Advanced Biotech Products (P) Ltd

USP MONOGRAPH

HELICOLL™

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Under the Licence from :

ENCOLL

Fremont, CA, USA

BACKGROUND

1.1 Wound Healing and Collagen:

The wound healing process is a complex series of events that begins at the moment of injury and can continue for months to years. This process has four phases: the blood clotting phase, inflammatory phase, the proliferative phase, and the maturational phase.[1]

Collagen, the most abundant protein found in the body, is the main supportive protein of cartilage, connective tissue, tendon, skin, and bone. There are at least 13 different types of collagen. Types 1, 3, 4, 5, and 7 are specific for skin.[2]

Collagen plays an integral part during each phase of wound healing and is an excellent hemostatic agent as it absorbs 40 - 60 times its weight in fluid. Collagen exposed during wound formation activates the clotting phase, when the collagen is native and bioactive, and is responsible for cell signalling that influences the migration of inflammatory cells to the wound bed.[1-4]

Collagen dressings have been used in various forms for tissue repair and wound healing[5] as it constitutes more than 80% of the structural proteins of the body. Compared to many other modern non-biological dressings, collagen dressings remain a poorly understood and probably underused material. Biodegradable (bio utilized) collagen dressings are derived from animal tissues. These collagen dressings maintain a physiologically moist microenvironment that promotes healing and the formation of granulation tissue.[6]

The healing of skin tissue requires the development of a vascularized granular tissue bed, filling of large tissue defects by dermal regeneration, and the restoration of a continuous epidermal keratinocyte layer. Several experimental results suggest that collagen is an ideal material for tissue regeneration compared to other non-biological wound healing materials.[6-8]

In a wound where the basement membrane has been destroyed, similar to a second or third degree burn, the wound is re-epithelialised from the normal cells in the periphery and from the skin appendages provided the basement is intact (e.g., hair follicles, sweat glands). The granulation phase and tissue deposition require nutrients supplied by the capillaries, and failure for this to occur results in a chronically unhealed wound. Fibroblasts differentiate and produce ground substance and then collagen. Many different cytokines are involved in the proliferative phase of wound repair. The steps and the exact mechanism of control have not been elucidated. Some of the cytokines include PDGF, insulin-like growth factor (IGF), and EGF. All are necessary for collagen formation. Epithelialization, angiogenesis, granulation tissue formation, and collagen deposition are the principal steps in this anabolic portion of wound healing.[9,10]

1.2. Helicoll Regulatory:

Helicoll was approved by the FDA as a medical device on August 5, 2004 with 510(k) number K040314. The product comes from USDA approved bovine sources with FDA required regulatory documentation to maintain and monitor the safety and quality of the procured animal derived raw materials.

1.3 Helicoll Manufacturing and Chemistry:

Helicoll is an acellular collagen matrix free of contaminants (the final production, processing and packaging of Helicoll occurs in an FDA approved clean room). Contaminants not eliminated during processing or packaging could cause an immunological response when applied to the host wound which interferes with the healing process.[7] Contamination from other types of collagen such as Type-II and Type-III are potentially immunogenic and such types of collagen are completely removed in preparing Helicoll.

Our method was developed in order to address the problems presented by other commonly used collagen preparations. Our EnColl process is predicated in part on the discovery that collagen may be prepared in a manner in which all non-collagenous materials are removed, while retaining the native molecular quaternary structure and other characteristic features of collagen (e.g., length, diameter, and periodicity of collagen Type-I fibrils; see **Figure 1**).

Figure 1: Microphotographs of Helicoll collagen fibrils[11]

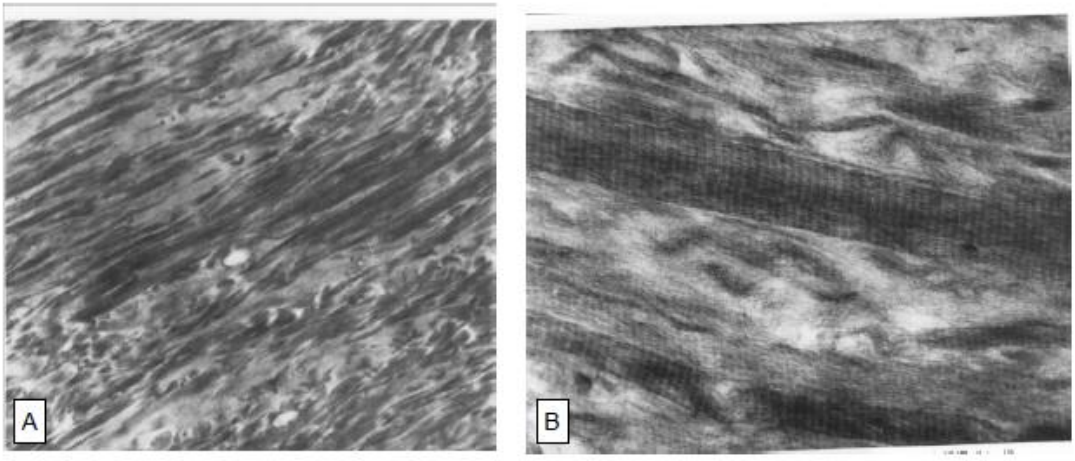


Image of meshwork of collagen fibrils. A: 100X; B: 1000X, showing periodic banding.

Helicoll is tested and manufactured in the FDA-certified clean room which is a controlled environment that filters all incoming air to remove all dust particles and possible contaminants that may interfere with the healing process. To be FDA certified, the clean room must meet the standards for controlled environments set forth in ISO 14644-1.

Helicoll collagen dressing does not require refrigeration and can be stored at normal room temperature for three years as stated in the FDA approval (**Error! Reference source not**

found.). NASA scientists in 2010, upon reviewing the product information and in consideration possible use of the product on the 21-month Mars missions in 2035 and beyond, determined that the product is ideal for their missions. They stated that they believe the product has an incredible nine-year shelf life at standard temperature and pressure. Important for their missions is ease of application, storage requirements, size and healing rate.

The EnColl process may be used to prepare highly purified collagen from various animal sources (including humans) as most, if not all, contaminating conjugated proteolipids and phospholipids are removed through use of a specific mixture of organic solvents. Unlike previously reported enzymatic methods and patents filed for collagen preparation,[12] the EnColl method utilizes a two-step enzyme treatment process. This two-step treatment processes ("Twice Treatment Process" or "TTP") renders collagen polymers non-inflammatory when implanted.[13]

The use of papain, an enzyme extracted from papaya, is known to break the disulfide bonds of cysteine[14]. As many immunogenic molecules contain cysteine disulfide bonds[15], papain may be used to degrade these molecules and render them non-immunogenic. In comparison with other collagen preparations for biomedical applications, better results in terms of reduced immunogenicity are obtained with EnColl's collagen.[13]

In addition, papain has been reported to have a lytic effect on elastin, one of the contaminants that is difficult to remove from purified collagen.[12,13] Initial experiments involving a one-step papain treatment to remove immunogenic sites from collagen were largely unsuccessful in altering the *in vivo* performance of purified collagen. These observations led to the development of the EnColl processes, which result in the breaking and loosening of the natural crosslinks of collagen fibers (e.g., aldol condensation). In this manner, the papain used in the second treatment step of EnColl's patented process (i.e., papain is used in two treatment steps) is provided access to most, if not all of the collagen molecules' surfaces, and facilitates the release of trapped immunogenic sites from the collagen preparation. These developments resulted in one embodiment of the two-stage EnColl process, in which papain is used at two specific stages of the process (i.e., before and after the treatment of the collagen with a reducing and/or an unfolding agent). These methods therefore, provide means to produce highly purified collagen that is non-immunogenic.[16]

The collagen is further bioactivated by varied degrees of controlled modification of phosphorylation. Purified collagen can be chemically modified by covalently binding phosphates to hydroxyl groups of hydroxylated amino acids. This reaction (an example for serine is given below in

Figure 2) likely involves covalent bonding of phosphate to hydroxyl group of serine, tyrosine and/or threonine, hydroxylysine and hydroxyproline.[17] The reaction is controlled, in order to limit the degree of reaction. EnColl's phosphorylated collagen renders unique abilities in the growth of soft or hard tissue as needed by the physiological system.

