Whitepaper

PERFECTING THE SOFTGEL FORMAT

Your guide to the tools, techniques and science behind crafting the ideal softgel capsule.

Executive summary

With its many multifunctional properties, gelatin is the ultimate excipient for the manufacture of softgel capsules.

However, a poorly constructed or ill-suited gelatin excipient can result in reduced process efficiency, higher costs, increased waste and generally underwhelming softgels.

By drawing on highly-specialized research, this whitepaper aims to help pharmaceutical brands and Contract Development Manufacturing Organizations (CDMOs) overcome common production challenges and optimize operations to create defect-free capsules; from the specific gelatin characteristics they should consider, to optimal processing techniques and how they can lay a stable foundation for the next big innovation in softgels.

Introduction

The quest for perfection: What's holding softgels back?

Softgel capsules are one of the most popular delivery formats seen across the pharmaceutical and nutraceutical sectors. Convenient, safe and endlessly versatile, they offer patients an attractive proposition, particularly in terms of taste masking and bioavailability.

It would be easy to argue that softgels represent a "perfect" dosage form, but it takes a lot to truly deliver on this promise.

First, capsule producers need a dependable source of high-quality gelatin. Safety and consistency are king in the pharma world, so it's crucial that softgel producers can count on a reliable supply of raw materials and ultimately deliver consistent products that meet the demands of the market for capsules. More than just being available though, the gelatin excipient selected must also exhibit all the right functionalities and properties, including low foaming capacity, a strong ability to yield a stable gel mass, good film-forming capabilities, a low risk of active pharmaceutical ingredient (API) interaction, and minimal propensity for crosslinking. If even one of these parameters falls short, producers can find themselves with cloudy, leak-prone or even misshapen softgels.

Beyond the gelatin itself, how the excipient is processed during the encapsulation is equally critical to ensuring softgel success. Precise control over processing temperature and ribbon thickness, as well as establishing the correct drying protocol are all vital for avoiding bubbles, stickiness and improper sealing to create impeccably formed capsules that stay stable throughout their shelf life.

It can be a complex process, but we are here to offer guidance every step of the way. Let's explore each production stage in closer detail, and discover what exactly it takes to make the perfect softgel.

Gelatin: The natural choice for softgels

Softgel capsules can be made using a variety of polymeric excipients, including plant-based additives like carrageenan and modified starches. But, as shown by the results of the softgel degradation study (Graph 1), it's naturally-versatile animal gelatin that by far tops the list of softgel ingredients.[1]

Gelatin is a fully digestible, natural protein extracted from collagen. As an additional product produced by the meat industry, it is also the ultimate upcycled ingredient, addressing the current drive for more environmentally responsible pharmaceutical ingredients. What's more, gelatin's availability, versatility and unique functional capabilities make it both a smart, and sustainable choice.

Looking at the softgel delivery format in specific, gelatin's capacity for film forming, thermo-reversibility and rapid in-body dissolution make it the excipient of choice for the manufacture of the shiny, liquid-filled capsules patients know and love.

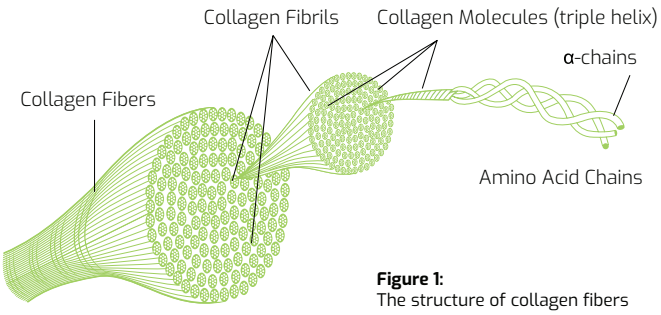
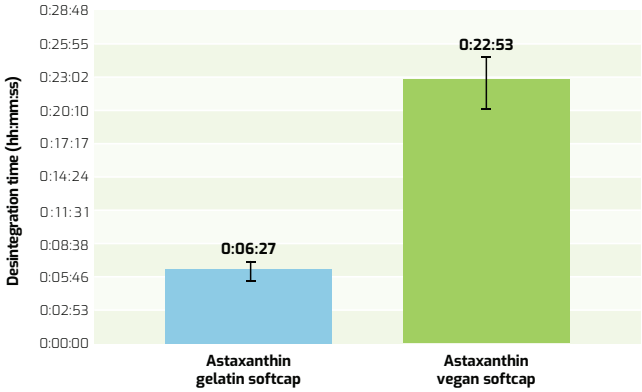


Figure 1:
The structure of collagen fibers

Achieving this high standard of production is not always an easy task, however. The dynamic nature of softgel products and the sophisticated technology required in their manufacturing process means manufacturers need to select the right type of gelatin to give them the best possible base for an efficient, defect-free production process.



