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Comparative Evaluation of Commonly Employed Plasticizers in Soft Gelatin Capsules

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PURPOSE

From a basic standpoint, the shell of soft gelatin capsule is composed of gelatin, plasticizer(s), and water. The formation of a soft gel shell requires the use of a non-volatile plasticizer for mechanical ductility. The choice of plasticizer contributes greatly the stability behavior of the finished dosage form. To illustrate, glycerin is a commonly employed plasticizer for oil filled soft gelatin capsules, while sorbitol-sorbitan solutions are the plasticizers of choice for soft gelatin capsules with PEG fills because they do not migrate into the PEG as glycerin does.[1]

The present study aims to evaluate and compare the effect of plasticizers on the soft gelatin capsules mechanical properties at different plasticizer ratios in gel mass and study their drying behavior. Most manufacturers of soft gelatin capsules use capsule hardness as the main end-point of process whilst monitoring capsule shell LOD. Therefore, understanding the influence of different plasticizers and their percentage levels in gel mass on reaching the end point is of significant interest to the formulator.

OBJECTIVE(S)

1) Prepare soft gelatin capsules using gel mass containing 15%, 20% and 25% of SPI Pharma's sorbitol range of plasticizers and glycerin separately using PEG 400 as a fill
2) Measure the hardness, water content of fill, and LOD of shell
3) Compare the different plasticizers in terms of hardening rate

METHOD(S)

Five plasticizers in total were evaluated in this study:
Four Sorbitol Special® grades from SPI Pharma (Sorbitol Special, Sorbitol Special MDF 85, Sorbitol Special GC and Sorbitol Special A-810) and glycerin. These plasticizers vary in their total solids content and contents of 1, 4 sorbitan, sorbitol, maltitol. Sorbitol Special A-810 also contains glycerin.

Each of the five plasticizers were evaluated in this study at 15%, 20% and 25% w/w concentrations in the gel mass for a total of 15 trials. Gelatin 150 – 180 Bloom from Nitta Gelatin was employed in all trials, along with Miglyol 812 N from Cremer as a lubricant, and PEG 400 from Thermo Fisher Scientific as the fill. The gel masses were prepared at 60 ˚C under vacuum to remove the dissolved gases. Encapsulation was carried out in a rotary die encapsulation machine (Bochang, BCM GB3). Formed capsules were initially dried in a tumble dryer (Bochang) at temperature of 31 °C (±4) and 38 % (±2) RH and then in a drying chamber (ETSP, TH216S) at 20 °C and 20 % RH. The formed capsules were evaluated for shell LOD (%) at 105 °C for 16 hours in a oven, moisture content of fill was determined by Karl Fischer titrator (Mettler, V20S) and hardness (N) using a texture analyzer (Stable Microsystems, TA-XT Plus).

RESULT(S)

Soft gelatin capsules manufactured with plasticizer concentrations at 15 % w/w were found to be unsuitable as they did not produce physically stable capsules. The gelatin ribbons were tough and less ductile, attributable to insufficient plasticization. The capsule shells were brittle, leading to a large number of leaking capsules produced during encapsulation and also during drying. Therefore, capsules produced with 15 % plasticizer level were not evaluated further. Plasticizer concentrations of 20 % and 25 % w/w were found to produce acceptable ribbons and soft gel capsules. The hardness was measured using 10 capsules. The hardening rate used here is regression slope of capsules hardness(N) versus drying time (Hours). All plasticizers displayed higher hardening rates at the median concentration of plasticizer (20 %), this can be attributed to the fact that lower plasticizer levels produce less plasticization. The compositions of Sorbitol Special (sorbitan-sorbitol) plasticizers show higher hardening rate compared to glycerin in PEG based fills. Additional studies, not shown here, also demonstrate this trend in hydrophobic fills like oils. The plots of hardness vs drying time and LOD of capsules shell vs drying time were as given in Figure 1 and Figure 2 respectively. The hardening rate of capsules with different plasticizers at 20% level were as given in Table 1.