Phosphorylation exposes multiple free binding sites which allow the collagen-connective tissue framework to develop quickly. This proper alignment and binding of collagen fibres causes the maturation process to accelerate wound healing. This allows epithelial regeneration to occur leaving no scar formation.

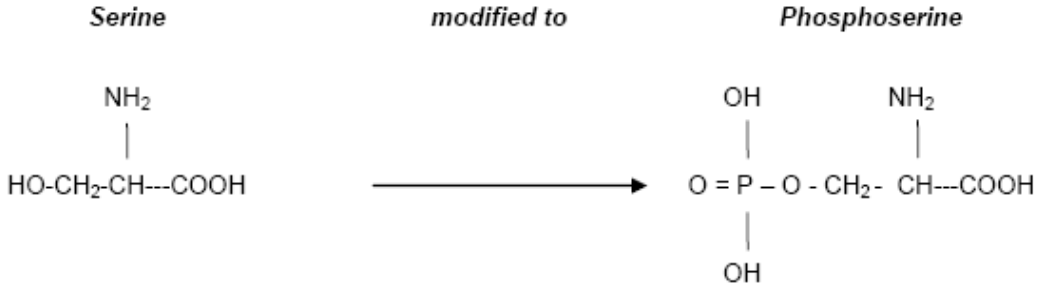
Using patented technology, Helicoll collagen is phosphorylated to provide better healing. Protein phosphorylation is reversible through protein phosphatases, enzymes that hydrolytically remove specific phosphoryl groups from modified proteins. These protein phosphatases are one mechanism for the termination of a signaling process.

Proteins undergo a huge number of post translational modifications. Only certain covalent modifications such as acetylation, fatty acid acylation, glycosylation and phosphorylation are reversible. Among these modifications, phosphorylation is an important and ubiquitous one. The majority of the proteins involved in cell activation are subjected to reversible phosphorylation. The sites of phosphorylation are serine, threonine and tyrosine hydroxyl groups. Aspartic acid, histidine and lysine can also be phosphorylated. Phosphorylation of tissue proteins is involved in natural cell differentiation of stem cells and in preventing pathogenic bacterial invasion.

In nature, the phosphorylation of extra-cellular matrix protein is evidenced by the accumulation of alkaline phosphatase in the regions of tissue formation or repair. The significance of protein phosphorylation is to induce cell signal transduction through a cascade of enzymatic reactions which are all documented in the literature. Collagen is the largest native structural protein present at the sites of tissue repair remodeling or growth. Phosphorylation of collagen makes the molecule biologically more active and becomes essential for the cell signal transduction to happen.

Collagen has specific binding regions for all active components such as cell membrane receptors, ligands, platelets, growth factors and other cytokines for proper interaction that can result in repair, remodeling and regeneration of tissues. Phosphorylated collagen plays an important role due to its ability to bring all necessary factors together and to activate them for the desired result. Additionally, the phosphorylated collagen tends to attract divalent cations such as Ca and Mg. Such divalent cations are essential for activating platelets and other physiological events for faster wound repair or tissue growth. EnColl's patented and FDA approved technology focuses on "collagen - phosphorylation" - and exploit the same for extra-ordinary biomedical applications.

Figure 2: Serine phosphorylation



1.4. Biological Characteristics of Manufactured Collagen:

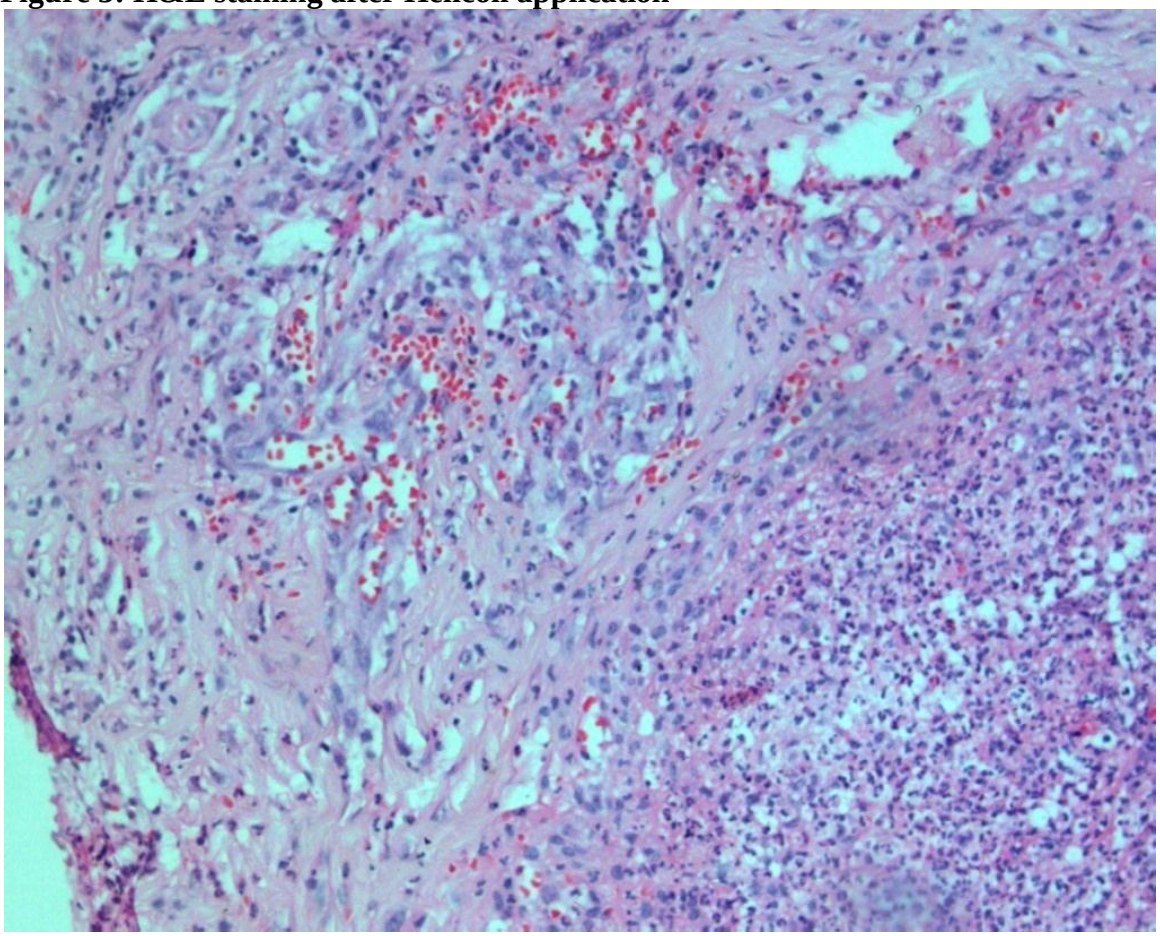
EnColl's modified collagen has been shown to possess improved biological characteristics. The modified collagen was found to have increased solubility features under neutral conditions, which helps in the formulation of bioactive coatings on inactive surfaces.[13]