Graph 1: Comparative study of softgel degradation rates: Vegan vs gelatin (Internal Rousselot study, Global Application Center, 2023)

Figure 2: The functional capabilities and properties of gelatin

1 Grand View Research, Softgel Capsules Market Size, Share & Growth Report, 2030, https://www.grandviewresearch.com/industry-analysis/softgel-capsules-market-report

Just your (gelatin) type

Gelatin's baseline benefits already mean it is well suited to the role of optimal softgel excipient. But to achieve the intended therapeutic action in the final product and ensure reliable consistency, producers often need to engineer a specific gelatin with the precise properties and functionalities required to meet patient needs.

The right partner. The right knowledge. The right gelatin.

Formulating the right gelatin excipient takes skill, experience and a fundamental understanding of the softgel production process. With more than 130 years of gelatin manufacturing underpinning our constant drive for scientific innovation, Rousselot will help you develop high quality pharmaceutical softgels.

Excipient engineering: Key considerations for softgel formulations

For some it may be 'perfect' already, but there are many ways to further elevate the softgel format. This could mean altering formulations to accommodate specific fill types, incorporating new delivery mechanisms such as delayed release or chewable capsules, or simply reducing production costs to help make softgels accessible to a wider audience, while protecting profits.

In addition, as new active pharmaceutical ingredients (APIs) continue to be developed, drug manufacturers must constantly reevaluate their gelatin shell's propensity for interaction, particularly when working with novel softgel fills such as solutions and solid/liquid dispersions. All these considerations, and often more, should influence the selection of a gelatin ingredient, well before the first softgels go into production.

Case study: Minimizing capsule leakage

Lecithin is the term used to describe a collection of fatty substances that are essential for normal bodily function. As such, it is a common inclusion in softgel fills, but its high viscosity can lead to 'tailing' during encapsulation, creating holes in the capsule seal from which the fill can leak.

This issue is especially pronounced at high manufacturing speeds, meaning producers must choose between achieving high output at the expense of increased defects, or less waste at the cost of a slower, less efficient production line.

To help break through this compromise, Rousselot set out to investigate the effect various gelatin preparation factors have on the rate of capsule leakage, specifically in softgels containing lecithin [See Table 1 and 2].

In all instances, capsules were able to be produced that exhibited a low leakage rate, some at higher processing speeds and with shorter drying times. Achieving this low defect output however required the careful handling of both the gelatin preparation and process parameters. The higher moisture Type A gelatin for example was able to be processed at higher speeds, but also required increased drying time to produced leak-free capsules.

Gelatin type	Type A	Type B	Type C
Gel strength (Bloom g)	200	140	160
Viscosity (mPa.s)	4.4	3.3	2.2
Formulation			
Gelatin (%)	44	50	52
Glycerin (%)	22	20	20
Pure water (%)	44	30	28

Gel mass & softgel encapsulation	Type A	Type B	Type C
Gelmass viscosity (60ºC) (mPa.s)	20,000 – 25,000	20,000 – 25,000	20,000 – 25,000
Moisture of gel mass (%)	43~45	36~40	30~35
Running speed (RPM)	3.0~4.0	3.0~3.2	3.0~3.2
Gelatin ribbon thickness (mm)	0.80~0.82	0.80~0.82	0.80~0.82
Drying time (hours)	48~72	18~24	18~24
Leak rate (%)	0	0	0

Table 1 and 2: Gelatin types in the production of lecithin softgels (Internal Rousselot study, Wenzhou Application lab, 2024)

The key takeaway?

With the help of Rousselot's gelatin experts, even the most challenging softgel fills can be managed to ensure secure seals, every time.

