

**Chitosan
and
SoftSeal®-STF
Hemostatic Pad**

Technology Description

Prepared by Chitogen Inc.

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Introduction

The Chitogen Inc., SoftSeal®-STF Hemostatic Pad is a non-woven pad made of a proprietary formulation of chitosan (poly-D glucosamine and poly-N-acetyl glucosamine). The natural biological property of this material gives the SoftSeal®-STF an advantage as an effective hemostat while providing for an optimal wound-healing environment.

History of Chitosan Use

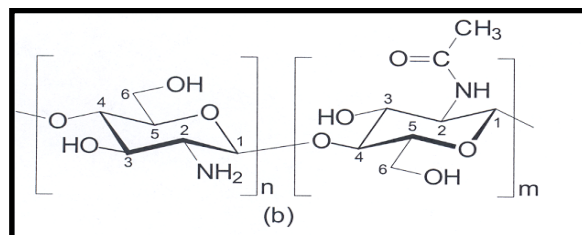
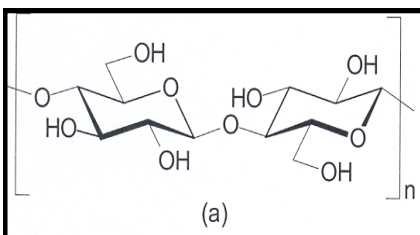
Several biomedical applications of chitosan have been reported, most specifically for wound dressings, hemostatic pads, antimicrobial dressings, and drug delivery matrices. The studies represent research on the safety and use of these materials, published over a period of decades by scientists from around the world. This large body of scientific literature satisfies the requirement that a general recognition of safety is commonly accepted throughout the scientific community. This material has many advantageous properties in applications as a wound dressing, such as biocompatibility, biodegradability, hemostatic activity, and anti-infective activity. Chitosan is a positively charged polymer that forms strong associations with the negative charges found on tissue and blood components. The resulting bioadhesion is believed to be a major component in the effectiveness of chitosan as a hemostatic agent.

Chitosan and SoftSeal®-STF

Chitogen has developed a unique and proprietary chitosan structure and formulation. The structure is a nonwoven fleece, and the formulation is a high molecular weight fiber that offers a significant improvement in hemostasis performance and reliability. This material provides a strong technology platform that can be used to create a family of products each with its own indications for use.

Chitosan is a water soluble polymer made from chitin by chemical treatment. Chitin is an abundant natural product that is the primary structural material in the shells of shrimp, lobsters and other crustaceans. SoftSeal®-STF uses Alaskan king crab shell exclusively due to its uniformity and reliability, both important for manufacturing quality and cost efficiency. Chitin's structural role in shells is similar to the role of cellulose in

CHEMICAL STRUCTURES OF CELLULOSE (Image a) AND CHITIN AND CHITOSAN (Image b)



plants. Both chitin and cellulose are high molecular weight polymers containing glucose molecules linked together to form long, linear polysaccharide chains.

Chitin is recovered from the crab shell by treatment with acid to remove the minerals and with alkali to remove protein. After these treatments, purified chitin remains as thin, white sheets that are further processed into chitosan. Chitosan is made by heating purified chitin with strong alkali to remove some of the acetyl groups from the polymer chains. These exposed amino groups have a positive (also known as cationic) charge in water or dilute acid. When 50% or more of the amino groups have been exposed the material becomes soluble in water or dilute acid due to the repulsion of the charged groups along the polymer chain. Thus, chitosan is defined as a derivative of chitin in which 50% or more of the amino groups are exposed or the chemical term is deacetylated.

The SoftSeal®-STF is a non-woven pad composed of chitosan fibers attached to a thin polypropylene backing material. The pad is intended to be used as an aid in the management of topical bleeding wounds such as vascular access sites and topical lacerations.

The principle of operation of SoftSeal®-STF is believed to result from bioadhesion between the chitosan polymer chains (positive charge) and blood and tissue components (negative charge) as well as pressure related tamponade. The charge density and uniformity of the positive charge is enhanced by the surface treated fiber (STF) process.

Structure

SoftSeal®-STF structure is unique. The non-woven structure (fleece) is completely unlike other hemostatic pads that are lyophilized (freeze-dried), dried flake or similar shape, or prepared as a gel. This nonwoven structure is covered by the Company's world-wide patents and patent applications.

The soft, fleece-like pad consists of fine (10 to 100 micrometers) chitosan fibers spun from high molecular weight chitosan. The unique SoftSeal®-STF fleece structure promotes adherence to bleeding tissues and the number of fibers increases the available chitosan surface area to promote stable clot formation. The SoftSeal®-STF is formed as a square pad, 0.4" thick. The fleece structure is soft, pliable and conformable.