In one of the implant experiments, the modified collagen implants were analyzed for their alkaline phosphatase (an enzyme involved in new tissue formation) activity. The assay used[15,18] was a calorimetric method using the measurement of o-carboxy-phenyl phosphate (OCCP) following the hydrolysis by alkaline phosphatase enzyme. Briefly, samples of approximately 10 mg from each of the harvested collagen implants were dispersed at a rate of 1 mg in 1 mL of Tris buffer (0.1M Tris, pH 8.5) for five minutes. A small amount of detergent (to a final concentration of 0.1M sodium deoxycholate) was added to the dispersed samples to release of membrane-bound enzymes. The optical density was determined at 300 nm, at room temperature. The activity is expressed in units per mg of tissue, as based on the number of micromoles of OCCP hydrolyzed per minute at 25°C, under the conditions described above. The results showed significantly elevated amounts of alkaline phosphatase (34% increase; $p<0.0005$) activity in the modified collagen implants as compared to the unmodified implants.[13]

EnColl's patented technology includes chemical modifications in solution or solid form of collagen which can be used for a variety of purposes, including, but not limited to, biological implants[13,19-21], grafts[13,22], transplants[11,13], and drug delivery[13,23].

A bioactive collagen dressing, such as Helicoll, induces platelet aggregation. Inflammatory cells, neutrophils and macrophages invade the clotting area. After 4 days (refer to Figure 1) of wound healing, there is a complete connective tissue bridge covering the wound. The site fills with neutrophils and macrophages. At seven days, the inflammatory process recedes and the repair process (proliferative phase) begins with the fibroblastic synthesis and deposition of the extracellular matrix and collagen. Matured skin tissue develops consisting of bricks of fibroblast cells that are mortared by the collagen produced by fibroblasts (see Figure 3). A combination of cells and collagen provides a secure bridge over the interrupted skin tissue.[24]

Figure 3: H&E staining after Helicoll application



After Helicoll application the acute inflammatory cells, fibroblasts and blood vessels proliferate into the collagen matrix. (50x). Absence of Lymphocytes indicates the non-immunogenic property of the collagen in Helicoll.[11]

The role of pure bioactive Type I, non-immunogenic collagen, such as Helicoll, is to provide binding and bridging sites for multiple chemokines (epidermal growth factor (EGF), fibronectin, fibrinogen, histamine, platelet-derived growth factor (PDGF), serotonin, and von Willebrand factor), necessary for building a connective tissue framework for epithelial regeneration to occur.[25-28]

2. PRE-CLINICAL EXPERIENCE:

Numerous *in vitro* pre-clinical studies were conducted and are included in the Helicoll patent 5814328.[13]

The *in vivo* and *in vitro* tissue culture experiments using mice and rabbits demonstrated that the delivery of growth factors was more effective when delivered through EnColl prepared collagen as compared to native Type-I collagen.[13]

In Vivo Evaluation of Chemically Modified Collagen in adult New Zealand white rabbit experiments showed more vascularization and fibroblastic in-growth in both of the experimental groups (Example 6 and Example 2, see the Patent reference for further details). Six of the rabbits (24 sites) were operated on bilaterally, with implants placed on both sides of the dorsal mid-line. Each implant comprised 50 mg of dried collagen sample was rolled into an approximately round ball and placed subcutaneously at each site. The animals were observed for three weeks for gross indications of inflammation (e.g., redness, swelling, etc.). No adverse responses were observed for any of the animals. After 3 weeks, the animals were sacrificed and the implants were surgically removed and subjected to histology evaluations. The control samples had relatively poor vascularization, as well as a prevalence of multi-nucleated giant cells, reflecting the lesser biocompatibility of these samples.

2. CLINICAL EXPERIENCE WITH HELICOLL:

Figure 4: Clinical indications of subjects in Helicoll studies[11]

Clinical Situation	Helicoll Used Patients	Control Patients
Donor Site	**81**	**77**
2nd Degree Burns	**10**	**11**
Diabetic Ulcers	**6**	**5**
Chronic Venous Ulcers	**10**	**10**
Contracture release & Bare tendons, bones and joints	**10**	**10**

158 patients with split thickness skin grafts (STSG) were successfully treated with Helicoll in 2010. Study included measurement of pain reduction of patients treated with Helicoll compared to control patients.[11]

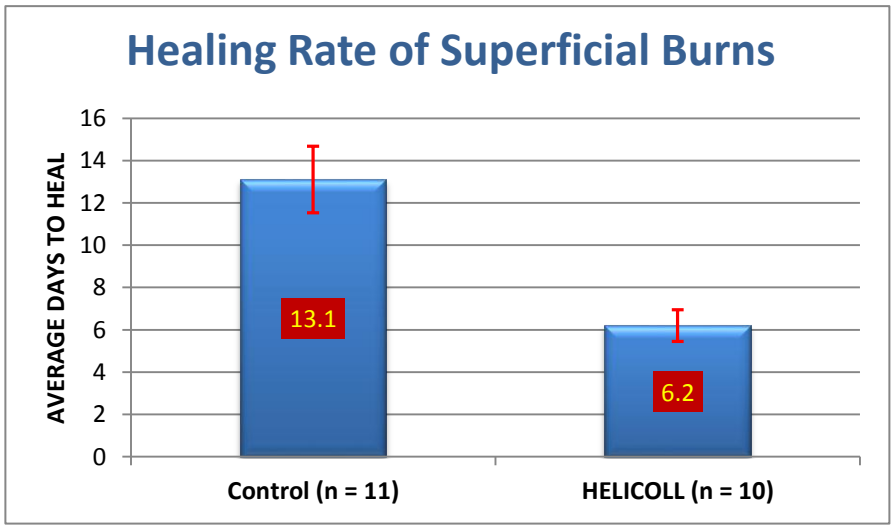
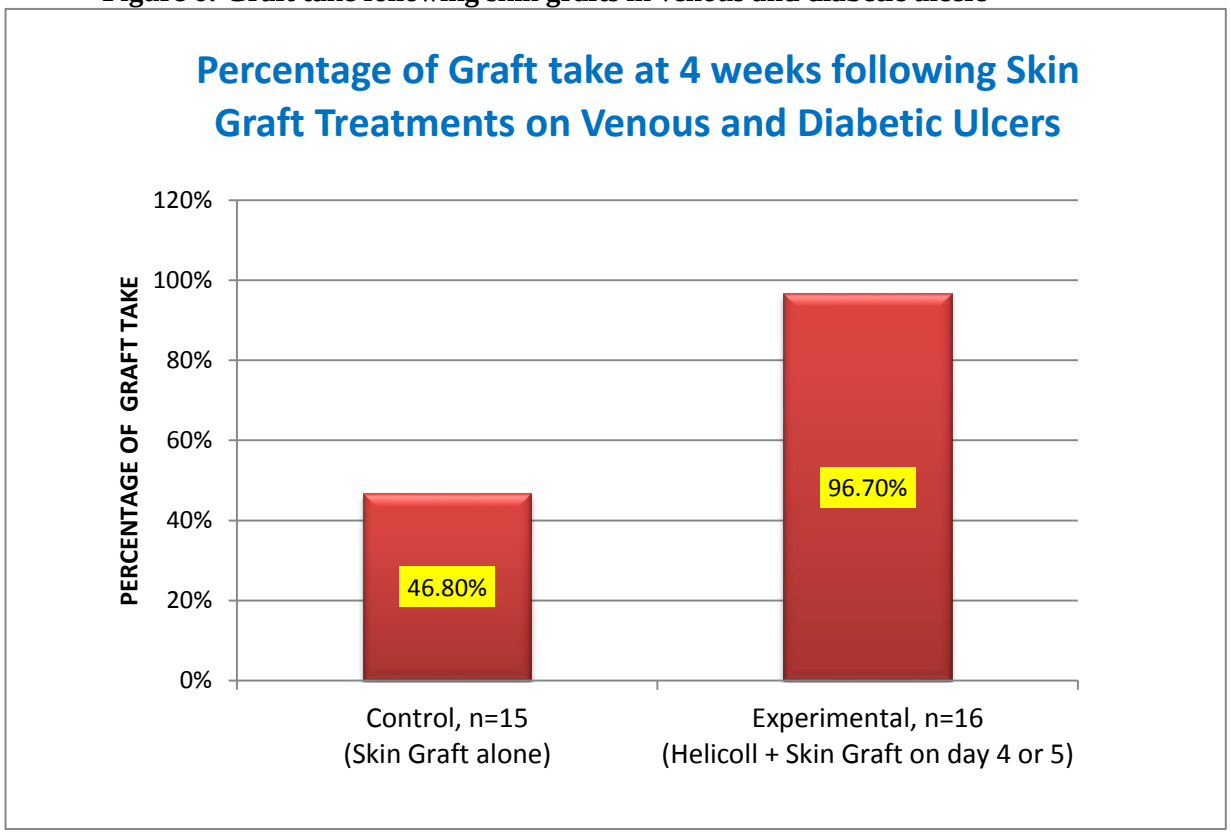


