WHITE PAPER

X-pure
ADVANCING MEDICAL SCIENCE

LOW ENDOTOXIN GELATINS IN PARENTERAL APPLICATIONS

THE MULTIPLE BENEFITS OF HIGHLY PURIFIED GELATINS IN PARENTERAL APPLICATIONS

As a biomaterial of choice, gelatin is widely recognized for its use in parenteral applications. Highly biocompatible, purified gelatin helps provide drug protection, offers superior drug loading rates, and great flexibility in the control of drug release. It helps stabilize vaccines and other formulations and minimizes side reactions while ensuring patient safety. These are just few examples of the many benefits provided by purified gelatins.
This white paper explores these various advantages and describes how X-Pure® extra purified GMP quality gelatins can help realize superior parenteral formulations.

By Dr. Bjorn Vegauwen, Scientific Director Product & Process Development, March 2020

INTRODUCTION

Gelatin is a highly versatile drug delivery platform and a trusted excipient and stabilizer in a wide range of parenteral applications. Its natural origin and tuneable physiochemical properties render benefits such as biocompatibility, stability enhancement, improved bioavailability, and reduced toxicity. However, the in-body use of standard pharmaceutical grade gelatin is challenged by its potential impurities such as endotoxins. These are remnants of the outer membrane of bacteria, which are highly immunogenic, and are associated with tissue inflammation, increased sensitivity to other allergens, and an increased risk of fatal shock[1]. Even low levels of endotoxins have been found to cause significant immune responses, which has led to the enforcing of strict regulatory limits on endotoxin content in parenteral applications, notably for applications in contacts with the central nervous system[2].

X-Pure® – the most advanced gelatin solution

- The X-Pure range of gelatin is currently the most complete range of purified gelatins available on the market.
- X-Pure is based on Rousselot's patented process, which overcomes the limitations of other approaches that only work in a subset of applications or that change the composition of the gelatin as part of the endotoxin removal process. Some endotoxin removal methods additionally risk leaving significant levels of new impurities in the gelatin.
- With X-Pure it is now possible to ensure a pure gelatin that already has low endotoxin levels at the sourcing stage. This minimizes the need for extra processing steps and avoids the risk of varying/uncontrolled levels of endotoxins in finished products. It also eliminates the risk of contaminants of concern by using multiple fail-safe controls.
- X-pure is derived from different animal sources and available both as type A and type B gelatin, as gelling or non-gelling product. Furthermore, it can be used to customize formulations that are required for specific applications. These might include chemical derivatizations.

X-Pure is ultrapure without compromising the unique tunable and biocompatible characteristics of natural gelatin and collagen.

Introducing Dr. Bjorn Vergauwen

Dr. Bjorn Vergauwen is the Scientific Director of Product & Process Development at Rousselot. He currently coordinates R&D projects that aim to unlock the potential of gelatin. His main expertise relates to the biophysical and biochemical principles underpinning gelatin's behavior in food and pharma applications and to its use in pharmaceutical dosage forms.
Dr. Vergauwen has a PhD in biochemistry from Ghent University, Belgium. Before joining Rousselot in 2014, he had several missions as Post-Doctoral Researcher at Ghent University, where he conducted research in molecular biology and enzymology for 17 years.

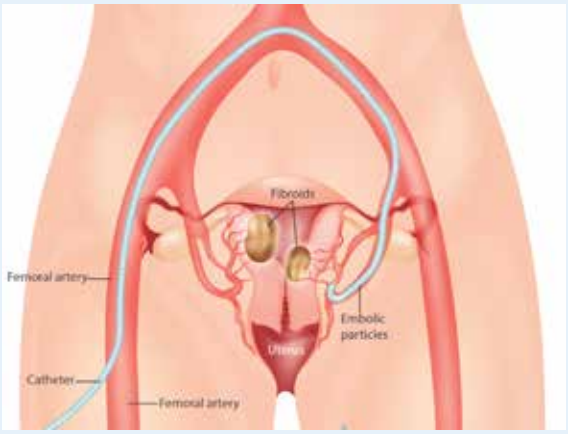
APPLICATION AREAS FOR ULTRA-PURE GMP GRADE GELATINS

Low endotoxin gelatin is an ideal product across parenteral applications where physicochemical tuneability, biocompatibility, stability, bioavailability or purity are desired. Application areas that are ideal for ultra-purified gelatins include, but are not limited to, the following:

• **Prolonged drug release**: in intramuscular, intra-articular or subcutaneous injections, by delaying the release of drugs from a gelatin hydrogel or particles. Examples of products using gelatin as the basis for controlled release include Acthar® (corticotropin) and Lupron® (leuprolide acetate). Gelatin often has superior loading rates compared to alternative materials such as poly lactic-co-glycoloic acid (PLGA) and polycaprolactone (PCL) for bio-therapeutics[3], enabling smaller injection volumes for the same rate of drug delivery. X-Pure gelatin can readily be cross-linked for a formulation, meeting almost any persistency requirements with excellent biocompatibility and with low risk of local or systemic inflammation.

