SurgiSeal® Tissue Adhesive

Whitepaper Summary

Prepared by: Sheng Zhang, Chief Scientist, Adhezion Biomedical and Rafael Ruiz, General Manager, Adhezion Biomedical

H.B. Fuller | Medical Adhesive Technologies

H.B. Fuller Medical Adhesive Technologies, LLC 506 Pine Mountain Road, Hudson, NC 28638, USA
Phone: 484.334.2929 · Toll Free: 866.579.4508 · medical.orders@hbfuller.com · www.hbfuller.com/medical

SST-WP01-2400

The objective of this paper is to provide a scientific and technological perspective on SurgiSeal, a new 2-octyl cyanoacrylate (2-OCA) tissue adhesive from H.B. Fuller Medical Adhesive Technologies, LLC (formerly Adhezion Biomedical, LLC), with unique features and characteristics resulting from innovations in formulation, manufacturing process, and applicator designs.

SurgiSeal has been evaluated based on various internal and external laboratory test results. In many cases, the test results have been benchmarked against the leading competitor, which currently sells the only 2-OCA tissue adhesive on the market. The details of these tests can be referenced in the Investigational Device Exemption application summary [1].

CYANOACRYLATE ADHESIVES

Cyanoacrylate tissue adhesives are safe and have proven to be an effective method of tissue closure for surgical procedures and laceration repair, as demonstrated by an extensive literature review that references a minimum of 3,200 surgeries and 2,600 lacerations [2]. Studies also demonstrate that cyanoacrylate tissue adhesives can act as a microbial barrier [3].

In early 1980, Histoacryl was approved for clinical use in Europe and Canada as the first cyanoacrylate for application as a tissue adhesive [4]. In United States, the leading competitor was approved by the FDA as a topical wound closure in 1998, and Indermil was approved by the FDA in 2002. A list of commercially available cyanoacrylate tissue adhesives is summarized in Table 1. SurgiSeal is expected to obtain FDA approval as a topical wound closure in the near future.

TABLE 1. COMMERCIAL CYANOACRYLATE ADHESIVES

Cyanoacrylate Formula	Trade Name	Company
2-Octyl Cyanoacrylate	Dermabond	Ethicon (U.S.)
	SurgiSeal	Adhezion Biomedical (U.S.)
n-Butyl-2 Cyanoacrylate	Histoacryl	B.Braun (Germany)
	Indermil	Covidien (U.S.)
	Glubran 2*	GEM srl (Italy)
	LIQUIBAND	Advanced Medical Solutions (UK)
	Skin Link	Advanced Medical Solutions (UK)
Ethyl-2 Cyanoacrylate	EpiGlue	Meyer-Haake (Germany)

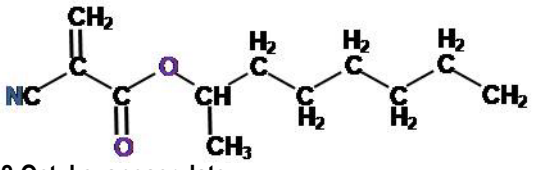
* also contains another monomer

OCTYL CYANOACRYLATE VS. BUTYL CYANOACRYLATE

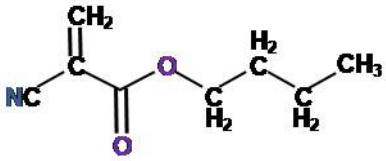
Early studies show that short-chain (methyl, ethyl) CAs can be toxic to tissue [5,6]. These short-chain CAs polymerize quickly and then degrade rapidly into formaldehyde and alkyl cyanoacetate, both of which can cause significant histotoxicity [4,7]. However, there is little concern about the toxicity of intermediate-chain butyl cyanoacrylate (BCA) and long-chain octyl cyanoacrylate (OCA) when applied topically. These CA polymers degrade slowly, forming few toxic degradation products before the polymers slough off [8]. In theory, the longer the chain (e.g., octyl), the slower the polymer degrades and thus the less probability of cytotoxicity or histotoxicity as the chain length increases.

The heat released during the polymerization of OCA is less than that of BCA because of OCA's slower rate of polymerization. While a polymer film of OCA is stronger and more flexible, OCA's setting time is longer than BCA's in general. The structures of 2-OCA and BCA are shown in Figure 1 and a comparison of BCA and OCA characteristics is shown in Table 2.

Figure 1. Chemical structures of 2-OCA and BCA.



2-Octyl cyanoacrylate



n-Butyl cyanoacrylate

TABLE 2. COMPARISON OF OCA AND BCA IN GENERAL.