Figure 5: Healing rate of superficial burns treated with Helicoll or control[11]

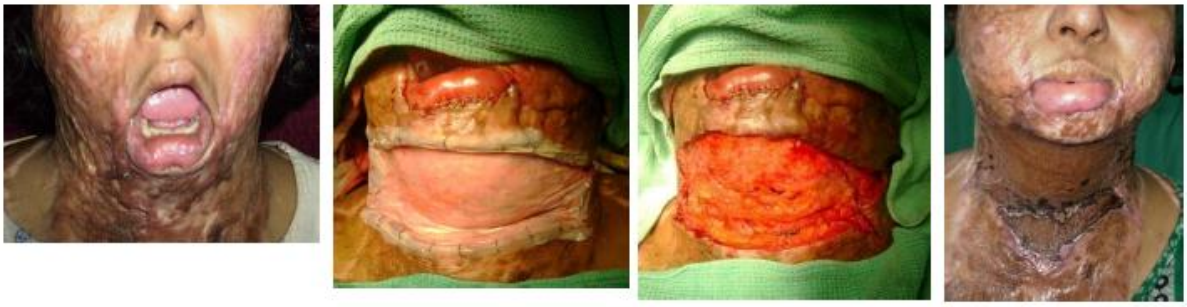
Helicoll, in the clinical setting[11] significantly reduced burn healing time, provided rapid pain relief at the wound site, achieved 99.9% skin graft retention and reduced scarring, as well as return of native skin color to the patient after several months. Helicoll also significantly reduced the amount of hospital staff time required (dressing changes are less frequent as, Helicoll can remain on wound for several days, wound inspection simplified as Helicoll is semitransparent and wound can be assessed without removal of Helicoll), as well as total cost of care by up to 50% over current therapies (product cost is up to 92 less expensive than some competitors (Figure 10). Helicoll is available in large sizes so burns can be covered quickly.

Figure 6: Graft take following skin grafts in venous and diabetic ulcers[11]



Helicoll is used for first and second degree burns, partial and full-thickness wounds, post laser treatment, as well as pressure, venous, vascular, and diabetic ulcers. Trauma wounds such as: Abrasions, lacerations, skin tears and donor sites are also indicated uses.

Figure 7: Treatment of Post-Burn Contracture with Helicoll[11]



Post-burn neck contracture

Contracture release and Helicoll application

Day 5 post-Helicoll application

After graft has taken

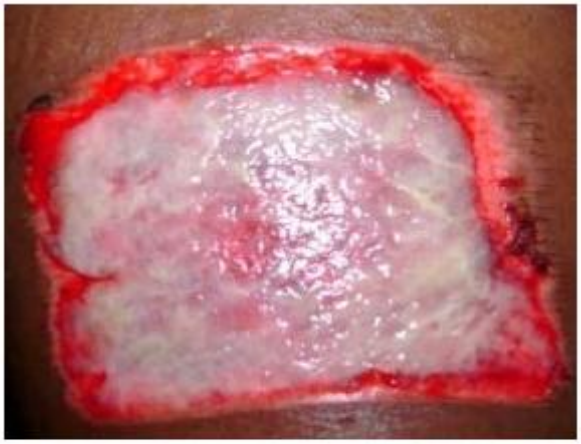
Helicoll can be placed on wounds caused by soft tissue necrosis secondary to radiation, chemical burns or corrosives. The Helicoll is moistened with sterile water or normal saline for six to ten minutes and placed in direct contact with the necrotic tissue. Daily dressing changes are recommended with mechanical debridement of the necrotic tissue to reduce the bioburden of the necrotic tissue and assist with autolysis.

Oxygen enhances the wound healing activity of collagen so Helicoll can be applied to wounds that are undergoing treatment with hyperbaric oxygen.

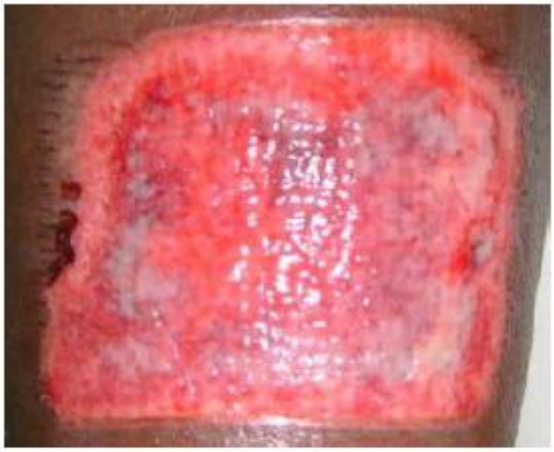
It does not matter which surface of the Helicoll Wound Dressings is placed against the wound surface. Helicoll must remain in contact with the wound by light pressure to ensure the contact of the wound surface with the collagen to ensure proper healing.

Only areas with skin damage will interact with Helicoll. Any excess collagen (see Figure 8) can be rinsed away with saline irrigation, so removal of the dressing does not interfere with healing granulation tissue nor does it cause a painful experience for the patient. Helicoll is also semi-translucent so that observation of the healing can be accomplished without disturbing the healing tissue.