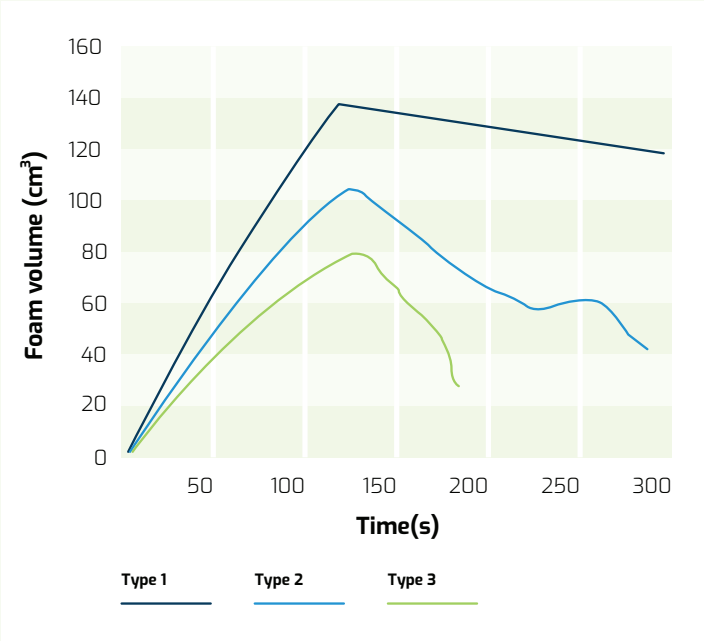
Smoothly does it: Building an efficient production process

We have our ideal gelatin solution so, what's next?

Identifying the optimal parameters for each processing step can be a complex and daunting task. This is where partnering with Rousselot experts adds real value. From gel mass preparation, to ribbon forming and capsule drying, let's explore what makes a 'gold standard' production process according to our experts.

Hold the foam: Preparing an optimal gel mass

Consistent formulation performance and minimal foaming; these are the critical factors producers should look for when preparing a gel mass. Due to its amphiphilic nature (meaning it exhibits both hydrophobic and hydrophilic properties), gelatin decreases interfacial tension in aqueous solutions, leading to the development of foam.



Graph 2: Comparative analysis of foam capacity and foam stability of different gelatin types (Internal Rousselot study, Ghent R&D Lab, 2016)

Understanding a specific gelatin type's foam capability and stability is essential for maintaining complete control over the softgel manufacturing process, since more voluminous, stable foam means additional vacuum time, lowered productivity and even increases the risk of shell sealing defects.

To help producers more effectively evaluate the intrinsic foam-forming capacity of different gelatin types, Rousselot has developed a comparative analysis test.

Graph 2 displays three curves, representing three distinct gelatin types; type 1 which exhibits high foam function and high stability, type 2 with a high foam function but low stability, and type 3, which shows a low foam function and stability. Each curve on the graph describes two phases, the first showing the increase of foam value following the injection of an inert gas, and the second denoting the value decrease after the gas injection. From the results we can see that type 3 is best suited to softgel formulations, as it will require the least vacuum time to remove any seal-compromising bubbles.

Armed with this method for accurately predicting the behavior of various gelatins, producers are better equipped to select a low-foam-forming, low-foam-stability ingredient to optimize process efficiency.

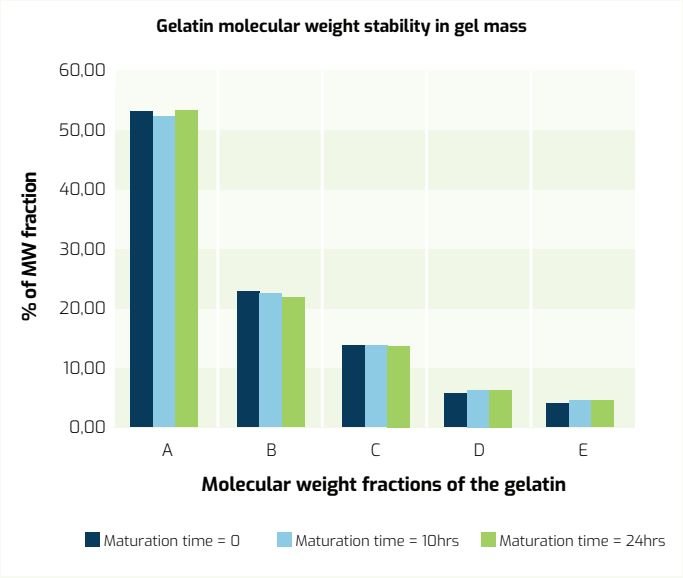
A strong and stable gel mass

Following gelatin melting and de-aeration, the gel mass can be prepared for casting into gelatin films. At this stage, it is vital that molecular weight of the gel mass remains stable.