	OCA	BCA
Degradation	slower	slow
Firm flexibility	higher	high
Bonding Strength	stronger	strong
Heat released	less	more
Setting time	short	shorter

SURGISEAL VS. THE LEADING COMPETITOR

SurgiSeal was developed with the goal of improving and enhancing 2-OCA's characteristics as a tissue adhesive. Even though the active ingredient of both SurgiSeal and the leading competitor is 2-OCA, SurgiSeal integrates many innovations in formulation, manufacturing process and applicator design.

SurgiSeal consists of more than 98% 2-OCA with a trace amount of polymerization accelerator[9]. The 2-OCA is stabilized with a free radical inhibitor and an anionic inhibitor. For visual detection, a trace amount of the colorant is also included. SurgiSeal is packaged in a user-friendly and single use plastic applicator containing 0.35mL of adhesive. SurgiSeal is sterilized inside the final packaging by a certified sterilization method. The plastic applicator seal is connected to a piece of sponge, allowing the adhesive to be easily dispensed onto the sponge once the sponge connection is folded. A uniform sealing film is formed by applying the adhesive-saturated sponge tip to wounds.

The leading competitor is composed of more than 90% of 2-OCA, with other small amounts of components including a plasticizer, a radical stabilizer, an anionic stabilizer and a colorant [8]. The leading competitor is packaged in a single-use sterile vial with an outside plastic casing. The vial contains 0.5 mL of adhesive stored in an inner glass ampoule that can be expressed through the applicator tip once the vial has been crushed. An accelerator is stored separately in the applicator tip. Once the adhesive moves through the applicator tip, it mixes with the accelerator, which initiates polymerization. Moisture on the skin's surface adds another catalyst to form a polymer bond with the wound edges.

In addition to the chemical, physical and mechanical properties, another practical aspect of cyanoacrylate adhesive is ease of use, which is often related to the applicator design of the adhesive.

MEDICAL APPLICATION PERFORMANCES

I. Adhesive strength and flexibility

SurgiSeal has been evaluated for key adhesive properties, such as tensile strength, overlap shear strength, peel adhesive strength and impact strength. The leading competitor also has been evaluated for reference. All the tests were conducted according to the standard methods of ASTM (the American Society for Testing and Materials): F2255-05, F2256-05, F2258-08, and F2458-05.

SurgiSeal demonstrated strong adhesive strength in all testing. SurgiSeal is significantly stronger in the test of T-Peel loading and is comparable in the tests of Tensile loading, Lap shear tensile loading and Wound closure strength (Table 3).

TABLE 3. TESTING RESULTS OF ADHESIVE PROPERTIES

	SurgiSeal	The Leading Competitor	ASTM method
Tensile loading (lbs/in^2)	14.16±1.39	10.88±1.41	F2255-05
Lap-Shear tensile loading (lbs/in^2)	14.58±1.63	15.68±1.93	F2258-08
T-Peel loading (peak lbs)	39.64±4.73	27.14±2.97	F2256-05
Wound closure strength (peak lbs)	2.67±0.93	2.36±0.87	F2458-05

Flexibility was also tested using the mandrel bend technique according to ASTM D4338-97. Both SurgiSeal and the leading competitor passed the test and showed no signs of cracks, blistering, blushing, fractures or flaking.

To assess the efficacy of SurgiSeal for the application of incision wound closure, in vivo biomechanical evaluation was performed using the rat linear incision wound model. The average ultimate pressures applied at the wound site for SurgiSeal and the leading competitor were the same, indicating that SurgiSeal possesses bonding strength comparable to the leading competitor's.

II. Heat release

Polymerization of CA is an exothermal process; in other words, it generates heat during the process. The heat released is positively correlated to the polymerization rate and with the adhesive amounts. If too much heat is released, patients may experience pain. The heat of polymerization for SurgiSeal is 225J/g as determined by differential scanning calorimetry.

III. Setting time

Setting time is also positively correlated to polymerization rate. In general, as previously discussed, OCA has a slower polymerization rate compared to BCA and thus has a longer setting time. To achieve a shorter setting time, a trace amount of an accelerator is included in the formulation of SurgiSeal [9]. The setting time of SurgiSeal is slightly shorter than that of the leading competitor.

IV. Surface coverage

Applicator dispensing width is defined as the dispensed adhesive width of an individual stroke of an applicator, and the surface coverage area is measured by the applicator dispensing width and length. Both SurgiSeal and the leading competitor were tested on pig skin. The average dispensing width of SurgiSeal was 17.6mm, compared to the 7.7mm average dispensing width of the leading competitor. The average surface coverages of SurgiSeal and the leading competitor were 27.9 and 11.5 inch^2, respectively. The tests demonstrate that SurgiSeal can provide much larger and wider coverage per applicator compared to the leading competitor. Thus, among other things, SurgiSeal is more cost-effective.