Figure 8: Photographs of wounds treated with Helicoll[11]

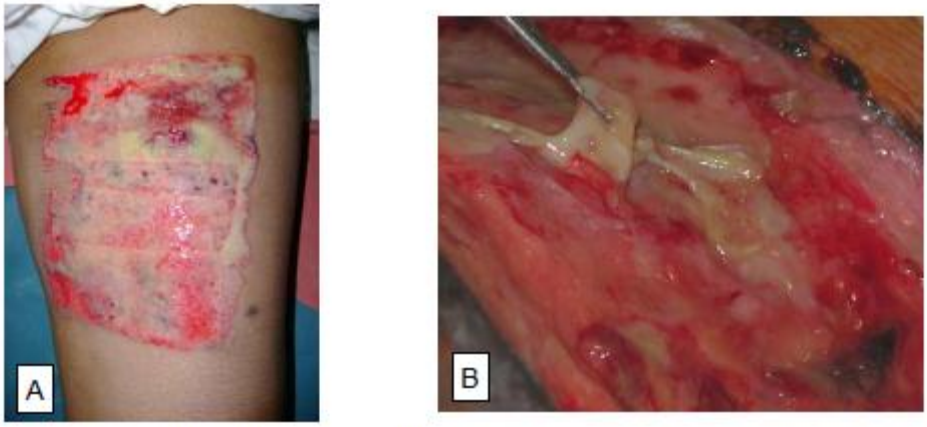


Helicoll degradation product (White gel-like substance) incorporating into collagen matrix on Day 4



Incorporation of Helicoll into deeper structures on Day 9

Figure 9: Photograph of wounds showing Helicoll incorporation[11]



Collagen consistently is incorporated into the wound by Day 4-5. Capillary bleeding and incorporation of Helicoll into deeper structures seen above. Induction of neo-vascularization and incorporation of collagen was assessed using histological and electron microscopic studies (not shown).

2.1. Helicoll Advantages:

The usefulness of Helicoll over any other dressings in the market is well documented for the treatment of diabetic ulcers, donor sites, burn treatments and other types of wounds. Refer to Figure 4 for distribution of types of wounds treated in clinical studies.

With Helicoll, epithelialization occurs even in the inner areas of the wound site. This did not happen with other collagen preparations used on the same wounds.[7]

As described in Section 1.3 of this document, native type-I collagen creates adhesion sites for growth factors and also triggers "cell signal transduction" through which floating stem cells convert into appropriate cell-lines to regenerate damaged tissue. Other collagen preparations may not maintain the native chemistry of type-I collagen. The high purity type I collagen dressing of Helicoll avoids any potential health risks normally caused by contaminating immunogenic molecules like type-III, type-II collagens, elastin, glycosaminglycans, some proteolipids, oligopeptides etc. Accordingly, the other dressings are cross-linked to minimize the immunogenicity of contaminants at the expense of the needed bio-activity of collagen for enhanced wound healing.

EnColl Corporation's patented process uses a unique enzymatic process that result in a highly purified collagen that is relatively non-immunogenic. It also renders a native un-crosslinked collagen. Certain preparation methods of collagen products use crosslinking by chemicals such as aldehyde without realizing that the resulting collagen is cross-linked and no longer bioactive. If a collagen molecule is crosslinked, it loses the natural binding abilities to adhere to cell surface receptors, growth factors, and other potential active molecules necessary for the healing process to move forward. This impedes the natural cell-signaling properties of collagen and thereby the crosslinked collagen reduces the wound healing capabilities of un-crosslinked native collagen. If the collagen is native the cell-matrix interactions and the bioactivity of cells will increase. Helicoll collagen provides this environment. It works to reduce pain, scar formation and loss of pigmentation. Further it may also help to heal wounds with limited blood supply in cases of arterial insufficiency.

Another advantage of Helicoll is that it has been shown to be safe for use on patients of all ages from birth to centenarians. Helicoll provides hemostasis and accelerates tissue remodeling and acts as an acellular dermal replacement product similar to Integra. Like the Integra model, Helicoll promotes healing and neo-vascularization.

Some dressings are considered cytotoxic. Helicoll, however, has been shown to be extremely bioactive, biocompatible and non-cytotoxic in vivo and in vitro.

Common benefits of Helicoll over other commercially available collagens in the market are:

- Improved biocompatibility
- Non-immunogenicity
- Controlled bioresorbability
- Cell attractability
- Hemostatic ability
- Structural stability
- Target specificity

The disadvantages of using human skin allografts that do not apply to Helicoll include:

- fear of HIV and other human infections
- cross-linking or use of preservatives that can reduce the bioactivity of the graft
- biohazardous material disposal concerns
- immediate availability is quite difficult
- limited shelf life
- possible bacterial contamination
- many eventually are rejected, making them a temporary rather than permanent wound covering

Figure 10: Helicoll comparison with currently recognized skin substitutes

HELICOLL™ COMPARISION WITH OTHER FDA APPROVED PRODUCTS

PRODUCT	HELICOLL™	DERMAGRAFT®	APLIGRAF®	OASIS™	INTEGRA™
Matrix	Patented high purity bovine Type-I collagen, reconstituted into sheets	Human fibroblast-derived dermal substitute on a polyglactin mesh	Bi-layered neonatal fibroblast - keratinocyte (dermal - epidermal) skin substitute on bovine Type I collagen	Porcine derived acellular small intestinal submucosa (SIS)	Comprised of collagen and glycosaminoglycan and a silicone layer
Size/shape	5x5 cm to 60x60 cm in sizes with 0.2 mm thickness	Rectangular, 5x7.5 cm	Circular, 8 cm diameter, 0.75 mm thickness	3x3.5 cm to 7x20 cm in sizes	5x5 cm to 20x25 cm in sizes
Sterilization	Terminal sterilization	Aseptically processed	Aseptically processed	Terminal sterilization	Aseptically processed
Shelf life	3 years at room temperature	30 minutes at room temperature; up to 6 months at -75°C	5 days at room temperature	2 years at room temperature	1 year at room temp.
Handling	Rehydrates in saline in 5 min.; easily handled, sutured & stapled	Shipped frozen; elaborate prep and appln procedures; fragile	Shipped fresh on an agarose nutrient medium; difficult to handle; fragile	Rehydrates in saline; easily sutured & stapled	Can be sutured & stapled; easily handled
Applications to Heal	1-4 applications	Up to 8 applications	Up to 5 applications	variable	variable
Approximate cost per application	US $100 per application	US $500 per application	US $1,200 per application	US $800 per application	US $1,100 per application
Total Advantages of the product	7 of 7	0 of 7	0 of 7	2 of 7	1 of 7

Helicoll collagen dressing normally comes in sizes from 2x2 inch to 15.75 x 15.75 inches. Larger sizes can be easily produced to cover large body areas.

To date, Helicoll has been used on over 77,000 patients (by May 2012) primarily by private and university hospital professional health care providers. There have been no signs of adverse reactions. We believe that the product Helicoll is the most effective (faster wound healing), efficient (shorter time to apply and less dressing changes are required) , durable (has high tensile strength) and easy to use (training physicians, nurses, medical assistants, patients and care givers takes less than 15 minutes) wound-healing product on the market. It is safe for neonates and infants or geriatrics and is currently used on wounds and burns. Helicoll wound dressings are biocompatible and hypoallergenic.

