

EXCIPIENT SELECTION FOR OPHTHALMIC OINTMENTS

In this piece, Janice Cacace, PhD, Director of Formulation, and Travis Webb, MsPharm, Senior Research Formulation Associate, both of CoreRx, describe the physical properties of petrolatums as they relate to the comfort and efficacy of formulations of ophthalmic ointments.

One would think that, in the 21st century, dosage forms would be more advanced and that the ophthalmic ointment would have gone by the wayside. Anyone who has had to use one knows that they are “gooey and sticky”, leave a film, and often “glue” your eyelids together. And based on recent US FDA product approvals they do not appear to be very prevalent (<https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/13/>

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ophthalmology). However, the ophthalmic ointment still plays an important part in the ophthalmic market overall as there are at least a dozen products on the market in the US (<https://masshealthdruglist.ehs.state.ma.us/MHDL/pubtheradetail.do?id=34>), primarily for antibiotic and anti-inflammatory products.

The base for an ophthalmic ointment is primarily petrolatum. This is what gives them that characteristic “gooey, sticky” feeling. But this is also what gives them desirable properties for some ophthalmic applications. Their advantages include:

- Pseudoplastic – solid state behaviour at low shear increases stability and prevents phase separation and settling of suspended particles
- Thixotropic – excellent for retaining drug in suspension, and yet capable of spreading in the eye. As shear force is applied (when blinking) the product becomes more fluid and retains fluidity, which helps coat the eye
- Non-Aqueous – spreads and softens but won't be flushed out of the eye with tears. Ensures it gets delivered and stays where you want it. Doesn't get “rinsed away” like aqueous solutions

- Non-aqueous and non-hygroscopic – eliminates issues with hydrolysis as compared to aqueous solutions, and protects active components from hydrolytic degradation
- Insoluble – May limit the treatment to local delivery with very little systemic absorption. The latter can be important for minimising side effects.

So, in certain instances, such as with drugs that are susceptible to hydrolysis, the petrolatum-based ointment is ideal. And also for indications where prolonged contact with the infected area in the eye is important, they are ideal.

Petrolatums for pharmaceutical products are classified as Petrolatum USP and White Petrolatum USP. For ophthalmic products, the white petrolatums are preferred. However, even within white petrolatums, there are differences, they vary in:

- Colour and clarity
- Consistency
- Flow
- Yield Stress.

So what can be done to optimise the elegance of a petrolatum based ointment?

As can be seen in Figure 1, White Petrolatum can differ in colour and clarity. The petrolatum on the left is the clearest and most “white” as

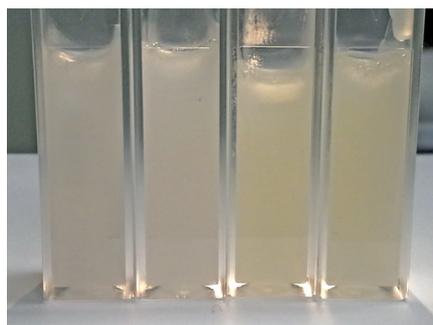


Figure 1: Colour and Clarity of four petrolatums.



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compared with the other three petrolatums, with the sample on the right having a distinct yellow hue. Any of these can be used but the most “white” may provide more elegance from an appearance perspective.

The last three properties – consistency, flow and yield stress, are related to product rheology. These properties can be used to assess effects of formulation variables in order to attain the desired physical properties or benchmark a product for comparison with another product. These can be assessed using a rheological model such as the Power Law (or Ostwald) Model. This will fit a typical viscosity *versus* shear rate, or shear stress *versus* shear rate curve within the range of about one to a few hundred reciprocal seconds.

Petrolatum	Yield Stress, Pa	Flow Index	Consistency Index
A	30	0.30	25318
B	60	0.22	59244
C	36	0.34	36050
D	22	0.54	22111

Table 1: Flow Index and Consistency Index for four different petrolatums.

The Power Law model takes the form of:

$$\tau = Ky^n$$

Where: shear stress (τ) is the cross-sectional stress experienced by the material and is expressed in Pascals (Pa); consistency index (k), is simply the viscosity (or stress) at a shear rate of reciprocal second. and describes, in a sense, how thick (viscous) a material is at low shear; and shear Rate (y), is the rate at which a progressive shearing deformation is applied to some material expressed in reciprocal seconds (1/s).

These values can be used to obtain yield stress, which is the amount of force that must be applied to induce plastic deformation; and the viscosity, which describes a material’s resistance to flow. All of these values can then be used to evaluate the physical characteristics and

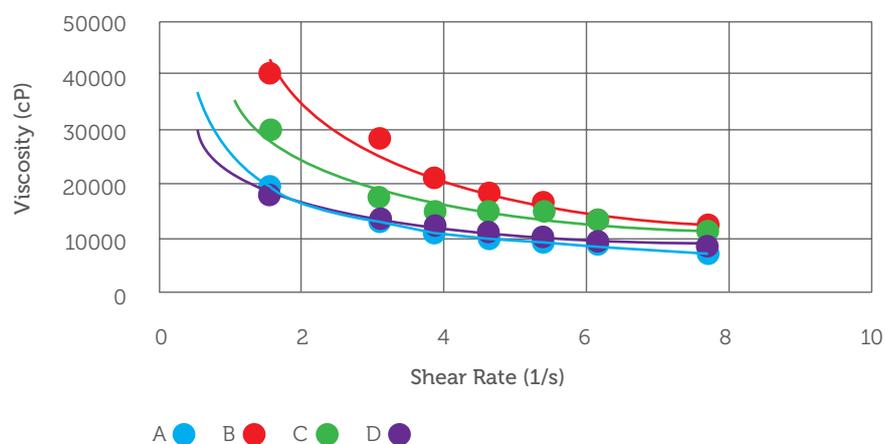


Figure 2: Graph showing Shear Rate against Viscosity for four different petrolatums.

flow behaviour of a product.

They can also be used to calculate flow index (n). This is a measure of non-Newtonian-ness, in essence, the magnitude of shear thinning or shear thickening.

For a Newtonian fluid Flow Index = 1; for a shear-thinning fluid it is between 0 and 1 and for a shear thickening fluid it is greater than 1.

In Table 1, the Flow Index, or shear thinning index, indicates how smoothly the ointment will flow as shear is applied. Materials with a high degree of shear thinning tend to feel softer and spread more smoothly. As can be seen in the table, all of the petrolatums tested had a Flow Index between 0 and 1, and therefore are shear-thinning. Petrolatum D has the lowest consistency index but it also has the highest Flow Index, and thus is the least shear thinning of the four materials so it tends to have much more of a waxy feel than petrolatums A or B. However, the higher consistency index of petrolatums A and B may lead to difficulty in dosing smaller quantities and feel more “goopy” in the eye. These can be important factors in dose effectiveness as well as patient compliance.

Another important factor to consider when choosing which type of petrolatum to use is the formulation composition. Additional excipients such as mineral oil, surfactants, and preservatives can lower the apparent viscosity and yield stress relative to their concentration in the formulation.

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thinning. By plotting the natural log of the shear rate and shear stress according to the Power Law model we can obtain the Flow index and approximate yield stress of each material. Figure 2 and Table 1 show the comparison of the shear thinning behaviour and viscosity at low shear rates.

This is an important factor for the formulator when deciding which type of petrolatum to use. An ointment with a high yield stress and viscosity might feel very thick and sticky in the eye. However, if these parameters are too low the medication will not be retained and the effectiveness of delivery will suffer.