This white paper outlines the key considerations to ensure gelatin is enhanced for soft gel formulation, efficient gel production and optimal API delivery as well as the potential challenges that Contract Development and Manufacturing Organizations (CDMO) could face if the right gelatin is not selected. It also discusses research that Rousselot has conducted, highlighting the impact of factors including ingredient compatibility, molecular weight and gelatin bloom on the quality and stability of soft gel capsules.

Due to its unique functional capabilities and full compliance with the human body, gelatin is the main ingredient in soft gelatin capsules, commonly known as soft gels. Soft gel manufacturers constantly work on new formulations to accommodate specific fills, develop new types of soft gels such as delayed release or chewable capsules, or to reduce costs. However, creating a soft gel delivery system that fulfills the latest specifications and end-use requirements is a complex and highly challenging process.

Choosing a high quality gelatin with the right characteristics is fundamental to achieving optimum soft gel capsules and this often requires a specific gelatin type. For instance, the soft gel capsule must allow optimal delivery of the active pharmaceutical ingredient (API) to the body. Therefore, soft gel stability and crosslinking properties of the gelatin used in manufacture should be understood and taken into consideration. Moreover, using the right gelatin is also central to promoting an efficient and smooth manufacturing process so as to avoid typical soft gel defects such as twin, leakages, odds and brittleness. Critical steps include preparation of a gel mass that displays consistent quality and minimal foaming, film manufacture and drying, therefore, gelatin must be soluble, easy to use and exhibit good mechanical strength.

**GELATIN, A KEY EXCIPIENT FOR SOFT GELS**

Gelatin is a fully digestible, natural protein extracted from collagen found in the skin, bones and connective tissues of animals. Its availability, versatility and unique functional capabilities including film forming, thermo-reversibility and rapid absorption contribute to its extensive use in a number of pharmaceutical applications. These include soft gel capsules whose popularity among consumers is driving the research into the development of new formulations.

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**INTRODUCING PIERRE-ALBERT THOMAS**

Pierre-Albert Thomas is the Global Technical Support Manager at Rousselot, he and his team are responsible for bringing technical solutions to all pharma, food and nutrition accounts worldwide. Pierre-Albert joined Rousselot in 2003 as the Technical Account Manager for Japan. From 2006 to 2011 he was responsible for the Technical Support and the Application Laboratory of the Asian Pacific region. With a degree in Food Science from the AgroParisTech University, Pierre-Albert has 20 years’ experience in the food industry and an extensive knowledge of gelatin and its use in pharmaceutical and food applications.
Producing soft gels with consistent quality and integrity remains a high priority for the pharmaceutical industry. However, this is often difficult due to the dynamic nature of soft gel products and the sophisticated technology required in their manufacturing process. A key and vital ingredient in soft gels is gelatin. Choosing the right type of gelatin with the appropriate functional properties plays a critical role in an efficient and smooth manufacturing process which will yield an optimally performing capsule without any defects.

**GELATIN FOR OPTIMAL FORMULATION**

CDMOs are increasingly looking to develop new soft gel formulations. The objectives for this may be to accommodate specific fills, to develop new types of soft gels such as delayed release or chewable capsules or to reduce costs. Moreover, the increasing number of APIs being developed means that manufacturers need to take into consideration the interactions that may occur between the shell and the fill when developing new formulations. Choosing a high quality gelatin with specific characteristics that will fulfill the objective of the end-product is crucial. However, to meet the specific needs of the product’s therapeutic action as well as consumer preferences, an appropriate gelatin with the right properties and functionalities often needs to be constructed.

Tests on lecithin soft gel formulations prove that factors including gelatin type and processing conditions can have a significant impact on the leakage risk of the soft gel shell. For example, without using a high wedge temperature during manufacture, gelatin types with greater molecular weight form seals less readily due to their high viscosity, causing soft gel mis-shape and leakage. Tests also concluded that, in the conditions of the experiment, alkaline or mixed-process gelatin soft gel capsules showed less leakage than gelatins manufactured through acid processes; and optimizing the type of gelatin and encapsulation wedge used during soft gel manufacture decreased the rate of leakage from 2% to almost 0% (Internal Rousselot study, Wenzhou Application Lab, April 2016).