Hydrogels are gaining popularity as long-term controlled release systems, which can be administered subcutaneously through injection. Gelatin-based hydrogels are ideal for making this drug delivery platform safe, effective and reliable. For instance, a gelatin-based injectable subcutaneous hydrogel might appropriately activate the immune system with its biological cargo as a novel vaccination or immune system modulation strategy.

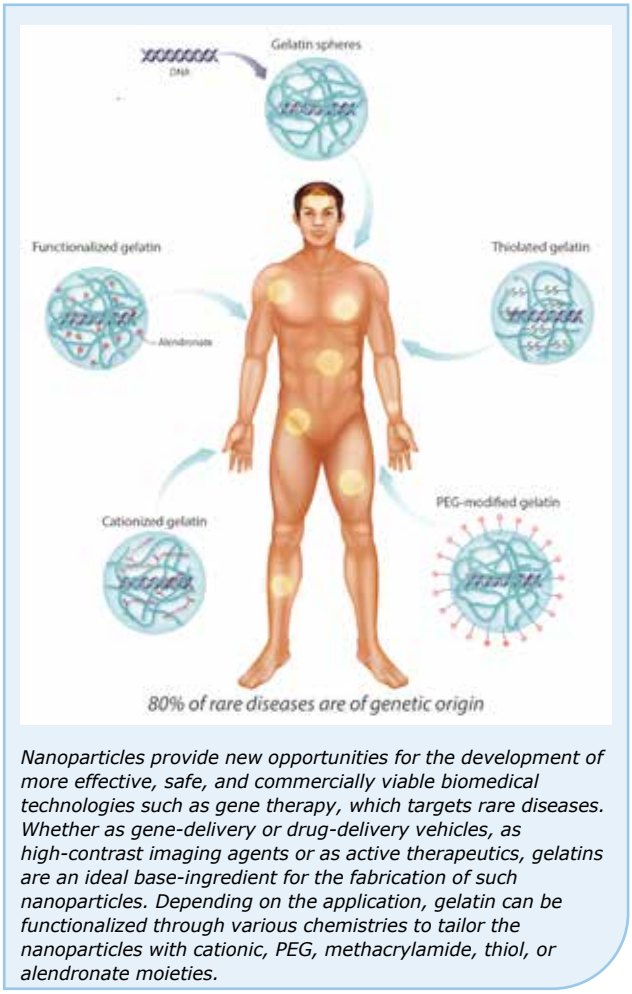
• **Embolization particles**: to stop uncontrolled bleeding or to block arterial blood flow into cancerous or otherwise unwanted tissue, with or without additional drugs or clotting factors. For many years, gelatin particles have been used in embolization applications such as fibroids, and more recently, tris-acryl gelatin microspheres have proven similarly effective[4]. Gelatin particles are increasingly considered for other embolization applications, for example as adjunct or substitute to polyvinyl alcohol (PVA) in bronchial artery embolization to stop bleeding in the bronchial tree[5,6], for control of intraoperative bleeding[7], or for embolization of carcinomas[8]. X-Pure is an ideal gelatin for embolization application as it provides a flexible material that can act as particles, foams, or as coating for other particles (for example PVA particles), to enable effective blockage of arterial blood flow while minimizing additional tissue inflammation.



Uterine fibroid embolization is a minimally invasive treatment for uterine fibroids (noncancerous growths in the uterus). Porous gelatin particles (embolic agents) are injected through a small catheter into the uterine artery. The gelatin particles then flow to the fibroids and lodge in the arteries that feed them. The ultimate goal is to block the fibroid blood vessels, starving the fibroids and causing them to shrink and die.

