Formulating CARBOWAX™ SENTRY™ PEGs in ointment applications

Topical drugs are often preferred due to their ease of application and affordability, which make them ideal for at-home consumer use and high patient compliance. The market for these drugs is expected to grow at an average of six percent over the next several years, driven by high rates of both skin diseases and burn injuries, as well as an increasing incidence of diabetes and eye diseases.

Topical drugs come in many forms, the most common of which are creams, ointments and gels. Ointments usually contain greater than 50% hydrocarbons, waxes or polyols and less than 20% water and other volatiles. They are typically divided into four classes according to the type of base: hydrocarbon, absorption, water-removable, and water-soluble. Polyethylene glycols (PEGs) are commonly used as water-soluble bases in ointments because they spread evenly over application areas and can be easily removed with water. The following study will focus on ointment formulations and the role of PEG excipients, such as CARBOWAX™ SENTRY™ on desired finished drug properties including formulation stability, melting point and mechanical and rheological properties.

Choosing the proper molecular weight (MW) and and ratio of solid and liquid PEGs for an ointment formulation can be challenging due to tradeoffs in performance among the required properties of the finished product. Therefore, formulating is often a matter of optimizing performance across a range of desired attributes, as shown in the figure below. Each of these elements is explored in more detail on the following pages.

Definitions

The ratio and molecular weight (MW) of PEGs used in the ointment formulation impact the physical properties of the finished formula. For simplicity, a low MW PEG can be considered a PEG that is liquid at room temperature, such as CARBOWAX™ SENTRY™ PEG 300 and CARBOWAX™ SENTRY™ PEG 400. Conversely, a high MW PEG can be considered a PEG that is solid at room temperature, such as CARBOWAX™ SENTRY™ PEG 1450 and higher. Throughout the study below the blend ratio is often referenced. The blend ratio (BR) is defined as:

$$BR = \frac{wt\%\ liquid\ PEG}{wt\%\ liquid\ PEG + wt\%\ solid\ PEG}$$

YIELD STRESS

high

- MW ↑
- Solid PEG weight % ↑
- Overall a thicker formulation

- MW ↓
- Liquid PEG weight % ↑
- Easier to squeeze out of tube

low

SHEAR THINNING

high

- Solid PEG weight % ↑
- More effort to spread

- Liquid PEG weight % ↑
- Easier to spread

low

MELTING POINT

high

- MW ↑
- Solid PEG weight % ↑
- Stays firmer on the skin

- MW ↓
- Liquid PEG weight % ↑
- Readily softens on contact with skin

low

ADHESION

high

- MW ↓
- Liquid PEG weight % ↑
- Ointment remains readily at treatment area

- MW ↑
- Solid PEG weight % ↑
- Ointment drifts from treatment area

low

VISCOSITY

high

- MW ↑
- Solid PEG weight % ↑
- Ointment remains readily at treatment area

- MW ↑
- Liquid PEG weight % ↑
- Thicker ointment

low

Our testing capabilities and R&D expertise can help you pinpoint the best blend ratios for your formulation.

Yield stress

The first step to applying an ointment is to exert a force to squeeze the ointment out of tube. Yield stress can be used to characterize this process. A higher yield stress means greater force is required to squeeze the product out of the tube and onto the skin. The yield stress can be increased by increasing the MW of the solid PEG or increasing its use level (thereby decreasing the BR), as shown in Figure 1 below.

