This edition of Eye on Excipients compares the performance and stability characteristics of glycerin and sorbitol-sorbitan solution when used as plasticizers for softgel capsule formulation.

Soft gelatin capsules (softgels) are an important dosage form option for pharmaceutical manufacturers because many patients prefer them over other solid oral dosage forms and perceive them as easy to swallow, which leads to improved patient compliance [1]. Softgels can also allow formulators to increase the absorption rate of the active pharmaceutical ingredient (API) by altering the fill formulation (from lipophilic to hydrophilic, for example), help ensure dose uniformity with low-dose drug products, and help improve drug stability.

However, softgels require formulators to carefully select the right combination of shell ingredients and liquid-fill composition to ensure dosage integrity. A key shell ingredient that greatly influences how the shell and liquid fill interact is the plasticizer.

A plasticizer is a substance added to the capsule shell’s gelatin base to improve its elasticity and durability. Selecting the best plasticizer minimizes the risk of defects such as sticking, brittleness, and leaking and can even improve productivity. Historically, softgel manufacturers have used glycerin as a plasticizer, but glycerin presents two major challenges when used in softgel capsule formulation.

First, glycerin is hygroscopic. While water is the one of the most effective plasticizers, it is also very mobile and volatile. A hygroscopic plasticizer cannot ensure constant and long-term plasticization in a softgel formulation unless the capsules are kept in tightly controlled temperature and humidity conditions. This is because the water content is able to migrate between the capsule shell and the liquid fill and/or between the shell and the surrounding environment, as shown in Figure 1.

Second, glycerin has the capacity to migrate out of the gelatin network in the capsule shell and into the liquid fill (Figure 1), causing a progressive hardening of the shell. Indeed, softgels with a hydrophilic fill (based on low-molecular-weight PEG) or a self-emulsifying system can lose mechanical integrity after just several months of storage, resulting in leaks and performance loss. Both of these challenges are common with formulations that use glycerin.

One way to prevent such migration phenomena is to use a plasticizer made from an aqueous solution of sorbitol and sorbitan. Sorbitol is a sugar alcohol derived from glucose, and sorbitan (Figure 2) is obtained by partially dehydrating liquid sorbitol. A sorbitol-sorbitan solution (such as Roquette’s Polysorb 85/70/00) provides the same plasticizing benefits as glycerin but without significant migration phenomena and the related loss in plasticity. Also, due to its complex composition, sorbitol-sorbitan solution is anti-crystallized, which helps prevent the sorbitol from crystallizing at the capsule surface during storage, causing undesirable shell cloudiness.

Figure 3 compares the hardness over time for softgels plasticized with glycerin versus softgels plasticized with sorbitol-sorbitan solution (Polysorb 85/70/00). The softgel formulations contained PEG 400 as a filler and were evaluated for their elasticity over a 6-month period, with the only difference between the two samples...
being the shell plasticizer. As the figure shows, the glycerin-plasticized softgels increased in hardness by 360 percent after six months, whereas the softgels plasticized with sorbitol-sorbitan solution only increased in hardness by 30 percent.

Formulators should choose plasticizers and their ratios carefully, considering factors such as the gelatin quality, the capsule size, and the nature of the liquid fill. Many different tools are available to quantify plasticizer activity. One well-known method is to conduct differential scanning calorimetry (DSC) studies with isolated films [2]. This method gives access to important values, including the shell's specific melting enthalpy, melting temperature, and glass transition temperature. The specific melting enthalpy indicates the crystallinity of the formulated gelatin and can help formulators in adjusting the relative levels of the excipients in the shell to obtain the necessary gelling for film formation and sealing. Table 1 shows DSC data illustrating the impact of glycerin, sorbitol-sorbitan, and a 50/50 blend of the two on isolated gelatin films.

Both excipients demonstrated a remarkable ability to soften gelatin. Formulations containing sorbitol-sorbitan as the sole plasticizer had a lower impact on the gelatin's melting temperature and a greater impact on its melting enthalpy than formulations containing glycerin at the same concentration. As the data show, sorbitol-sorbitan solution can also be used in combination with glycerin.

Because sorbitol-sorbitan solution is less hygroscopic than glycerin, as shown in Figure 4, it offers various advantages for softgel production and storage. First, softgels made with sorbitol-sorbitan solution require 10 to 20 percent less drying time after production than softgels plasticized with glycerin, which reduces production costs.

Second, since softgels made with sorbitol-sorbitan solution are less hygroscopic than those made with glycerin, they are more able to resist challenging storage condi-
Temperature and humidity fluctuations during storage are less likely to over-plasticize the gelatin shell causing softening, stickiness, and cold flow.

Storage tests at increased humidity levels demonstrate that substituting half of the glycerin in a softgel formulation with sorbitol-sorbitan solution reduces the shell’s water uptake and limits its melting temperature reduction, as shown in Figure 5. This can help prevent the shell’s melting temperature from reaching a minimum temperature below which sticking begins to become a problem.

An additional benefit of the lower moisture uptake is that it limits the capsule shell’s oxygen permeability, improving stability for drugs sensitive to oxidation [3].

Sorbitol-sorbitan solution can be a key ingredient in developing a versatile softgel formulation that’s well suited to a variety of fill compositions, including those designed to solubilize or suspend APIs (such as oil, PEG, and self-emulsifying systems). Its unique properties allow it to not just plasticize softgels efficiently, but also to increase productivity and widen the stability conditions for this sensitive dosage form.

**References**


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