Figure 1: Hardness Profile of Soft Gelatin Capsules Manufactured By Different Plasticizers

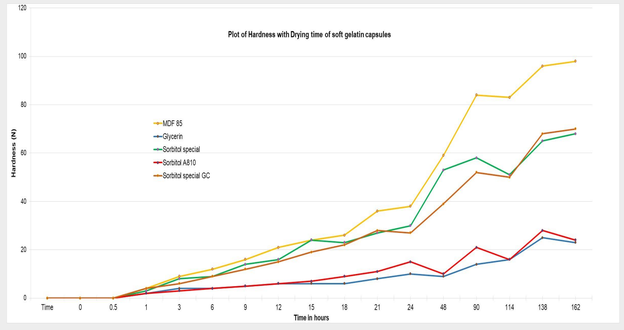
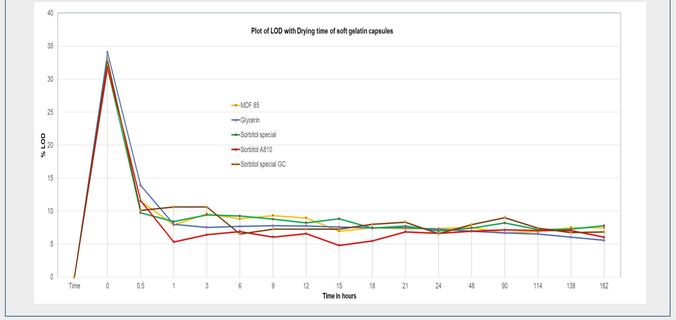


Figure 2: Loss on Drying Profile of Soft Gelatin Capsules Manufactured By Different Plasticizers



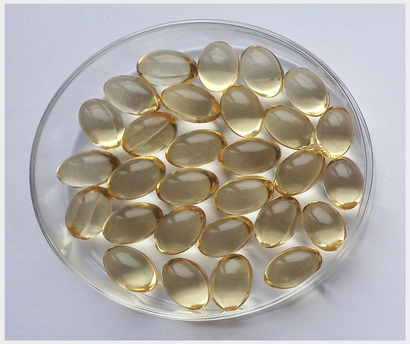


Figure 3: Soft Gelatin Capsules Manufactured Using Sorbitol Special, SPI Pharma Plasticizer

Table 1: Hardening Rate of Soft Gelatin Capsules

Plasticizer	Concentration (% w/w)	Hardening Rate x 10^{-3} (N/min)
Sorbitol Special MDF 85	20	9.2
	25	3.3
Sorbitol Special	20	6.4
	25	2.5
Sorbitol Special GC	20	6.0
	25	2.3
Sorbitol Special A810	20	4.1
	25	1.5
Glycerin	20	2.4
	25	1.1

CONCLUSION(S)

Sorbitol-sorbitan solutions are widely used as plasticizers in the manufacture of soft gelatin capsules. This study confirms their functional advantage through a rank order of soft gel plasticizers in terms of their drying behavior and associated time to impart hardness into the final capsule. Given the only difference between sorbitol-sorbitan grades of plasticizer is their proprietary quantitative chemical composition, it's reasonable to conclude that this may be the driving variable. Interestingly, the plasticizers meeting the same pharmacopeia monograph behave differently in terms of their drying and hardening characteristics due to difference in the chemical composition.

These results showed that considering only 'water loss' or 'loss on drying' may not really be a true indicator for the end of drying as after primary drying (tumble drying), as the overall LOD remains fairly constant with only small reduction seen during the tray drying process. Capsule hardness is a better criterion to determine 'end of drying' to obtain physically robust capsules and is commonly used commercially to determine the end point. In terms of hardening rates, the plasticizers can be rank ordered as Sorbitol Special MDF 85 > Sorbitol Special ≈ Sorbitol Special GC > Sorbitol Special A-810 > glycerin for capsules with PEG 400 as fill. Thus, different soft gel plasticizers give significantly different drying and hardening rates. Interestingly, in work not presented here, we found using a model system with significantly longer overall drying times (up to 7 days) based on ibuprofen in a PEG fill (containing KOH and water) Sorbitol Special plasticized capsules hardened more rapidly (by 21%) than Sorbitol Special MDF 85. Thus, one has to judiciously choose the type and level of plasticizer as the overall hardening process is influenced by both the plasticizer used and capsule fill composition. This phenomenon is one that is not regularly assessed during formulation development despite the criticality in terms of the overall process efficiency; judicious choice of the right plasticizer for the specific fill under development could help save significant process time and result in cost savings where production capacity is limited.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

1. Rampurna Prasad Gullapalli, "Soft Gelatin Capsules" *Journal of pharmaceutical sciences*, VOL. 99, NO. 10, 5 April 2010, page 4107-4148

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