Formulating and manufacturing gelatin softgels

Biocompatible and versatile, gelatin offers unique functional capabilities that make it an unrivalled excipient in softgel applications. Here are some tips to ensure defect-free softgels that meet market expectations and deliver the active as intended.

Across the pharmaceutical and nutraceutical industries, the popularity of capsules continues to rise. Together, hard and soft gelatin capsules account for more than 10 percent of the total dosage forms and 20 percent of all prescription drug products [1]. Softgels in particular have seen a significant upturn [2]. In fact, the value of the global market for softgel products is forecast to increase at a compound annual growth rate of 5.4 percent over the
next decade, reaching $316.6 billion by 2025 [3]. This growth stems from several factors, including the increase in consumption of pharmaceuticals and supplements, technological advances, and the expansion of investment opportunities [4, 5]. Softgels’ ability to encapsulate liquid or semi-solid formulations of hydrophobic medications is another important growth factor. Softgels also allow rapid dissolution in the digestive tract, which enhances the absorption and bioavailability of otherwise poorly water-soluble active ingredients.

In addition to the multiple advantages softgels offer formulators and manufacturers, they increasingly appeal to consumers over other dosage forms because they are easier to swallow and because their airtight seal masks unpleasant odors and tastes. Furthermore, as the "clean" and "clear" label trend continues to gain mainstream appeal, gelatin capsules are well placed to help companies meet growing demand.

That is because gelatin, the main excipient in softgels, is a naturally sourced ingredient. It is a fully digestible protein obtained through the partial hydrolysis of collagen found in the skin, bones, and connective tissues of animals. A clean-label ingredient, gelatin contains 18 different amino acids, including eight of the nine essential amino acids that the human body requires. From raw material selection to production, gelatin undergoes strict and continuous testing and control to ensure maximum traceability, quality, and safety before it is used in softgels.

**Optimizing API delivery**

Because gelatin is non-allergenic, gelatin capsules are fully compatible with the human body and can be completely metabolized. In addition, they melt at body temperature within 15 minutes, ensuring complete dissolution and an ideally timed release of the active. Gelatin's neutral organoleptic properties and masking capabilities also help R&D specialists to deliver challenging concepts without affecting the finished product's taste or odor. Choosing the correct high-quality gelatin—one with the right functional characteristics—is critical for efficient softgel development, production, and API delivery. To protect the fill from the damaging effects of oxygen and light, for example, the gelatin shell can include opacifiers.

Manufacturers are continuously innovating and many of them use tailored gelatin to streamline manufacturing by increasing encapsulation efficiency and optimizing delivery of the active ingredient(s). The right gelatin also helps manufacturers produce high-quality, effective softgels consistently, meeting both consumer demands and stringent regulatory requirements. (Gelatin is also used in a number of other pharmaceutical applications.) In addition, gelatin has gelling and film-forming functionalities, thermo-reversible properties, and a unique mechanical resilience, all of which allow formulators to achieve the desired texture and mechanical stability in softgel capsules. And again, because gelatin softgels accept liquid compounds, they can improve the bioavailability of poorly soluble actives.

**Protective barrier**

Softgels are sealed airtight and provide a protective barrier that shields active ingredients from environmental contamination and oxidation. The seal also prevents ingredients from leaking before their intended release. Tests on lecithin-based softgel formulations have shown that several factors, including gelatin type and processing conditions, have a significant impact on the shell’s risk of leakage in critical conditions. Gelatin that is too viscous, for instance, prevents the formation of an effective seal, which leads to misshapen capsules prone to leak. The results of one study showed that using a gelatin engineered to a suitable molecular weight, coupled with an optimized wedge during manufacture, decreased the rate of leaking capsules from 2 percent to almost zero. Those two modifications also boosted encapsulation yields [6].

**Effective softgel production**

The three main steps of softgel production are perfecting the gel mass, optimizing the ribbon, and drying the capsules properly. To minimize manufacturing costs and create state-of-the-art products, it is essential to prepare a gel mass that performs consistently and is not prone to foaming during production. Excessive foam can impair the performance of the vacuum and add costs because it prolongs the manufacturing process. To avoid those problems, conduct comparative analyses of the intrinsic foaming characteristics of various gelatin types. If the product requires a gelatin that foams, adjust the stirring conditions and vacuum to limit foam in the gel mass.