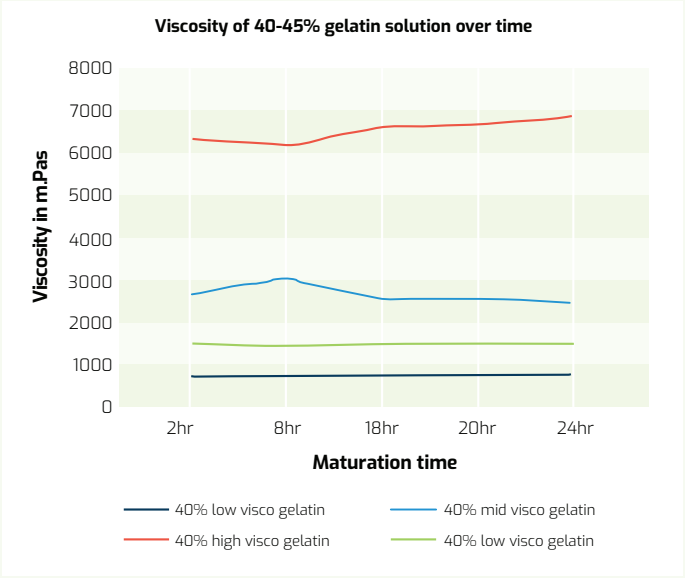
This is because drastic shifts in molecular weight during production could impact either the gelatin's bloom or viscosity – both of which are essential for maintaining capsule and seal integrity.[2]

Again, to assist softgel manufacturers in this important step, Rousselot developed a series of effective tests to evaluate a gel mass' molecular weight distribution over time.

The specific gelatin types vary, what remains consistent is the extreme stability of gel masses prepared using the Rousselot gelatin ingredients selected for the test. Moving ahead to the film-forming stage, we can see the value selecting quality gelatin solutions like these can bring to the production process.



Graph 3: Gelatin molecular weight stability in gel mass (Internal Rousselot study, Global Application Center, 2023)



Graph 4: Viscosity of 40-45% gelatin solution over time (Internal Rousselot study, Global Application Center, 2023)

Film review:
Forming the right ribbon

With its unique film-forming functionalities, gelatin is able to set quickly and form reproducible films of defined thickness known as ribbons.

In softgel production, these ribbons are the material out of which the capsule shell is stamped, before going on to filling and sealing. While every production stage requires precision, special care should be taken during the film-forming process to ensure the gel mass is kept at a high enough temperature to stay malleable until sealing, but not so hot that it becomes unstable or compromises the integrity of the API. The thickness of the forming ribbon should also be monitored closely since it will determine the capsule's seam width and fill quantity.

Here again, the properties of the gelatin excipient chosen have a huge role to play in the success of the ribbon forming stage. Viscosity is the key word in this context, as its this that represents the molecular weight of the gelatin and therefore the kinetics involved in the formation of the gelatin network.

Selecting a gelatin with the right visco-elastic behavior (melting behavior, tensile strength, setting temperature, etc.) then yields a range of processing benefits, from increased setting speed, to improved melting and resetting during encapsulation.

2 Damian F, Harati M, Schwartzenhauer J, Van Cauwenberghe O, Wettig SD. Challenges of Dissolution Methods Development for Soft Gelatin Capsules. Pharmaceutics. 2021 Feb 4;13(2):214. doi: 10.3390/pharmaceutics13020214. PMID: 33557167; PMCID: PMC7913951.

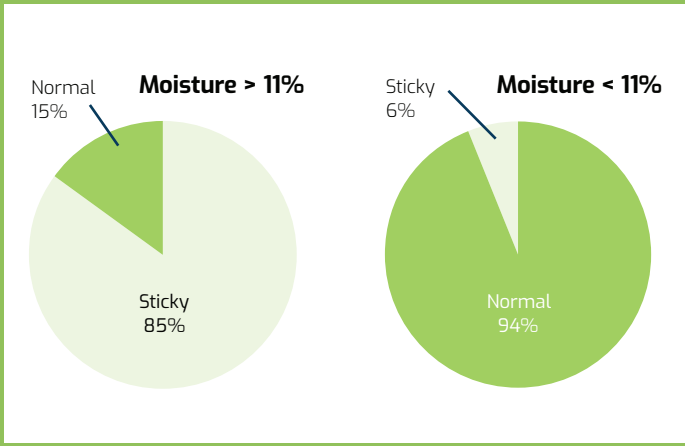
Give it a dry:
Mitigating capsule sticking

For softgels to stay their shiny, stable selves throughout their shelf-life, they must undergo a drying process. This step removes moisture from the gelatin capsule, preventing stickiness and helping protect the API from future degradation.