Clinical evidence for product efficacy:

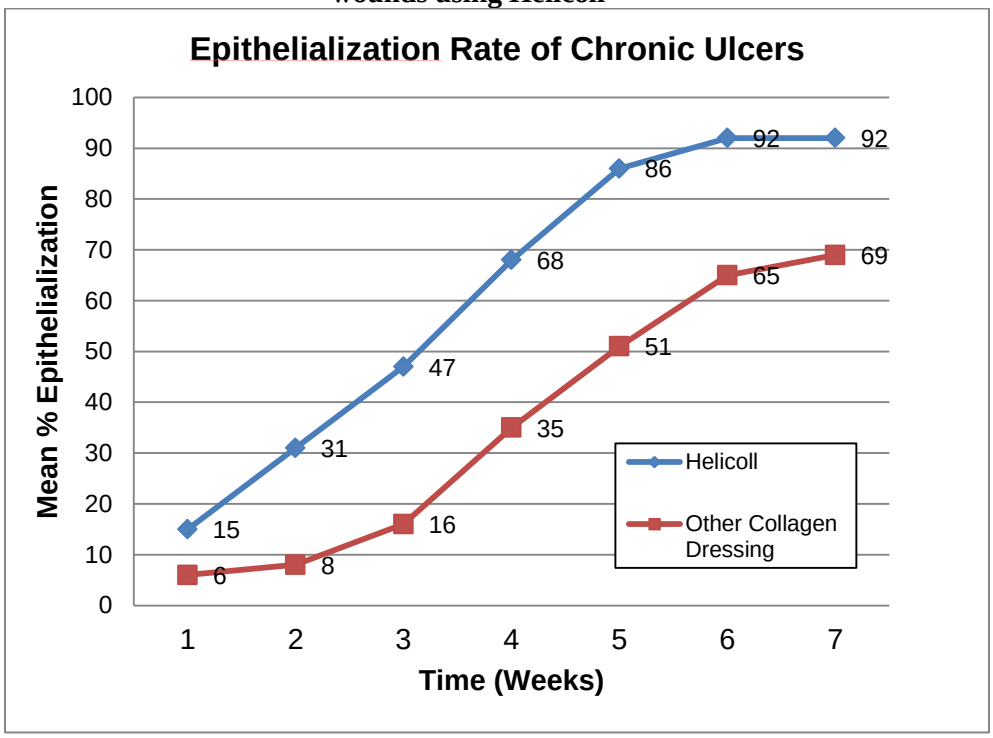
- faster wound healing[11]
- wound granulation and epithelialization in 4-5 days instead of 21–28 days (see
- Figure 9)
- reduced pain (see Figure 14)
- lesser scar formation,
- return of native skin pigmentation
- Helicoll expedited healing in all cases and contained infection,
- Promoted healthy granulation tissue, and stimulated a wound bed that better supported a skin graft.
- Itching was reduced.
- Time to healing was hastened, and hence, total cost of treatment was also lessened (see Figure 11, Figure 13)

3. CLINICAL TRIALS:

3.1. Use of Helicoll to treat skin ulcers:

3.1.1. 64 patients with ulcers were selected at random from different centers and treated with varied acellular dermal replacement collagen dressings to compare the effectiveness of Helicoll dressing with other collagen dressings. Healing was visible as early as the 5th day after Helicoll treatment. There was no pain on opening the dressing and patients had no discomfort. No adverse events were reported.[6]

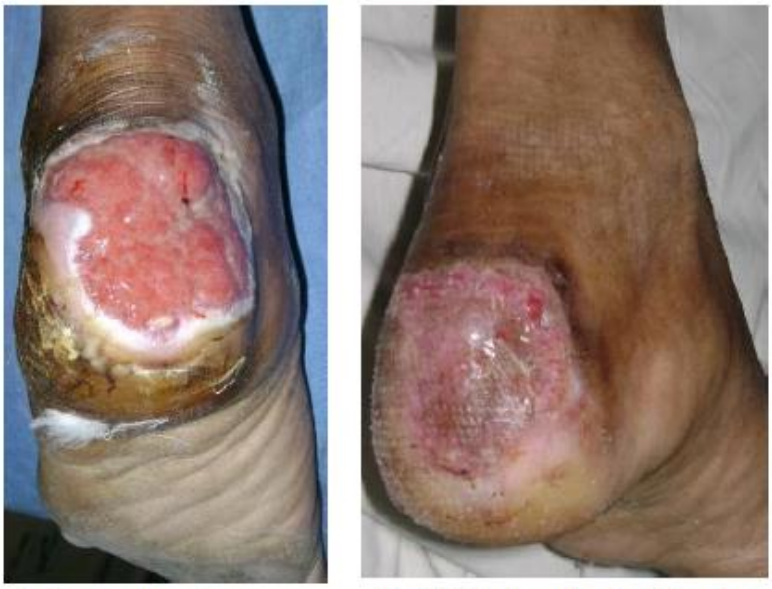
Figure 11: Rate of healing of wounds over 7 weeks in 64 patients with chronic ulcer wounds using Helicoll[6]



3.1.2. 20 patients with ulcers were included to undergo treatment with Helicoll. In all cases, wounds closed after a few bi-weekly and weekly applications. The wounds remained closed for several months. It was noticed that epithelialization occurred even in the inner areas of the wound sites, which did not occur when other dressings were used.7

3.1.3. Helicoll was compared to traditional cotton gauze dressings for the management of lower extremity ulcers in 18 patients. Although both study groups were comparable at baseline, data indicate that the use of Helicoll resulted in faster re-epithelialization.29

Figure 12: Diabetic Foot Ulcer Treated with Helicoll[25]



Before treatment Post-Helicoll application, Day 9

The role of Helicoll collagens in foot care was demonstrated[25] in independent clinical studies showing at least 45% epithelialization of the foot ulcer wound in 6 days. Further 30% healing improvement was observed with Helicoll over other collagen products used for leg ulcer treatments.

3.2. Usage of Helicoll in treating Burns

3.2.1. Clinical study of 43 patients with second degree burns, age range 1 to 57 years were randomized to receive Helicoll (n=23) or 1% silver sulphadiazine (n=22). Helicoll resulted in a statistically significantly shorter time to healing (7.2 days vs. 14.5 days, p=0.005). Healing was enhanced by 49.7% in the Helicoll group compared to the silver sulphadiazine group. Itching was significantly decreased in the Helicoll group (90.5% vs. 71.1% without itching).8,30

3.2.2. 26 burn patients were treated with Helicoll, compared to conventional dressings in a multi-center study. There was a 4-fold increase in rate of healing in the Helicoll group compared to the control gauze group.31

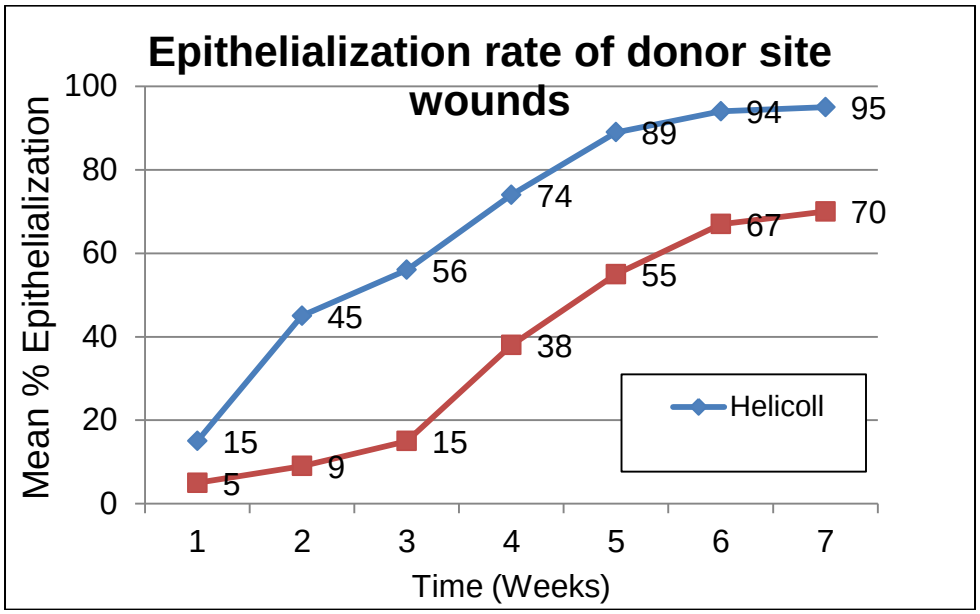
3.2.3. Vishal Mago, MD, unpublished report on "First & Second-Degree Burn Treatment Trial of Collagen [Helicoll] Dressing vs. Silver Sulphadiazine Alone," as randomized, controlled study of efficacy and safety on 15 patients with clinical burns, 2007. Better wound pain control with Helicoll.

