially organize more easily when compared with branched and cyclic alkanes for microcrystalline wax. This is in line with literature on the influence of branched and cyclic alkanes on the crystallization of *n*-paraffins[18].

The influence of the viscosity of the oil fraction on the consistency of the composite petrolatum blend was studied by mixing a pre-blend of paraffin wax and microcrystalline wax with oil fractions of different viscosity. The resulting composite petrolatum blend consisted of 40% wax pre-blend and 60% oil. Oil with a viscosity of 5 mPas (at 20 °C) resulted in petrolatum with a yield stress of 162 Pa, whereas oil with a viscosity of 203 mPas (at 20 °C) resulted in petrolatum with a yield stress of 482 Pa. Thus, it can be concluded that also oil viscosity may influence yield stress profoundly.

Because of these results, it can be concluded that crystallinity of petrolatum originate from paraffin wax in petrolatum and that also the viscosity of the oil fraction used in petrolatum has a profound impact on product yield stress.

Conclusion

The Pharmacopeia monograph for petrolatum poorly discriminates between grades of petrolatum. As a consequence, Pharmacopeia quality petrolatum products are not necessarily interchangeable. Petrolatum complying to the Pharmacopeia can show considerable variations in rheological properties. The results indicate that differences in structure of petrolatum are caused by differences in composition or thermal history. These may influence the amount of crystalline material present in petrolatum and, therefore, have a profound influence on the rheological properties.

Acknowledgements

This work was supported by the R&D tax credit of the Ministry of Economic Affairs, The Netherlands (Grant no. S016053527).

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Novelty statement

Rheological differences between petrolatum grades have been described before, however these have not been elucidated. Therefore, this work shows how not only composition but also thermal history can influence petrolatum rheological properties significantly.

Funding

This work was supported by the R&D tax credit of the Ministry of Economic Affairs, The Netherlands (Grant no. S016053527).

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