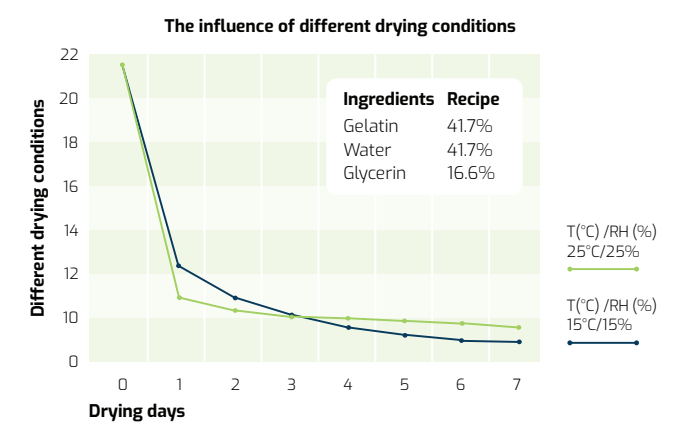
The challenge for producers is determining at what temperature and for how long a capsule should be dried to eliminate sticking and assure stability. Through extensive research, Rousselot has found that the parameters of the drying stage, including drying conditions and kinetics, have a major impact on achieving the required moisture level.

What's more, softgels prepared with different plasticizers, such as polyethylene glycol (PEG), require different drying regimes than softgels prepared using glycerol or sorbitol. A Rousselot study performed on fish oil formulations highlights the importance of managing all these factors during the drying phase, showing that a moisture level above 11% significantly increases the risk of stickiness (graph 5).

So, what are the ideal drying conditions for softgels? Graph 6 highlights the influence of different combinations of temperature and relative humidity (RH) on capsules' final moisture content. Through the results we can see that, although 25°C at 25% RH allows for increased water evaporation in the first two days of drying, the combination of 15°C at 15% RH is actually most effective for reaching the low moisture content needed to avoid a sticky situation.



Graph 5: The effect of final moisture level on soft gel (Internal Rousselot Study, Wenzhou Application Lab, 2013)



Graph 6: The influence of different drying conditions (Internal Rousselot study, Wenzhou Application lab, 2012)

The need for speed (and process efficiency)

Time is money in the production of pharmaceutical softgels. At Rousselot, its our mission to offer superior quality gelatin solutions with all the characteristics producers need to optimize efficiencies, on and off the production line.

But our expertise doesn't end there. We're committed to advising our customers on how to establish effective automation and process control, assure batch-to-batch consistency, and upscale their operations to seize the opportunities of a growing market.

The main event: API protection and delivery

No matter their specific functionality, the ultimate goal of any softgel should be to effectively deliver an active ingredient for the benefit of the end user, whether that's pain relief, nutritional support or specialized therapy.

Releasing an API at the right time, at the right site of action requires a delicate balance between stability and dissolution. A softgel must be capable of protecting active ingredients during storage, but equally able to overcome challenges like gastro-resistance to diffuse APIs into the target bodily tissues. While the latter issue can be overcome with the application of a biopolymer coating to improve digestibility, keeping capsules stable before use is a little more complex, requiring the management of both solute migration and crosslinking.

Shell inertness: Avoiding a reaction

Softgel capsules are highly dynamic systems. This essentially means it can be difficult to prevent components physically migrating between the gelatin shell and active fill, as well as stop external environment factors from impacting the chemical stability of the shell during storage.

Interactions like these can cause shell brittleness or softness, possible recrystallization and even a loss of shape exposing the API to the risk of oxidation.

Using the right gelatin ingredient and an effective drying process (see above), manufacturers can construct completely inert capsule shells, capable of remaining stable until they are called on to release the API into the body.