3.3. Helicoll used to Heal Split Thickness Skin Grafts (STSG)

3.3.1. 60 patients with donor sites were selected at random at different centers and treated with varied acellular dermal replacement collagen dressings to compare the effectiveness of Helicoll with other collagen dressings. There was no pain on

opening the dressing and patients had no discomfort. Helicoll achieved a greater patient comfort level as well as an accelerated healing rate compared to other collagen dressings.6

Figure 13: Rate of epithelialization in 60 patients whose donor sites were treated with Helicoll[6]



3.3.2. 22 patients with skin graft donor site wounds were included to undergo treatment with Helicoll. Twenty of these patients had no pain, no restriction of mobility, no infection when used per the protocol and the time to heal was significantly faster when compared to other conventional dressings.7

3.3.3. 158 patients with STSG were successfully treated with Helicoll in 2010. Study included measurement of pain reduction of patients treated with Helicoll compared to control patients.

3.3.4. Reduced itching, increased range of motion, and overall increased patient comfort were also experienced by patients treated with Helicoll for burns and STSGs in this study (see Figure 14).11

Helicoll collagen dressing treatment showed 41% improvement over other Standard Care Treatments in a Clinical Study of split skin graft donor sites. Helicoll treated wounds healed in 7-10 days compared with 10-12 days with a traditional treatment.11

Collagen reduces post-operative donor site pain. There was a significant reduction in post-operative pain in the collagen dressings upon application of the product, at days 1 and 2, and throughout the treatment process until complete healing when compared to the other gauze groups ($p < 0.02$).11

Figure 14 below shows slight increase in pain on Helicoll patients on days 4 and 5 which corresponds to the infiltration of the live tissue cells into Helicoll as part

of normal healing process.

Figure 14: Pain Response in Helicoll and Control Wounds[11]

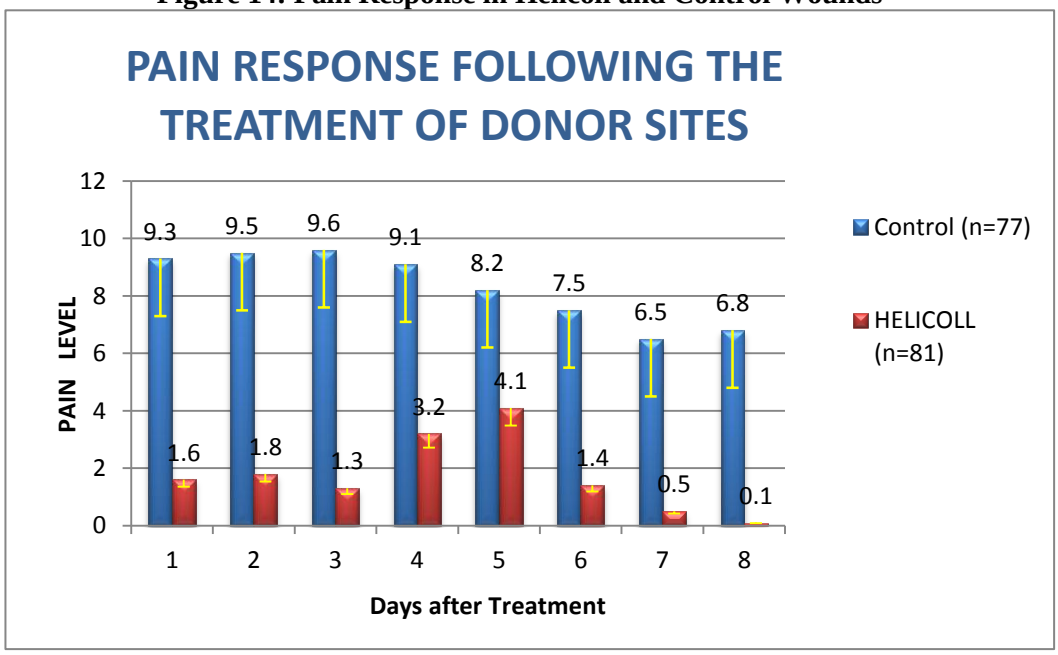


Figure 15: Donor site treatment using Helicoll[11]

Figure 16: Collagen Patents

US006127143A

United States Patent [19]

Gunasekaran

[11] **Patent Number: 6,127,143**

[45] **Date of Patent: *Oct. 3, 2000**

[54] **PREPARATION OF PURIFIED AND BIOCOMPATIBLE COLLAGEN USING TWO PROTEOLYTIC ENZYME TREATMENTS AND A REDUCING AGENT**

[76] Inventor: **Subramanian Gunasekaran**, 5686 Geranium Ct., Newark, Calif. 94560

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/162,319**

[22] Filed: **Sep. 28, 1998**

Related U.S. Application Data

[63] Continuation of application No. 08/782,138, Jan. 13, 1997, Pat. No. 5,814,328.

[51] **Int. Cl.**[7] **A61F 2/00**; A61K 38/17; C12P 21/06; C07K 1/14

[52] **U.S. Cl.** **435/68.1**; 424/426; 424/548; 435/267; 514/21; 530/356; 530/402; 530/412

[58] **Field of Search** 435/68.1, 267; 530/356, 402, 412; 424/426, 548; 514/21

[56] **References Cited**

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5,814,328	9/1998	Gunasekaran	424/426

Primary Examiner—David M. Naff
Attorney, Agent, or Firm—Medlen & Carroll, LLP

[57] **ABSTRACT**

Purified collagen is produced by a method containing steps of contacting a collagen sample with a first proteolytic enzyme followed by contacting with a reducing agent and a second proteolytic enzyme. Preferably, the first and second proteolytic enzymes are papain and the reducing agent is sodium sulfide, dithiothreitol, glutathionine or sodium borohydride. A biocompatible collagen is prepared by contacting the purified collagen with a delipidation agent such as chloroform or methanol to produce delipidated collagen, and then contacting the delipidated collagen with a phosphorylation agent such as sodium trimetaphosphate. Prior to phosphorylation, the delipidated collagen may be treated by compressing, dehydrating, dispersing and drying to form collagen fibers. Also, prior to phosphorylation, the delipidated collagen may be treated by filter-sterilizing. De-epithelializing of the collagen may carried out prior to treating with the first proteolytic enzyme. The purified and biocompatible collagen may be used in transplantation or hemostasis, and may be provided with compounds such as antimicrobials, antivirals, growth factors and other compounds suitable for biomedical use.