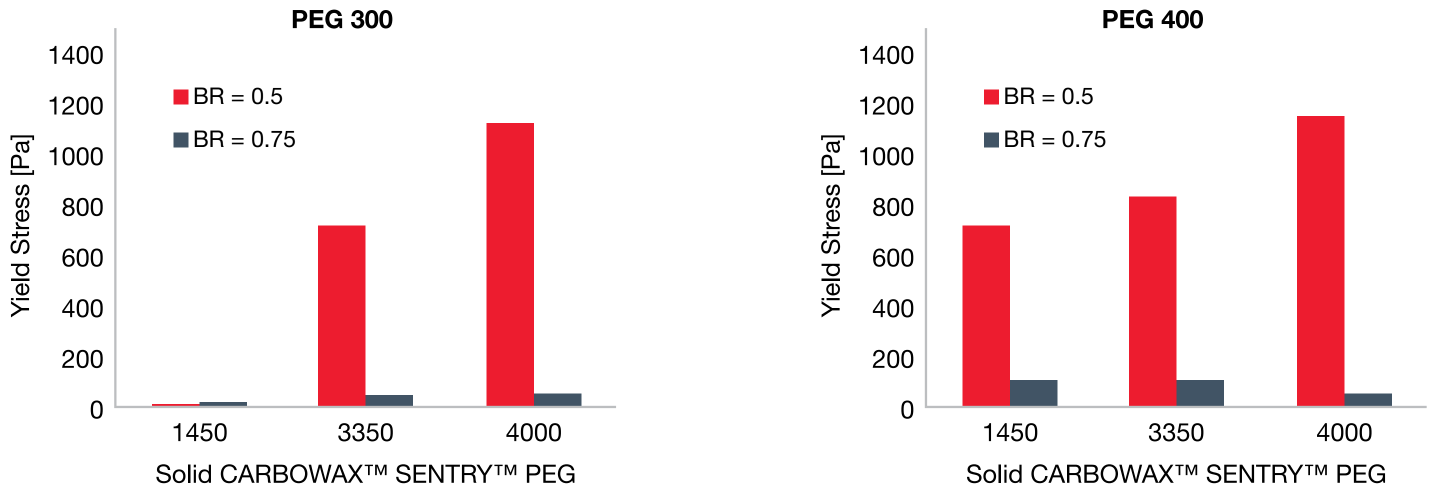
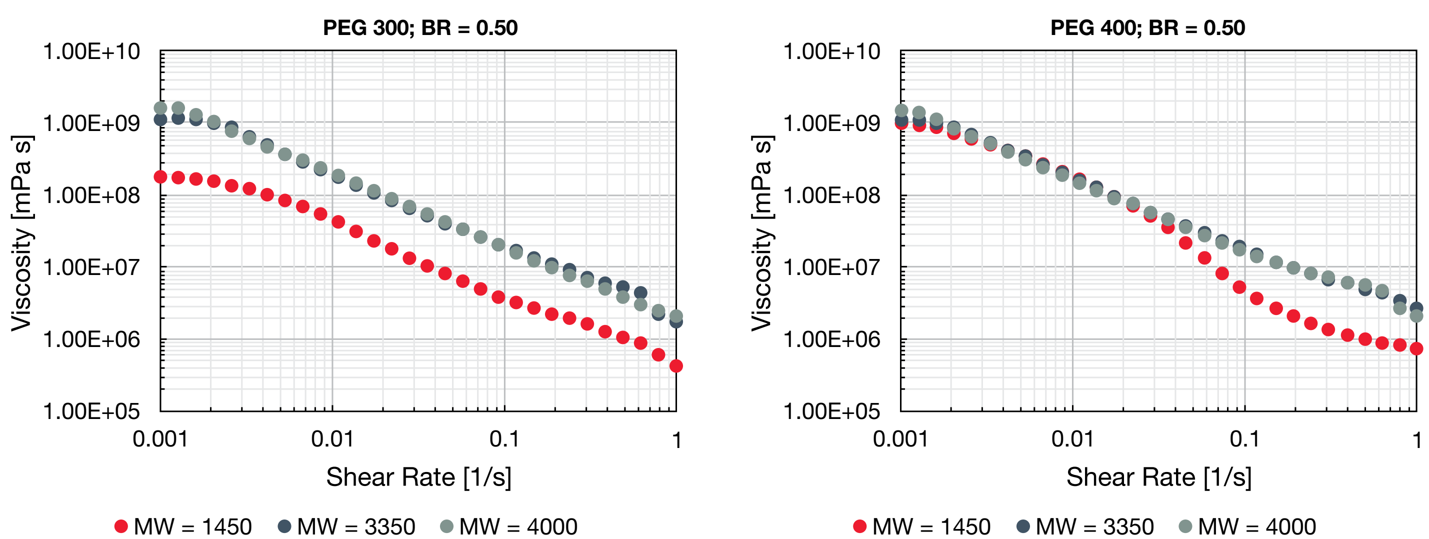


Figure 1. Yield stress for various PEG blends

Shear stress

After applying an ointment, a shear stress is applied to spread the ointment onto the skin. The shear rates used to apply topical ointments are typically in the range of upper hundreds to lower thousands of reciprocal seconds. Figure 2 below shows flow curves measured for different formulations. At higher shear rates, the formulation using high MW PEGs is higher in viscosity, indicating a higher resistance to application. The shear stress can be optimized by adjusting the blend ratio.



