
Nektar Hydrogels

SprayGel™ from Confluent Surgical
Offers the Potential to Prevent
Post-Surgical Adhesions

Prolonging Absorption Using Nektar Hydrogels

From preventing post-surgical adhesions to prolonging the drug absorption process from injection site to circulation, Nektar Hydrogels are highly biocompatible materials that can be used as drug-delivery systems, medical devices, or surgical materials.

Hydrogels, which are matrices of polyethylene (PEG) molecules, can reduce the frequency of dosing by prolonging the absorption process from the injection site to circulation, and thereby improve patient compliance. Unlike other thermal gelation polymers such as pluronics, Nektar Hydrogels are reversible and degradable and can be formulated so that they are liquids at room temperature and gels at physiological temperature, but have the added advantage of forming gels at much lower concentrations.

Nektar Hydrogels, part of the Nektar Molecule Engineering solution, are composed of chemically cross-linked or physically associated PEGs that create three-dimensional structures and can be generated *in situ*, injected, or implanted. Proteins, peptides, oligonucleotides, small-molecule drugs, and their PEGylated forms can be incorporated into PEG-based hydrogels.

The release of a therapeutic agent from a hydrogel can be controlled by the cross-linking density, PEG molecular weight, nature of the degradable linkages, and whether the therapeutic agent is covalently incorporated or physically entrapped within the polymer matrix.

The consistency of Nektar Hydrogels can range from nearly free-flowing gels to rigid plastics and may contain greater than 95% water. PEG-based hydrogels can be designed to degrade from within hours to months. Additionally, near zero-order release kinetics are possible.

History of Nektar Molecule Engineering

Nektar, formerly Inhale Therapeutic Systems, Inc., acquired Shearwater Corporation, the world leader in Advanced PEGylation, in 2001. Nektar scientists significantly improved and expanded the use of PEGylation to improve the performance and delivery of most drug classes.

Nektar Molecule Engineering, including Advanced PEGylation, was essential to the creation of the following products, approved in the United States and/or Europe.

- *Roche's PEGASYS*® (peginterferon alfa-2a) for hepatitis C.
 - *Amgen's Neulasta*™ (pegfilgrastim) for neutropenia associated with cancer chemotherapy.
 - *Schering-Plough's PEG-INTRON*® (peginterferon alfa-2b) for hepatitis C.
 - *Pharmacia's Somavert*® (pegvisomant) for acromegaly (Europe, filed in the United States).
 - *Confluent Surgical's SprayGel*™ for post-surgical adhesion prevention (Europe).
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Case Study: SprayGel™ from Confluent Surgical

The Challenge: As internal wounds heal following surgery, adhesions can form that connect two organs or surfaces that are normally separate in the body. These adhesions can cause severe pain and discomfort, as well as small bowel obstructions.

Adhesions are also the leading cause of infertility in women following gynecological surgery; approximately 500,000 surgical procedures are performed annually to remove this type of scar tissue. Previously available products for adhesion prevention had limitations in efficacy and ease of use.

Confluent Surgical, Inc., a privately held biosurgery company that develops products based on *in situ* cross-linked hydrogel polymers and associated systems for the delivery of the polymers, aimed to address these limitations by creating a product that would prevent surgical adhesions and would be easy for surgeons to use in routine practice, in particular, laparoscopically.

The Solution: Confluent Surgical licensed Nektar Hydrogel technology to create a biodegradable, post-surgical adhesion prevention product (SprayGel) that can be easily sprayed onto tissue, forming an adherent, flexible barrier that is safely absorbed after the tissue heals. The two-part aqueous solution is composed of two multifunctional PEGs, which react spontaneously to form a biodegradable hydrogel that can be delivered laparoscopically. The hydrogel is highly biocompatible, and the PEG reagents contain ester linkages that can be tuned to give the desired degradation rate.

The Results: The SprayGel Adhesion Barrier System received a CE mark (product certification) in November 2001 in Europe, and has been introduced in major European markets and Australia. Based on European and U.S. clinical pilot studies, the patented and proprietary synthetic material has been shown to significantly reduce adhesion formation following abdominopelvic surgery.