Figure 3 demonstrates the significance of optimizing encapsulation wedge during manufacture for better sealing in soft gel capsules, showing that an optimal range of gel mass viscosity has been determined as a function of the type of encapsulation wedge.

![Figure 3: The relation between encapsulation wedge and gel mass viscosity](image-url)
The aim for CDMOs is defect-free production of optimal soft gel capsules. However, the manufacturing process can prove challenging. The critical steps during this stage include gel mass preparation, ribbon formation and drying. The gelatin used must be soluble, easy to use and have good mechanical strength.

A quality gel mass
Preparing a gel mass that displays consistent formulation performance and minimal foaming is critical to prevent increased production costs and end product defects. Due to its amphiphilic nature, having both hydrophobic and hydrophilic properties, gelatin exhibits foaming characteristics by decreasing interfacial tension. A good understanding of foam capability and stability of the different types of gelatin is essential to have full control of the soft gel manufacturing process, where foaming can cost additional vacuum time to the manufacturing process and impact productivity.

Graph 1 shows three curves that represent three different gelatin types – Type 1 with high foam function and high stability, Type 2 with a high foam function but low stability, and Type 3, less foam function and stability.

Every curve shows two phases – Phase 1 showing the increase of foam value following the injection of an inert gas and Phase 2, the value decrease after the injection of gas.

As foaming is undesirable in soft gel formulations, Rousselot’s comparative test is valuable for the selection of gelatin and operating conditions.
The perfect ribbon

Gelatin’s unique film-forming functionalities allow it to set quickly and form reproducible films of defined thickness known as ribbons. This stage requires extreme precision, with manufacturers having to accurately monitor and control gelatin temperature, ribbon thickness, seam width and fill quantity. The gelatin’s film-forming and viscosity properties are crucial to the success of this producing step. For instance, gelatin’s processing procedures have a strong impact on its viscosity and therefore its film-forming capabilities. There is a strong relation between viscosity and film forming: viscosity represents the molecular weight of the gelatin and therefore influences the kinetics of the formation of the gelatin network. This has an impact not only on the speed at which the gelatin ribbon will set but also on its quality and it influences the temperature at which the gelatin will melt and reset during encapsulation. Finding the right visco-elastic behavior of the gelatin system is therefore essential to create the perfect ribbon for soft gel capsules as well as to ensure production efficiency.

Drying to preserve shelf-life

In order for soft gels to remain in perfect conditions during their shelf-life, they must undergo a drying process to prevent stickiness. A Rousselot study performed on fish oil formulations highlights the effect of final moisture level in soft gel capsules, showing that a moisture level above 11% significantly increases the risk of stickiness (Graph 2). Rousselot research also found that the parameters of the drying stage, such as drying conditions and kinetics, are key to achieving a suitable moisture level. In addition, soft gels prepared with different plasticizers, such as PEG, require different drying regimes than soft gels prepared using glycerol or sorbitol.

Graph 2: The effect of final moisture level on soft gel (Internal Rousselot Study, Wenzhou Application Lab, Sept. 2013)

Graph 3 highlights the influence of different temperature and relative humidity (RH) combinations on the final moisture content. The graph shows that although 25°C degrees at 25% relative humidity permits more water evaporation in the first two days of drying, it is 15°C degrees at 15% relative humidity conditions which are the most effective conditions to reach the optimal lower moisture content of capsules which will prevent stickiness during the shelf life².

Optimized process speed

Choosing a gelatin with high solubility, usability and low viscosity above 50°C is important for optimizing the speed of production. Gelling proximity, setting temperature as well as the thermoreversibility characteristics of the selected gelatin all influence high speed encapsulation. As well as this, gelatin must have optimal mechanical strength and elasticity properties to allow stretching during filling.