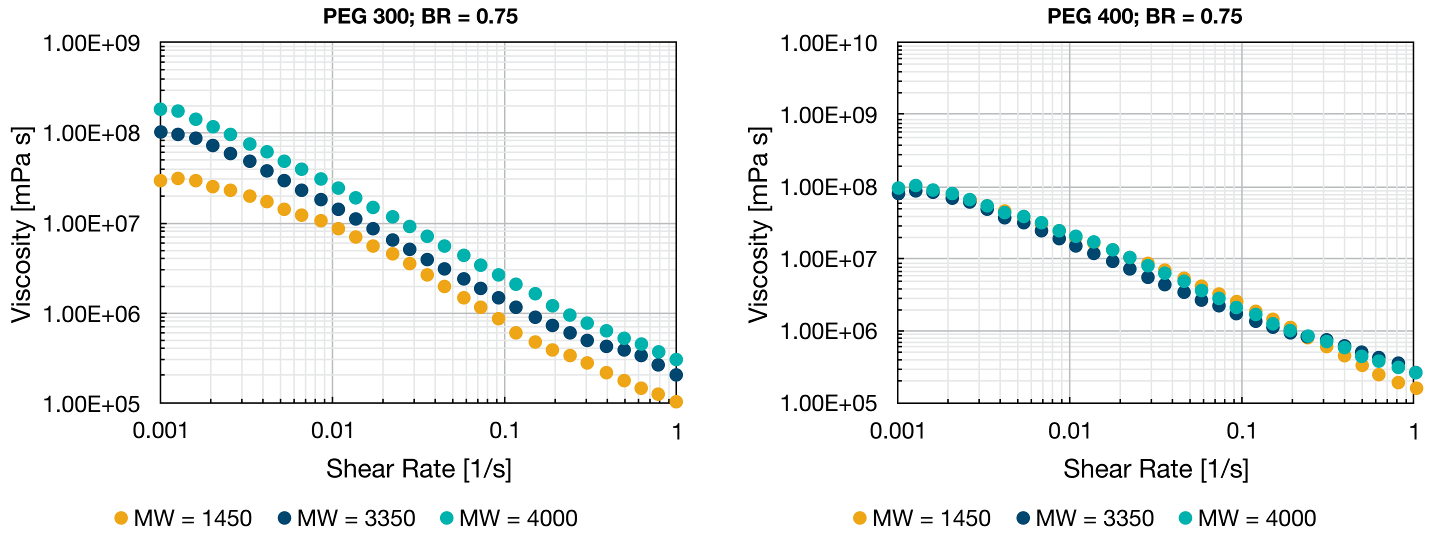


Figure 2. Shear rates curves for various PEG blends

Melting point

Ointments should have the ability to soften into a semi-solid during the application process so that they can be spread evenly over an application area. Softening can be adjusted by changing the PEG MW and BR between liquid and solid MW to tailor the melting point of the ointment. Solid PEG with MW above 1450 g/mol allows the melting point of the ointment to be above human body temperature about 37°C. This is critical to maintaining a semi-solid form so that the ointment remains localized at the application area.