The non-woven fabric is similar to natural tissues elasticity and strength. When initially hydrated with tissue fluids it retains its structure and then with additional moisture exposure it assumes a gel-like structure. The fiber structure remains intact and the structure and chemistry comprises a synthetic clot.

The surface treated fiber (STF) process, in addition to the nonwoven structure, enhances the hemostatic properties by creating a more uniform electric charge that is providing a more consistently charged matrix. The charge is positive (cationic) and available to biological molecules such as red blood cells (negative charge or anionic) to promote adherence.

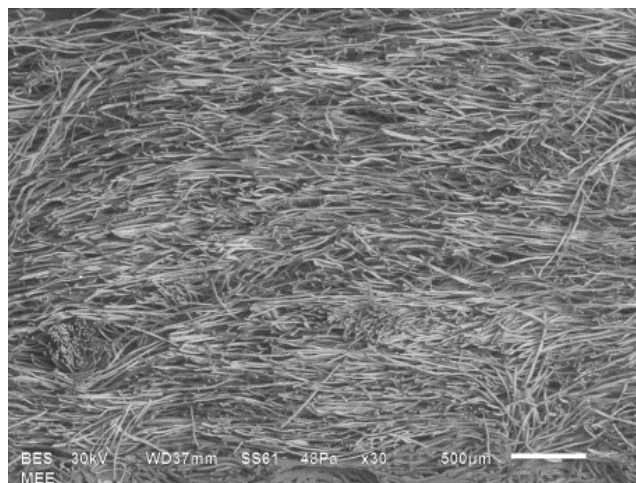
In summary, the nonwoven structure makes the positive charged chitosan molecules available to the negative charged blood components and this electrostatic and physical interaction promotes the clotting of the flowing blood.

The structure is depicted in these photographs that used a stereo light microscope and a scanning electron microscopy, commonly referred to as SEM.

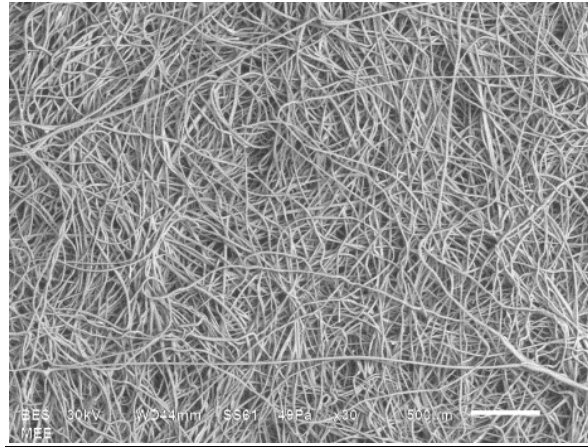
SoftSeal®-STF Hemostatic Pad, a photograph at low magnification showing the pad and its internal fibrous structure. The product is not intended to be teased apart as shown here.



The SEM view at 30X that depicts the edge view and shows the discrete and small fibers.



This SEM view is also at 30X and shows the fibrous matrix from the top. The mesh is on the other side and it is not visible.



Chitosan and Shellfish Allergy Potential

The Chitogen FDA approved labeling for the SoftSeal®STF Hemostatic Pad does not contain an allergy warning. Competitive chitosan containing product labels state that the product has not been found to be allergenic but recommends to people with known shellfish allergies to be cautious regarding its use.

Scientific Support for non-allergic properties

Chitin the material from which chitosan is derived is a known allergen. Chitin is treated with acid and alkaline solution to remove the protein and mineral content and to deacetylate the polymer. The cleaned, solubilized, and deproteinized polymer is chitosan.

The U.S. Army endorsed the use of chitosan containing hemostatic dressings and they published results confirming that the product did not illicit an allergenic response in people who were known to be allergic to shellfish.

Other studies from chitosan suppliers support the label claims with reports of no allergic reaction using pin prick testing methods

Manufacturing and Quality Systems

The Chitogen supply chain is reliable and cost effective. The product is manufactured using equipment designed and owned by Chitogen. Chitogen has implemented its own quality system consistent with the Quality System Regulations of the Food & Drug Administration (“FDA”) and the ISO Quality System that predominates in the EU. Chitogen received its Certification of Compliance with the ISO standards in 2015.

Final packaging is done by an FDA audited and ISO certified manufacturer. The package label states “Made in the USA.” The SoftSeal®-STF pad is packaged in a metalized / plastic film barrier pouch, heat sealed, and terminally sterilized by Cobalt-60

gamma irradiation. The product is ready-to-use and requires no out of package preparations.

References

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