V. Permeability

Adhesives with a high Moisture Vapor Transmission Rate (MVTR) improve wound care [10]. For these tests, MVTR was determined using a Mocon Permatran-W101 Water Vapor Permeability Instrument in accordance with ASTM D-6701. SurgiSeal and the leading competitor were applied and cured on a 2" square collagen film. MVTRs for SurgiSeal and the leading competitor were 2180 and 918 g/m2/day, respectively. SurgiSeal film is more vapor permeable than the leading competitor's film, which should contribute to better wound healing.

VI. Ease of use

The leading competitor's product is stored in a glass vial that is crushed prior to application. The vial is then squeezed to apply the adhesive smoothly while avoiding dripping of the adhesive.

A SurgiSeal applicator can be opened by simply folding the sponge connection.

VII. Faster wound sealing

According to the Instruction for Use, the leading competitor requires at least three layers of application [11].

SurgiSeal requires at least two layers of applications on a wound incision. The second layer can be applied after the first layer dries, usually after 30 seconds.

SurgiSeal has a shorter setting time, a wider dispensing width and a larger coverage area, giving it faster wound sealing than the leading competitor.

SAFETY

There are two areas related to the safety of CA tissue adhesives: I - chemical stability, and II - toxicity and biocompatibility. Chemical stability can be measured directly by hydrolytic analysis and indirectly by testing chemical, physical and mechanical properties, such as setting time and viscosity. The toxicity and biocompatibility of SurgiSeal have been evaluated under the guidelines of ISO 10993, Biological evaluation of medical devices. Based on the results of these tests, SurgiSeal is safe for its indicated use: topical tissue adhesive.

I. Chemical Stability

A. Hydrolytic analysis

Hydrolysis is the decomposition of a chemical compound by reaction with water. In the case of CA, hydrolytic analysis was used to detect any degradation of the polymers. Once polymerized, SurgiSeal was hydrolyzed at a 1:10 weight ratio in saline at 50ºC. The solutions were hydrolyzed for 0, 5, 10, and 15 days, respectively, and were analyzed using both HPLC and UV-VIS spectroscopy. No formaldehyde, cyanoacetate or colorant was detected. The detection limits are 200ug/mL for formaldehyde and cyanoacetate and 1ug/mL for the colorant.

B. Shelf life

The shelf life of SurgiSeal was determined by real time/shelf life stability of 2 years and by the accelerated aging test at 80ºC for 12 days, as well as the accelerated aging test at 40ºC for 6 months. The stability of SurgiSeal was assessed based on five chemical, physical, biological and mechanical characteristics: purity (2-OCA percentage), setting time, viscosity, color and sterility. Based on ASTM F1980-2, 12 days accelerated aging at 80ºC and 6 months at 40ºC is equal to 2 years shelf life at room temperature. The accelerated aging tests show that SurgiSeal has at least a two-year shelf life.

II. Toxicity and biocompatibilities

A. Intracutaneous reactivity

The intracutaneous reactivity test was used to detect tissue reactions, such as erythema, eschar and edema at 24, 48 and 72 hours, respectively, after an injection of a test article. Two Albino New Zealand white rabbits were used for testing. There were no differences between SurgiSeal and the blanks in the mean erythema scores observed within 72 hours after injections of the extract in both sodium chloride injection solutions (SCI) and cottonseed oil (OIL). In conclusion, SurgiSeal meets the requirements of hypersensitivity intracutaneous reactivity.

B. Delayed-type hypersensitivity

The delayed-type hypersensitivity test aims to determine to what extent a test article has the potential to elicit a contact dermal sensitization. Extracted SurgiSeal in SCI was tested in 10 guinea pigs and compared to the blank SCI tested in five guinea pigs. Extracted SurgiSeal in OIL was also tested in the same way. According to the test criteria, there is no contact dermal sensitization potential elicited by SurgiSeal in these guinea pigs.

C. Systemic toxicity

Systemic toxicity was tested by observing the morbidity and mortality of mice after an injection of a test article. Extracted SurgiSeal of 50ml/kg in SCI and in OIL was tested in five Swiss Webster mice, respectively, while the corresponding blanks (SCI and OIL without SurgiSeal) were also tested in five mice, respectively, as controls. Mice were observed within the 72 hours after an injection of the test article. The tests conclude that SurgiSeal meets the requirement for the systemic toxicity test.