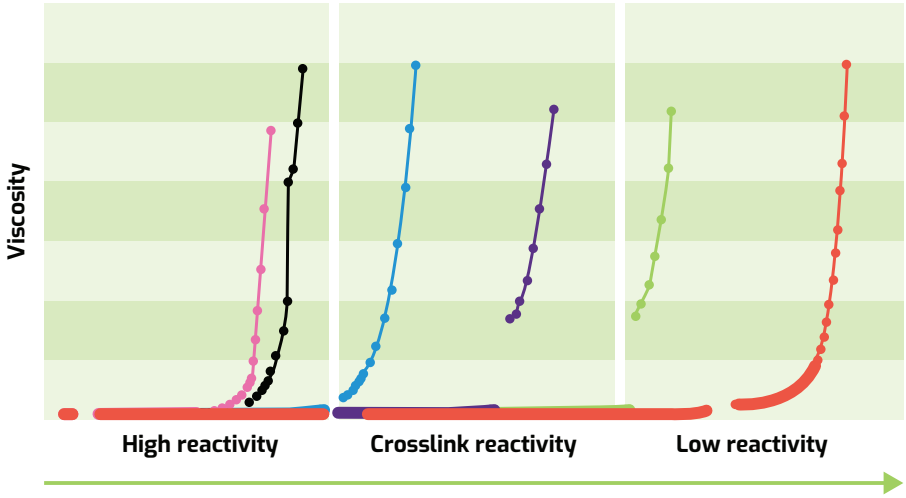
Crosslinking: Keeping chains unconnected

Crosslinking is the formation of strong chemical linkages between gelatin chains. This is a positive feature in some applications, but in softgel applications crosslinking can lead to the production of tough, rubbery and insoluble shells, impacting a capsule's stability and therapeutic effectiveness.

Studies have revealed that some parameters, including gelatin molecular weight distribution, may lead gelatin to crosslink. With this in mind, Rousselot has developed a two-pronged approach to helping producers mitigate damaging crosslinking.

The first is a dedicated protocol for predicting the behavior of gelatin in the presence of substances that can induce crosslinking, such as aldehydes. Graph 7 shows the results of the testing protocol, with the steep increases in viscosity corresponding to a rise in crosslinking.

As we can see, the gelatin represented by the red line significantly outperforms the rest in terms of resistance to crosslinking, but why? To answer this question, we need to introduce the second aspect to Rousselot's two-pronged approach to curbing crosslinking and creating effective softgels; StabiCaps.



Graph 7: 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, 2016)

STABICAPS™: Stability meets functionality

Improved shell stability, minimal crosslinking, enhanced API release; producers can achieve it all with StabiCaps gelatins.

With superior resistance to common crosslink contaminants, StabiCaps deliver ultimate shell stability alongside an effective dissolution profile, both of which have been recognized in patents issues by the European Patent Office (EPO) and U.S. Patent and Trademark Office (USPTO).

Even better, we have recently discovered further advantages to utilizing StabiCaps in large-scale industrial processing. During testing we observed a reduction in the maturation time of the gel mass and faster drying times, allowing for quicker, more efficient production runs.

Together with its already outstanding crosslinking resistance, these findings confirm StabiCaps' status as a reliable solution for successful softgel production.

Your trusted partner for softgels

It takes a lot to craft the perfect capsule, from the right ingredients, to fine-tuned production techniques.

Built on over 130 years of experience in the production and application of gelatin, Rousselot is here to offer it all:

- An unmatched range of cutting-edge, pharmacopeia-compliant gelatin solutions to suit any application, including Halal and Kosher certified products.
- Expert manufacturing, testing and regulatory knowledge for end-to-end support.
- A true commitment to science and innovation, with ingredients backed by peer-reviewed research.

Figure 3: Rousselot promises: Expertise supported locally, highest standards and full responsibility

Our locations

With the addition of six state-of-the-art Gelnex production sites to our already extensive global network of ten manufacturing facilities, we're able to offer assured ingredient quality, safety and reliability of supply to customers globally. Every one of our locations is dedicated to implementing sustainable production practices that help preserve the natural resources that inspire our leading collagen and gelatin solutions.

Wherever you are, we're ready to deliver.

North America

Europe

South America

Asia

Heritage. Quality. Science. Innovation.
Partnering with Rousselot, means reaching further, together.

Rousselot® Functional Ingredients

A clean label ingredient with a long tradition, gelatin is Rousselot's primary business, and our world-class gelatins are leading the market. Designed by nature, Rousselot's standard and specialty gelatins provide unmatched functional advantages, resulting in superior end-products for the consumers. Rousselot's gelatins are safe, derived from natural sources and contribute to a circular economy. Rousselot Functional Ingredients works in partnership with the food, pharmaceutical and technical industries and helps them achieve their formulation and business goals. With us, "The difference is clear!"

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