The three curves in Figure 1 represent three gelatin variations [7]. Type 1 (red) comes with a high foam function and high stability; type 2 (blue) has a high foam function and low stability; and type 3 (green) has less foam function and less stability. Each curve shows two phases. The first phase corresponds to the increasing amount of foam following the injection of an inert gas, and in the second phase, the amount of foam decreases over time. With this knowledge, it is possible to predict behavior and adjust the settings to prevent defects and maximize operational effectiveness.

The second step is perfecting the ribbon. This requires a gelatin that is soluble and versatile, with good mechanical strength. Formation of the ribbon—essentially a thick film—requires monitoring and controlling, temperature, seam width, and fill quantity. It is essential that these parameters be set correctly, because they have a significant impact on gelatin viscosity, and therefore the gelatin's film-forming capabilities. Other critical factors include the processing speed, gelling proximity, setting temperature, and thermo-reversibility characteristics. All have an effect on encapsulation. Choosing a gelatin with the optimal mechanical strength and elasticity will enable it to stretch during filling and ensure sufficient production speed.

The third step is drying, which ensures that the softgels reach and maintain a moisture level that prolongs their shelf-life. An adequate moisture level also prevents stickiness. See Figure 2, which illustrates that a moisture
level greater than 11 percent in fish oil formulations significantly increased the risk of stickiness [8]. Research also shows that drying constraints and thermal history have a significant effect on achieving ideal moisture levels.

**Overcoming challenges**

Creating softgels is complex, and their development often presents multifaceted challenges. For instance, the bioavailability of active ingredients relies on the dissolution of both the softgel shell and its fill, as well as the pharmacokinetic features of the API. During storage, however, the capsules may encounter excessive heat and moisture, which can degrade their stability and shelf-life [9]. To ensure stability and optimal API delivery, maintain moisture at the correct level, usually between 6 and 12 percent.

A softgel’s makeup can pose other challenges, including the migration of the product’s components and the physical and chemical reactions between the shell and fill. In addition, external environmental influences can cause instability, brittleness, softness, or loss of shape. Any of those changes can affect how well the API is protected against oxidation and/or cause recrystallization. Dynamic structures, such as polyethylene glycol-based (PEG) systems, are another example. They demonstrate a gradient in moisture level between the hydrophilic PEG fill and the shell, which can cause water to migrate after encapsulation. This leads to instability and reduces the product’s effectiveness. Preventing these effects requires careful selection of the shell formulation and precise gelatin processing.

An additional formulation challenge is the potential for extensive crosslinking, which occurs when strong chemical linkages form between gelatin chains. The result is a shell that becomes tough and rubbery, which
can render the capsule insoluble and unstable. The gelatin's molecular weight distribution can influence how susceptible it is to crosslinking, as can exposure to aldehydes. See Figure 3 [10]. However, gelatin that has been customized can prevent crosslinking and subsequent instability. It is also possible for manufacturers to predict the behavior of gelatin when faced with crosslinking and thus optimize production.

**Conclusion**

Whether the goal is to delay or control the release of ingredients or to reduce costs, manufacturers of pharmaceuticals and dietary supplements continue to seek new softgel formulations that provide better functionalities. Due to the complex nature of formulating softgels and operating the process, developing high-quality products that meet the expectations of consumers and regulators will always pose challenges. That's why it is important to work with reputable gelatin suppliers who can share their softgel expertise and provide guidance.

Our company, the global leader in gelatin and collagen peptides [11], conducts more than 100 safety checks and/or controls to ensure product quality and traceability from raw material to commercial batches. Furthermore, our experts provide comparative analyses and protocols to measure gelatin functionalities that optimize softgel production according to the encapsulation conditions, formulation, and active ingredients. As a result, manufacturers can create world-class pharmaceuticals and dietary supplements that appeal to today's demanding patients and consumers.

**References**


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