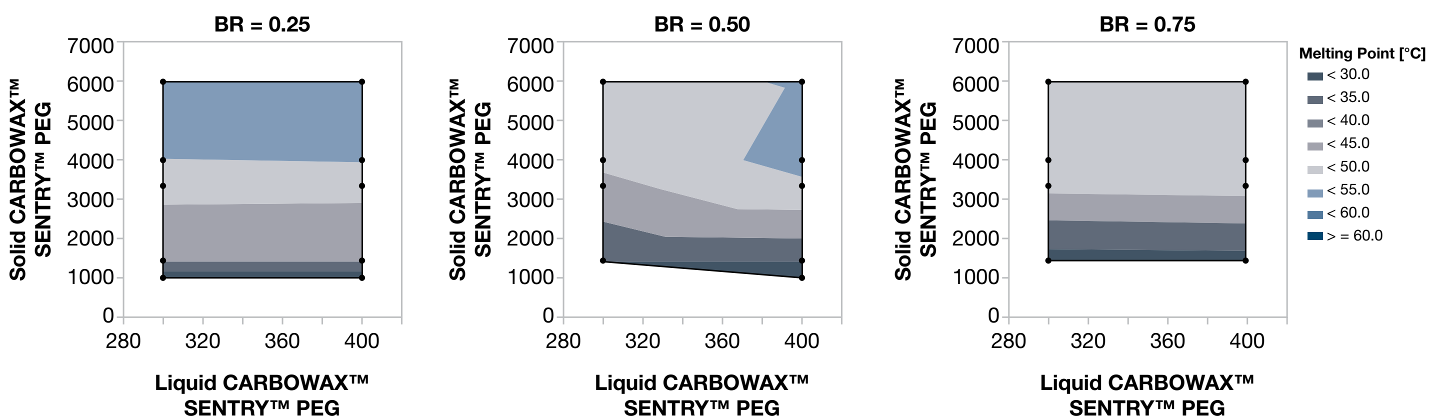


Figure 3. Melting point diagrams for various PEG blends

Firmness and adhesion

Texture parameters such as firmness and work of adhesion of semi-solids are important for product performance as well as for consumer acceptance. Firmness relates to the viscosity of the product, while adhesion relates to spreadability and governs the ability of the ointment to remained localized at a treatment area. PEG polymers have a unique property as they add a silky texture to the semi-solid product without an undesirable greasy feeling. At 0.50 blend ratios, firmness and adhesion are inversely related; as you increase the MW of the solid PEG, the firmness increases while adhesion decreases. Utilizing a higher blend ratio, such as 0.75, will cause the firmness and adhesion to move in parallel. Therefore, you can either increase both firmness and adhesion at the same time by utilizing a higher MW PEG.