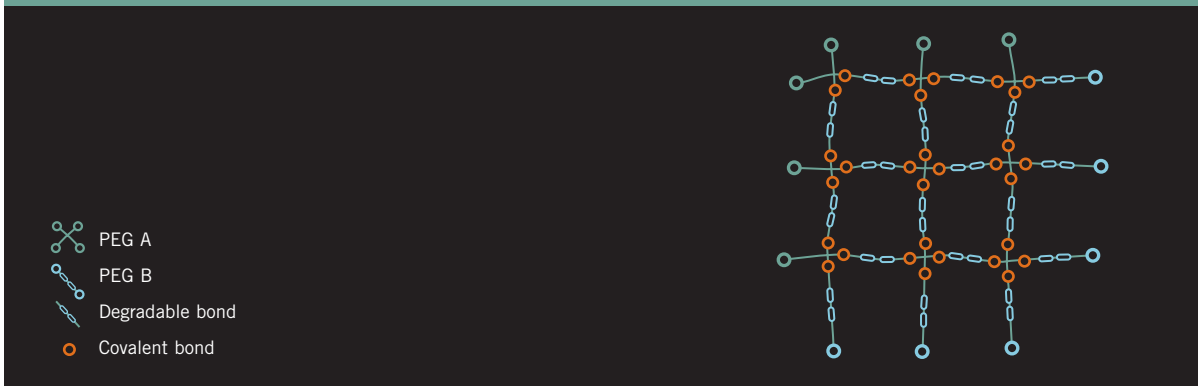
The pilot clinical study, conducted at two sites in the United States, consisted of 14 randomized patients undergoing surgery for removal of endometriosis and adhesions on the ovaries, fallopian tubes, and adjacent organs. The incidence of adhesion formation on the SprayGel-treated organs was reduced by 71% over that of the control organs in the same patient, relative to initial surgery. The extent of adhesions was reduced by 69%. Both differences were found to be statistically significant.

Testimonial

“Without Nektar’s manufacturing capability and knowledge of PEG reagents, SprayGel would not exist. Nektar technology has enabled us to tailor SprayGel for its unique properties. Due to PEG’s long track record of safety and biocompatibility, it is ideally suited for use in adhesion barriers.”

Amar Sawhney, President and CEO, Confluent Surgical

Nektar Hydrogel: PEG Matrix



Conclusion: Nektar Hydrogel technology was used to create the SprayGel Adhesion Barrier System for reducing adhesion formation following abdominopelvic surgery. SprayGel is currently undergoing a multicenter clinical trial in the United States for preventing abdominal adhesions and is being investigated for additional indications, including for the prevention of adhesion formation in cardiac surgery.

Hydrogels also offer promise for drug delivery systems, where PEG-based hydrogel matrices may prolong the absorption process for sustained drug release and dramatically decrease dosing frequency.

In addition to PEG-based hydrogels, Nektar offers a comprehensive solution for advanced molecule engineering, including catalog sales of activated PEG derivatives for research use, research collaborations, early clinical development of PEG drugs, CGMP manufacturing of PEG reagents, and industry-leading regulatory support.

Nektar provides a portfolio of leading drug delivery solutions and development expertise to help partners create breakthrough products that fuel their pipelines.

Market Status of SprayGel

The SprayGel Adhesion Barrier System is currently approved in Europe and is undergoing a multicenter clinical trial in the United States for the prevention of formation of adhesions in the abdominal or pelvic cavity after laparoscopic or open surgical procedures. Confluent expects that if the results from the initial pilot study are replicated in this pivotal multicenter study, SprayGel could prevent or significantly reduce patient trauma and costs associated with additional surgery for adhesions.

Selected References:

Johns, DA, et al. Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. *Fertil Steril* 2002;77:S21-22.

Mettler L, et al. Prospective clinical trial of SprayGel™ as a barrier to adhesion formation: an interim analysis. In *Proceedings of the 10th Congress of the European Society for Gynaecological Endoscopy*. Edited by Bruhat M, Silva Carvalho JL, Campo R, Fradique A, Dequesne J, Setubal A. Bologna, Italy, *Monduzzi Editore*, 2001;223-28.

To learn more about Nektar Hydrogels, part of the Nektar Molecule Engineering solution, or how Nektar can create and optimize a solution for your molecule, contact our Business Development team at **256.533.4201** or at partnerships@nektar.com. Or visit us on the web at www.nektar.com.

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