The term “excipient” describes a raw material that is added to a drug to provide suitable consistency or form. Ultimately designed to aid in the preparation of a stable drug formulation that has a particular shelf-life and bioavailability, it is an inactive material that can perform a variety of functions. These functions significantly differ between small-molecule pharmaceuticals and large-molecule biotherapeutic formulations.

Excipients can assist tablet formulation in small-molecule pharmaceuticals in a number of ways, for example, by affecting compressibility or performing the role of lubricant, glider, filler or disintegrant. However, in biotherapeutics (proteins, peptides and vaccines) although the goal of a stable, safe formulation is still essential, the process of formulation creates different challenges. Proteins can be made inactive by heat, denaturation from liquid shear or denaturation at air-liquid interfaces. In addition, solution pH and buffer components can also inactivate these molecules. As well as the usual drug degradation pathways such as oxidation, racemisation and hydrolysis, biotherapeutics are further subject to disulphide exchange, beta elimination, aggregation and deamidation. As with small molecules, while there is no typical formulation for biotherapeutics, some generalities can be considered.

CONSIDERATIONS IN THE FORMULATION OF BIOtherapeutics

The formulation of a biotherapeutic will contain salts and have an optimal solution pH. The pH of the formulation has two significant effects; the obvious one being that the pH has to be within a range in which the protein is stable and active. The second is that deviation from physiological pH will result in the patient suffering injection site pain during administration of the drug. The salts present are often targeted to physiological level or isotonicity. Therefore, if the protein is

“THIS SIMPLE APPROACH OF ADDING ANIMAL- OR HUMAN-DERIVED PROTEINS TO FORMULATIONS HAS BEEN THE SUBJECT OF CLOSE SCRUTINY OVER RECENT YEARS. MANY FORMULATION SCIENTISTS HAVE MOVED AWAY FROM USING THESE PROTEINS”
commonly used excipients in biotherapeutic formulations.

It is mostly used in oral drug delivery, such as capsule format. Due to the differences in extraction procedures from company-to-company and the relatively crude nature of the extraction procedure, there is significant source and batch-to-batch variability that can affect the physicochemical properties of the gelatin. This can in turn affect the product in which the gelatin is used.

HSA is the most abundant protein in blood, present at a concentration of approximately 42g/l. Since 1940, albumin has been fractionated from blood plasma for use as a blood volume replacement and to treat burns victims. Today, HSA can be considered as a low-cost side-fraction generated when purifying expensive blood components such as IgG and factor VIII.

HSA has been widely used as an excipient to stabilise a number of therapeutic proteins (see Table 2). Additionally, as it is a human-derived protein and there are instances of allergic response to animal-derived gelatins, it can be regarded as the stabiliser of choice, immunologically speaking. However, this simple approach of adding animal- or human-derived proteins to formulations has been the subject of close scrutiny over recent years. Many formulation scientists have moved away from using these proteins due to concerns that blood-borne contaminants such as mycoplasma, prions or viruses may potentially contaminate the final drug product.

RECOMBINANT PROTEIN EXCIPIENTS

The potential for prion and viral contamination of these excipients and the fact that gelatin and HSA are heterogeneous protein preparations and relatively impure, have driven the development of recombinant versions. Gelatin is a heterogeneous mixture of polypeptides, whilst HSA has a pharmacopeial purity of only 96% (USP), the rest of the protein present being a mixture of polymers of HSA and other plasma proteins that remain from the purification. Additionally, these other proteins are denatured during the pasteurisation process that HSA final product undergoes. Given the very high purity of recombinant DNA-derived biotherapeutics, it seems somewhat illogical to adulterate them with relatively poorly defined excipients.

In comparison, animal-free components offer an ethical, safe solution for the production of ingredients that form the basis of biological products. These ingredients are gaining popularity as regulatory authorities begin to implement strict quality control measures on products to improve safety, particularly with potential contamination risks. The development and application of animal-free solutions for the production of biopharmaceuticals has many safety and regulatory advantages, and in addition is economically viable and commercially scalable.

BENEFITS OF RECOMBINANT PROTEIN EXCIPIENTS

An alternative solution to the costly and time-consuming search for a new formulation for a product containing a protein excipient has emerged from the same source as the biotherapeutics, namely recombinant DNA technology. Using genetically modified yeast it has been possible to express and purify recombinant gelatin and recombinant human albumin for use as excipients.

FibroGen (San Francisco, CA, US) has engineered human gelatins from specific segments of human collagen genes. They are expressed in the methylotrophic yeast Pichia pastoris and manufactured avoiding the use of animal- or human-derived materials. FibroGen’s proprietary technology allows the production of discrete, reproducible batches of gelatin fragments

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Table 1: Commonly used excipients in biotherapeutic formulations.