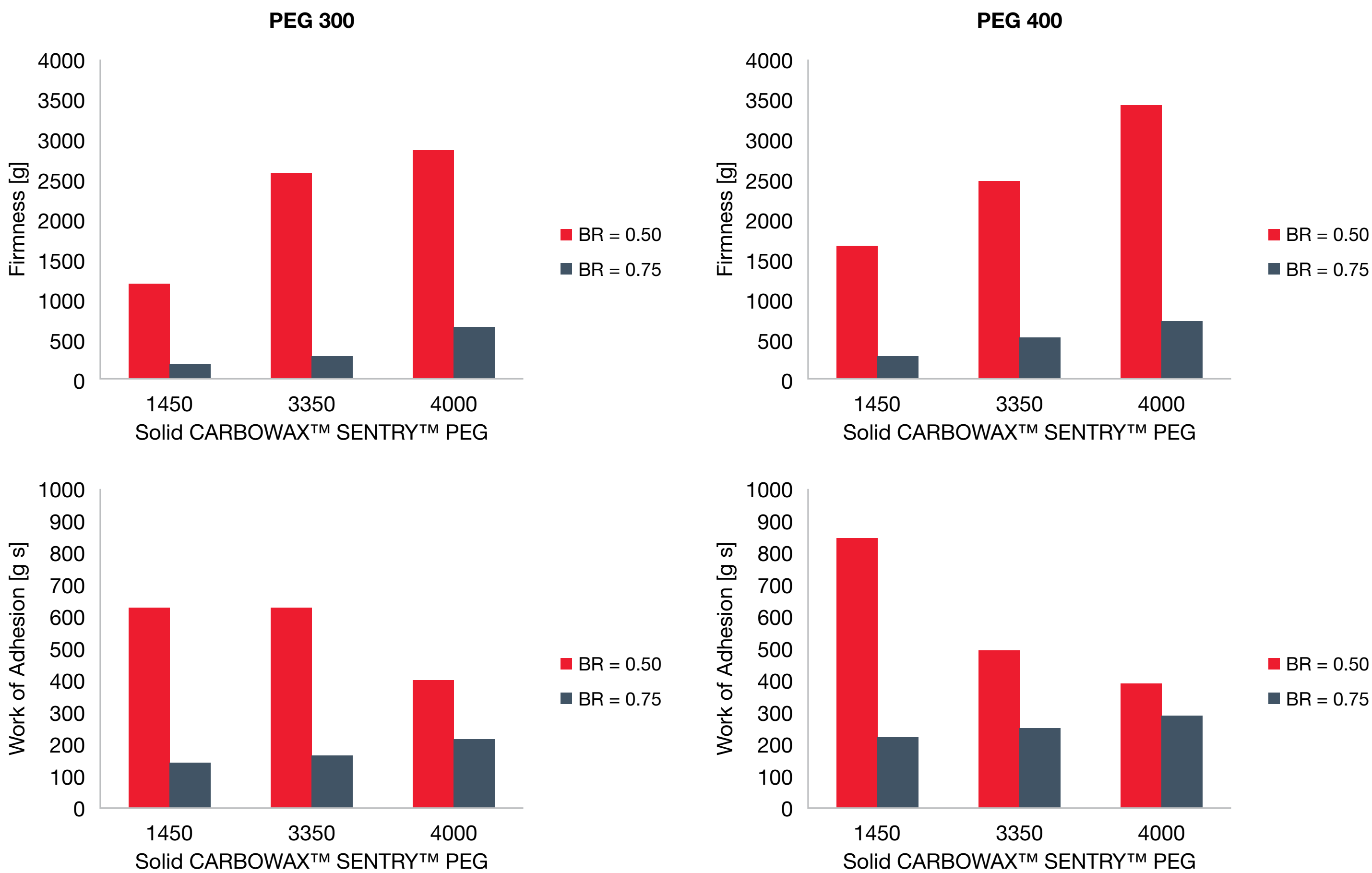


Figure 4. Firmness and adhesion for various PEG blends

Ointment stability

Ointment stability is critical to product shelf life both before and after consumer purchase. Certain combinations of PEGs and blend ratios can produce unstable ointments. In general, using higher MW solid PEGs produce a more stable ointment regardless of BR and choice of liquid PEG, as shown in the phase diagram below. Unstable ointments can be characterized as containing both solid and liquid domains with a glossier appearance. The texture may also be inconsistent throughout the mixture; for example, harder near the edges and softer at the center. By contrast, stable ointments have a uniform, matte appearance.

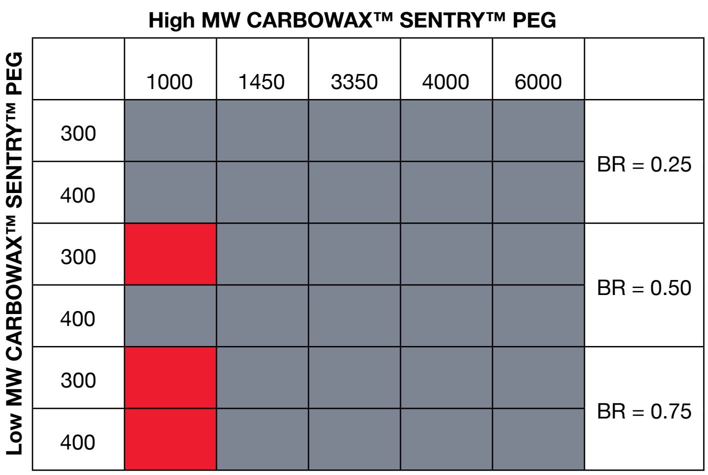


Figure 5. Phase Diagram Comparing PEG Blends. Red boxes denote unstable ointment formulations.

Drug release profile from ointments

A Franz diffusion cell is commonly used to measure drug release profiles in vitro. Dow can assist in testing formulations of various PEG compositions and blend ratios to optimize your formulation.

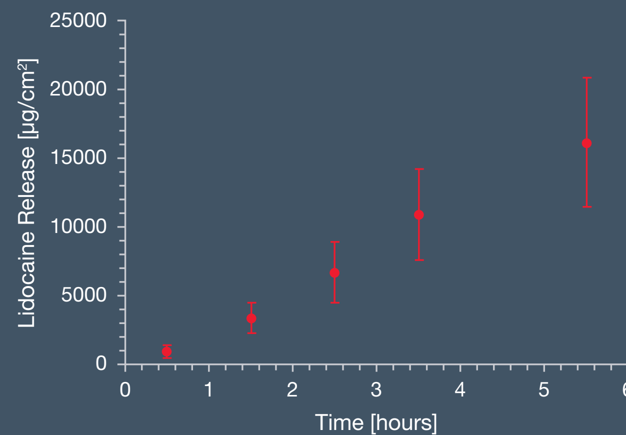


Figure 6. Release of Lidocaine from PEG 400/3350 Ointment, Blend Ratio = 0.50. Consistent with benchmark literature ointments, it took approximately 2.5 hours for 50% of the lidocaine to be released from the ointment.

Collaborate with us

There are many factors to consider when formulating an ointment and due to competing tradeoffs it can be very time consuming to test all parameters in the lab. In order to minimize this effort for our customers, Dow has developed an empirical model to predict the melting point, adhesiveness, and yield stress of ointments as a function of PEG molecular weight and blend ratio to assist customers with their PEG-based formulation development. This model can be leveraged to help optimize product formulation to achieve desired properties and minimize time spent in the lab, thereby accelerating the product development process.

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