² Liquid-filled Gelatin Capsules. Pharmacopeial Forum 2009 Vol. 35(4)
Ultimately, the reason for developing a soft gel capsule is so that it can effectively deliver an API. The bioavailability of actives in a soft gel depends on the dissolution of both its shell and fill as well as the gastro-resistance of the API. The capsule must also protect APIs during storage, only releasing them at the correct time and location in the body once consumed. However, soft gels can be sensitive to heat and moisture during storage, affecting the shelf-life stability. To prevent instability for optimal API delivery, solute migration and crosslink minimization can be avoided by choosing a compatible gelatin with the right characteristics; and gastro-resistance can be managed with the addition of a biopolymer coating.

Shell inertness
A major challenge in the development of soft gels is that they are very dynamic systems. The physical migration of components between shell and fill as well as from the external environment to the shell, and the occurrence of physical and chemical reactions between the shell and fill components can cause instability, brittleness and shell softness or even loss of shape affecting the protection of the API against oxidation and causing possible recrystallization.

PEG-based systems, for example, exhibit a gradient in the moisture levels between the hydrophilic PEG fill and the shell. This causes migration of water following encapsulation and subsequent instability, reducing the effectiveness of the capsule. However, this can be avoided with careful choice of gelatin processing techniques and shell formulation.

Crosslinking
Extensive crosslinking i.e. the formation of strong chemical linkages between gelatin chains, can cause the shell to become tough, rubbery and insoluble affecting soft gel stability. Research has revealed that some parameters, including gelatin molecular weight distribution, may impact the ability of gelatin to crosslink; however customized gelatins can prevent crosslinking and subsequent instability (graph 4). Rousselot has developed a protocol predicting the behavior of gelatin in the presence of cross linkers to help the pharmaceutical industry construct the optimal gelatin type for their soft gel product.

Graph 4: The effect of different gelatin types on crosslinking behavior in the presence of aldehydes. A steep increase in viscosity corresponds to increased crosslinking. (Internal Rousselot study, Ghent Application lab, Oct. 2016)

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CONCLUSION

The manufacture of high quality gelatin-based soft gels that fulfills the end-use requirements and meets consumer demands as well as stringent industry regulations, is a complex challenge for pharmaceutical manufacturers. A deep understanding of the soft gel market and the capsule production process is key to choosing the correct gelatin for optimal formulation, an efficient production process and effective API delivery. Rousselot can provide the support needed to succeed.

THE WORLD LEADING PRODUCER OF NATURAL GELATIN AND COLLAGEN PEPTIDES

Rousselot, the world leading producer of natural gelatin and collagen peptides, offers CDMOs in the pharmaceutical industry an extensive range of world class gelatin products and solutions as well as expertise and innovation in soft gel manufacture. Partnering with the Rousselot team means benefiting from an impressive heritage of 125 years’ worldwide experience in the production and application of pharmaceutical gelatin. Customers have access to a comprehensive service and exceptional understanding of the soft gel market helping to eliminate risk during manufacture, maximizing productivity at all stages of the process and saving costs.

Rousselot’s safe, non-allergenic and fully compatible gelatins are obtained by careful selection of raw materials and produced in full compliance with the highest quality, safety standards and practices including IFS, HACCP and GMP. A wide variety of certified Halal and Kosher gelatins is also proposed to Rousselot’s customers.

Rousselot guarantees consistent quality, safety and traceability to ensure the perfect gelatin is created for optimal soft gel success. Rousselot also proactively takes steps to achieve greater progress in its environmental and ethical business goals, implementing sustainable production methods to reduce energy use and water consumption for the protection of the planet.

Figure 5: Rousselot promises: Expertise supported locally, highest standards and full responsibility.
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Rousselot is a brand of Darling Ingredients Inc.
Rousselot is the global leader* of gelatin and collagen peptides.
Rousselot’s wide range of collagen peptides are marketed under the Peptan brand.
We work in partnership with our customers all over the world,
delivering innovative and advanced ingredient solutions manufactured
through state of the art operations. We help our customers achieve their goals,
ensuring that they create world class pharmaceutical, food and nutritional products
to inspire and excite today’s demanding consumers.


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