Approximately 50,000 metric tonnes of gelatin, chemically extracted from animal hides and bones, is produced annually for medical use.

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Recombumin® and Albucult® rAlbumins are a Saccharomyces cerevisiae yeast strain, Novozymes’ developed from a proprietary Saccharomyces caryophyllaea strain for use in drug delivery and formulation. These innovative products have been designed to deliver a more consistent source of albumin, while decreasing regulatory burden. As a result, manufacturers are able to improve the safety and performance of new drugs. These products are manufactured in large-scale facilities, ensuring the specific needs of customers to deliver improved products and performance.

In response to industry demands, Novozymes Biopharma has developed a range of high-quality, animal-free recombinant human albumins (rAlbumins) specifically for use in drug delivery and formulation. Developed from a proprietary Saccharomyces cerevisiae yeast strain, Novozymes’ Recombumin® and Albucult® rAlbumins are manufactured to cGMP quality standards and have been shown to stabilise proteins by preventing aggregation, especially amyloid-like fibril products, while also acting as an antioxidant in preventing protein oxidation and as a blocking agent to prevent nonspecific adsorption to surfaces. The products offer security of supply and batch-to-batch consistency, while providing increased efficiency for companies looking for a compliant albumin alternative.

rAlbumins are structurally identical to HSA but significantly purer and can act as multifunctional excipients. Their use reduces the requirement for multiple excipients, such as sugars, amino acids and detergents (SADs) in a formulation and delivers a safe and consistent ingredient that enhances the stability and performance of the manufacturer’s finished drug product. In addition, Novozymes rAlbumins have unprecedented technical and regulatory support. Manufactured in large-scale facilities, USP-NF compliant and supported by a strongly documented safety package and drug master file (DMF), they reduce registration and regulatory issues. By including rAlbumin in the formulation strategy, drug manufacturers can reduce development timelines, getting the final product to market sooner.

CONCLUSION

Over recent years, the demand for animal-free ingredients has increased, with regulatory authorities enforcing more stringent controls on pharmaceutical products to improve safety, particularly with potential contamination risks from animal-derived ingredients.

rAlbumins offer the industry a viable alternative to HSA, providing the potential to improve both the safety and performance of new drugs. These innovative products have been designed to deliver a more consistent source of albumin, while decreasing regulatory burden. As a result, manufacturers are able to optimise the safety, functionality and quality of their formulations, with the potential to offer significant benefits for patients.

REFERENCES


ABOUT NOVOZYMES

Novozymes Biopharma develops and manufactures high-quality, animal-free, and regulatory-compliant recombinant ingredients and technologies to provide pharmaceutical and medical device manufacturers the knowledge-based solutions needed to address the challenges in developing innovative, safer, and more consistent products. The company’s large-scale manufacturing facilities worldwide are run to cGMP Q7 quality standards, ensuring customers the highest level of product quality and consistency, as well as the security of long-term supply. Novozymes’ customer-integrated approach combines the company’s scientific know-how and the specific needs of customers to deliver improved products and performance.

With >25 years’ experience in the pharma industry, Novozymes is the world leader in the supply of recombinant products and technologies to the medical device and drug delivery market. Currently, 14% of the company’s revenue is spent on R&D, demonstrating a commitment to scientific innovation.

By combining Novozymes’ unique knowledge around our biological solutions such as recombinant albumin and hyaluronic acid with the specific application knowledge of our customers, we work with companies to deliver improved performance and safety for next-generation medical device and pharma products.

ABOUT THE AUTHOR

Mark Perkins is a formulation chemist with a PhD in Pharmaceutical Sciences from the University of Nottingham. He joined Novozymes Biopharma in 2010 as a customer solutions specialist. In this role he works with partners that are evaluating Novozymes’ recombinant albumin products and technologies in the areas of biopharmaceutical formulation and half-life extension. Prior to this position, Mark worked as a materials specialist at an inhaled drug development company and as a project manager at an analytical consultancy.
Recombinant albumin USP-NF* - An ideal drug stabilizer

Novozymes’ high quality recombinant albumins (rAlbumin) are developed and optimized for drug delivery and formulation. Manufactured to cGMP quality standards in large-scale facilities, our rAlbumins are supported by a comprehensive drug master file.

Ideal for stabilization, Novozymes’ rAlbumins can help:

- Achieve liquid formulations of protein therapeutics
- Limit protein loss due to non-specific adsorption
- Prevent functional or structural changes caused by oxidation
- Reduce aggregation/sub-visible particle formation and therefore potential immunogenicity concerns

Find out more about how our rAlbumins can help you stabilize your drug by visiting our website or email us at biopharma@novozymes.com

*Meets National Formulary (NF) standards as published by United States Pharmacopeia (USP).