D. Ocular irritation

The ocular irritation test assesses the potential of a test article to introduce irritation and corrosion to the eyes. A 270ppm accelerator component of SurgiSeal in 0.7% saline solution was tested on one eye of an Albino New Zealand white rabbit, while the other untreated eye was used as a control. The tested eye was observed at 1, 2, 25, 48 and 72 hours and finally at day 7. The positive conjunctivae irritation at 1-hour post-exposure subsided by the end of 24 hours. Transient conjunctivae irritation was observed at 48 and 72 hours post application, but it was completely recovery by day 7. SurgiSeal did not induce irritations on the cornea, cornea area, iris, chemosis and discharge.

E. Mutagenic activity

Bacterial reverse mutation assay was used to test mutagenic activity using S. Typhimurium strains. Potential mutagenicity was evaluated in the presence and absence of a mammalian liver S-9 activation system. Mammalian liver S-9 activation accounts for enzyme activation of pro-mutagens or deactivation of direct acting mutagens. SurgiSeal extracted in dimethyl sulfoxide (24 hours 37 ºC) demonstrated no mutagenic activity by this assay in the sample equivalent range of 15mg to 100mg.

F. Local effect after implantation

A test using three Albino New Zealand rabbits was conducted to assess the local effect of SurgiSeal on living tissue. Four strips of SurgiSeal and four strips of controls were implanted in every rabbit. The implants were excised with surrounding tissue after four weeks. The tissue was macroscopically examined for hemorrhage, necrosis, discolorations and infections. It was concluded that SurgiSeal did not produce adverse effects on living tissue. A microscopic examination indicates that SurgiSeal is a non-irritant to the tissue.

G. In vitro cytotoxicity

In vitro cytotoxicity was tested by determining the biological reactivity of mammalian cell cultures following indirect contact with a test article. The test results showed that SurgiSeal had a slight cytotoxic effect: there were some malformed and degenerated cells under specimen. The leading competitor was also tested as a reference control, which showed a slight-to-mild cytotoxic effect. The tests demonstrate that SurgiSeal has slightly less cytotoxic effect compared to the leading competitor per the study criteria.

SUMMARY

SurgiSeal has been evaluated with extensive chemical, physical and mechanical testing. Compared to its leading competitor, SurgiSeal has superior characteristics as a tissue adhesive. The outstanding features of SurgiSeal result from innovations in formulation, manufacturing process and applicator designs. While it has a comparable adhesive strength, SurgiSeal has a shorter setting time and a higher vapor permeability, both of which benefit wound sealing and healing. Offering a larger coverage area and dispensing width, SurgiSeal is more cost-effective, and its applicator is more user-friendly. SurgiSeal can be stored at room temperature, which promotes the users' convenience and facilitates medical treatments. Finally, SurgiSeal has safety characteristics comparable to those of its leading competitor.

NOTES

[1] Adhezion Biomedical. Investigational Device Exemption application summary of SurgiSeal. Submitted September 26, 2007.

[2] RCLI, Inc. 513(e) Petition for Reclassification Tissue Adhesive for Soft Tissue Approximation. 2006.

[3] Narang U, Mainwaring L, Spath G, Barefoot J. In-vitro analysis for microbial barrier properties of 2-octyl cyanoacrylate-derived wound treatment films. J Cutan Med Surg 2003;7(1):13-9.

[4] Quinn JV. Tissue adhesives in wound cares. Hamilton (ON): BC Decker Inc., 1998.

[5] Klime DG, Hayes GJ. An experimental evaluation of the effect of a plastic adhesive, methyl-2-cyanoacrylate, on neural tissue. J Neusosurg 1963;20:647-54.

[6] Woodward SC, Hermann JB, Leonard F. Histotoxicity of cyanoacrylate tissue adhesive. Fed Proc 1964;23:485.

[7] Trott A. Cyanoacrylate tissue adhesives [editorial] JAMA 1997;277:1559-60.

[8] Quinn JV. Tissue adhesives in clinical medicine. Hamilton (ON): BC Decker Inc., 2005.

[9] Zhang S. Curing Accelerator and Method of Making. US patent application. Submitted June 25, 2007.

[10] Hansen A. Fast Cure. Adhes Age 2003;22-25.

[11] Ethicon, Inc. Instruction for Use of Dermabond. 2008.

H.B. Fuller | Medical Adhesive Technologies

H.B. Fuller Medical Adhesive Technologies, LLC 506 Pine Mountain Road, Hudson, NC 28638, USA
Phone: 484.334.2929 · Toll Free: 866.579.4508 · medical.orders@hbfuller.com ·www.hbfuller.com/medical

SST-WP01-2400