• **Nanoparticles for drug and gene delivery**: providing drug protection, controlled release, extended circulation[9], targeted and co-delivery of drugs[10], as well as a route for transdermal drug delivery[11], including delivery through the cornea[12]. Gelatin nanoparticles are also promising non-viral vectors for intra-cellular delivery of siRNA[10] and gene therapy[9], with gelatin currently considered as one of the potentially most effective non-viral vectors for gene delivery[13]. X-Pure provides an ideal starting point for such applications, offering a full

range of gelatins with minimal endotoxin levels, removing the need for additional purification steps.



Nanoparticles provide new opportunities for the development of more effective, safe, and commercially viable biomedical technologies such as gene therapy, which targets rare diseases. Whether as gene-delivery or drug-delivery vehicles, as high-contrast imaging agents or as active therapeutics, gelatins are an ideal base-ingredient for the fabrication of such nanoparticles. Depending on the application, gelatin can be functionalized through various chemistries to tailor the nanoparticles with cationic, PEG, methacrylamide, thiol, or alendronate moieties.

• **Vaccine and large molecular stabilizer**: typically in combination with other stabilizers. This is particularly important for live vaccines, to protect the live viruses during freeze-drying and storage[14], where gelatin offers a generally effective strategy to improve stability of lyophilized products[15]. Concerns about the safety of gelatin caused some vaccine developers to switch to other stabilizers in the 1990s. However, sourcing requirements quickly resolved safety concerns, and gelatin is once again a preferred stabilizer in many vaccines, including key routine vaccines offered to children and the elderly, for example. These include: Fluenz Tetra (flu), MMR Vaxpro (measles, mumps, rubella), and Zostavax (shingles)[16]. In the case of Fluenz, the formulation using hydrolysed gelatin achieved significantly superior stability over a large number of alternative stabilizers evaluated[17]. X-Pure is

Gelatin is an important stabilizer for the manufacturing of live attenuated vaccines.

ideally suited for use in such applications where lyophilisation stability is required as it is also available in a hydrolysed and non-gelling form, has well controlled endotoxin levels below 10 EU/g, and ensured batch to batch consistency.

• **Plasma expander colloid**: as a colloid with less kidney toxicity than starch-based plasma expanders, gelatin is used to increase blood pressure and circulating volume in patients suffering shock or haemorrhage[18]. Accordinlgy, gelatin-based Polygeline is one of two plasma expanders on the WHO list[19] of essential medicines (the other is Dextran 70, a polysaccharide). X-Pure is an ideal gelatin source for use in plasma replacement products and for use in line with the WHO essential medicines list when crosslinked with hexamethylene diisocyanate to create a urea-linked gelatin solution. With endotoxin levels below 10 EU/g, large quantities or volumes can be used without exceeding recommended endotoxin limits.

• **Solubility and tolerability enhancer**: as a mean to emulsify lipophilic drugs and drugs with poor aqueous solubility, to reduce drug toxicity[10], or to increase dosing of drugs limited by their maximum tolerable dose, for example chloroquine phosphate. Gelatin can also be used to enhance other drug delivery systems, for example to coat liposomes to improve stability, viscosity and effective half-life while retaining the benefits of liposomes in improving drug delivery and reduced toxicity[10]. X-Pure is available in a comprehensive range of gel strengths and characteristics, ensuring the possibility to design an ideal gelatin solution without concern for endotoxin levels.

CONCLUSION

X-pure® is a complete range of purified gelatins, with a GMP quality grade that is consistent between batches and with complete traceability and documentation package.

The consistent and very low endotoxin levels in X-Pure gelatins, and the value-added expertise that Rousselot can offer, enable faster and simpler development, production and regulatory compliance for a wide range of parenteral applications.

When choosing X-Pure from Rousselot, customers will benefit from Rousselot's 125+ years of gelatin manufacturing experience, and the many partnerships that Rousselot has with leading universities, helping to ensure customers can design and source the best possible gelatin solution to meet their needs. As a customer, you can rely on world-class products that meet the highest quality and safety standards, delivered in spec and on time, and with all required source documentation. At Rousselot we adhere to the highest ethical standards, both in our commitment to respect the environment and through the integrity and transparency we show you.

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Rousselot® Biomedical

As the most recent strategic segment within Rousselot, we have drawn upon Rousselot's 125+ years of worldwide expertise and proven track record of pharmaceutical gelatins and collagens to develop X-Pure®, an innovative range of purified gelatins and collagens specifically designed for (bio)medical applications. Offering unique advantages to assure performance, quality and safety, X-Pure is backed by strong scientific data and on-going research. Rousselot Biomedical is committed to facilitating the use of X-Pure in your applications and to help "Advancing medical science". Rousselot is a brand of Darling Ingredients.

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