23 Claims, 2 Drawing Sheets

US006548077B1

(12) **United States Patent**
Gunasekaran

(10) **Patent No.: US 6,548,077 B1**
(45) **Date of Patent: *Apr. 15, 2003**

(54) **PURIFYING TYPE I COLLAGEN USING TWO PAPAIN TREATMENTS AND REDUCING AND DELIPIDATION AGENTS**

(76) Inventor: **Subramanian Gunasekaran**, 5686 Geranium Ct., Newark, CA (US) 94560

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/677,646**

(22) Filed: **Oct. 3, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/162,319, filed on Sep. 28, 1998, now Pat. No. 6,127,143, which is a continuation of application No. 08/782,138, filed on Jan. 13, 1997, now Pat. No. 5,814,328.

(51) **Int. Cl.**[7] **A61F 13/00**; A61F 2/00; A61K 38/17; C12P 21/06; C07K 1/14

(52) **U.S. Cl.** **424/422**; 424/426; 424/548; 435/68.1; 435/267; 514/21; 530/356; 530/402; 530/412

(58) **Field of Search** 424/422, 426, 424/548; 435/68.1, 267; 514/21; 530/356, 402, 412

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Primary Examiner—David M. Naff
(74) *Attorney, Agent, or Firm*—Medlen & Carroll LLP

(57) **ABSTRACT**

Purified collagen such a type I collagen is produced by a method containing steps of contacting collagen with a first proteolytic enzyme followed by contacting with a reducing agent and a second proteolytic enzyme. Preferably, the first and second proteolytic enzymes are papain and the reducing agent is sodium sulfide, dithiothreitol, glutathionine or sodium borohydride. In a further step, the purified collagen may be contacted with a delipidation agent such as a mixture of chloroform and methanol to produce delipidated collagen. The delipidated collagen may be filter-sterilized and contacted with a phosphorylation agent such as sodium trimetaphosphate to produce phosphorylated collagen. The delipidated collagen may also be treated by compressing, dehydrating, dispersing and drying to form collagen fibers. De-epithelializing of the collagen may carried out prior to treating with the first proteolytic enzyme. The collagen may be solubilized using a solubilizing agent such as acetic acid. The purified collagen is biocompatible and may be used in transplantation or hemostasis, and may be provided with compounds such as antimicrobials, antivirals, growth factors, anti-dehydration compounds and other compounds suitable for biomedical use.

20 Claims, 2 Drawing Sheets

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Attachment E - ASTM-F2212-2009 Collagen

Please refer to the attached Reference Document for the following Reference:

Standard Guide for Characterization of Type-I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs). ASTM F 2212-09. Published Aug 2009.

Attachment F
Support Letters from a few of the potential end users

STANFORD UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF DERMATOLOGY

ALFRED T. LANE, M.D.
PROFESSOR OF DERMATOLOGY AND PEDIATRICS, EMERITUS

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PALO ALTO, CA 94304
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June 19, 2013

Ms. Cynthia Hake
CMS HCPCS Workgroup Chair
Centers for Medicare and Medicaid Services
C5-08-27, 7500 Security Blvd.
Baltimore, MD 21244-1850

Re: Letter of Support for Helicoll HCPCS Code Modification

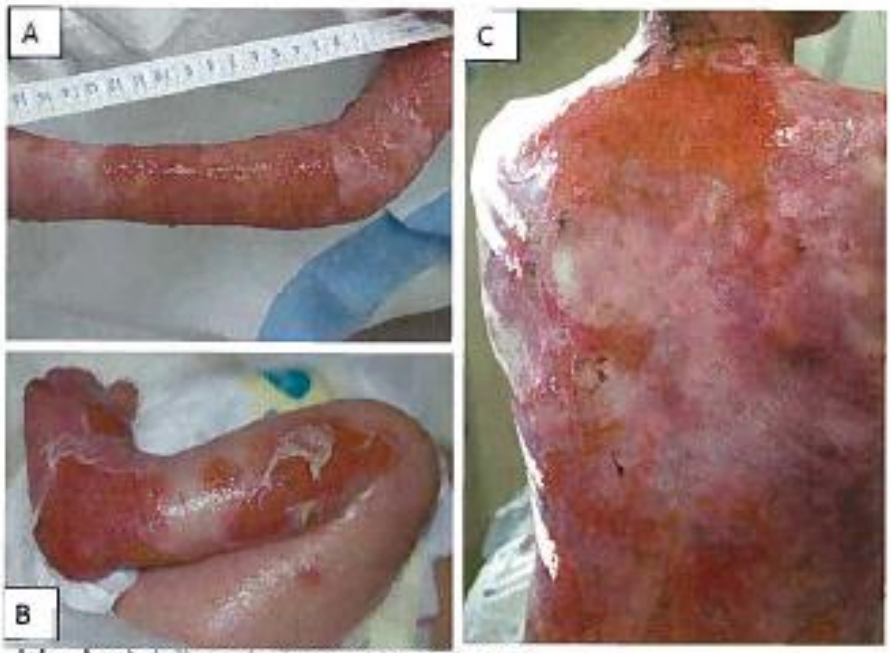
Dear Ms. Hake,

I am writing in support of EnColl's request to modify the HCPCS code for Helicoll, a purified type I collagen wound care product.

I am a Professor Emeritus of Dermatology and Pediatrics and was formerly the Chair of the Dermatology Department at the Stanford School of Medicine. I am currently the Principal Investigator of an Institutional Review Board approved clinical trial, being conducted at the Stanford School of Medicine, Stanford Hospital and Clinics, and the Lucile Packard Children's Hospital. In this study we are using Helicoll to treat the wounds of patients with epidermolysis bullosa (EB). Patients with this disease lack the proteins that anchor the epidermis to the dermis, resulting in widespread chronic wounds, which are often present for years without resolving completely. Patients with EB usually die young due to sepsis, malnutrition, or aggressive squamous cell carcinoma (SCC). Most SCCs grow from chronic, non-healing wounds.

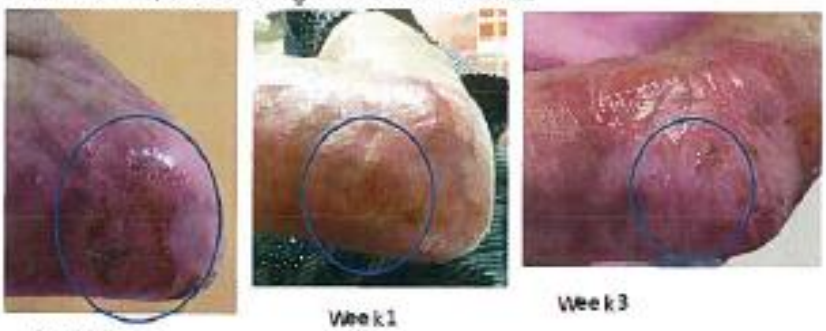
Our patients, physicians, and wound care nurses are well-versed in wound care products and have used most of the products currently on the market. We have enrolled five subjects in our clinical trial and we have found in four subjects that Helicoll may have a clinical advantage over other similar wound dressings. It is effective in healing chronic wounds, while also reducing pain, itch, and burning/stinging sensations. Furthermore, Helicoll is less expensive than either long-term use of specialized bandages or single-use biologics. We are continuing to enroll subjects with a goal of studying 10 subjects.

Figure 1: Examples of chronic wounds in patients with epidermolysis bullosa, treated with standard dressings:

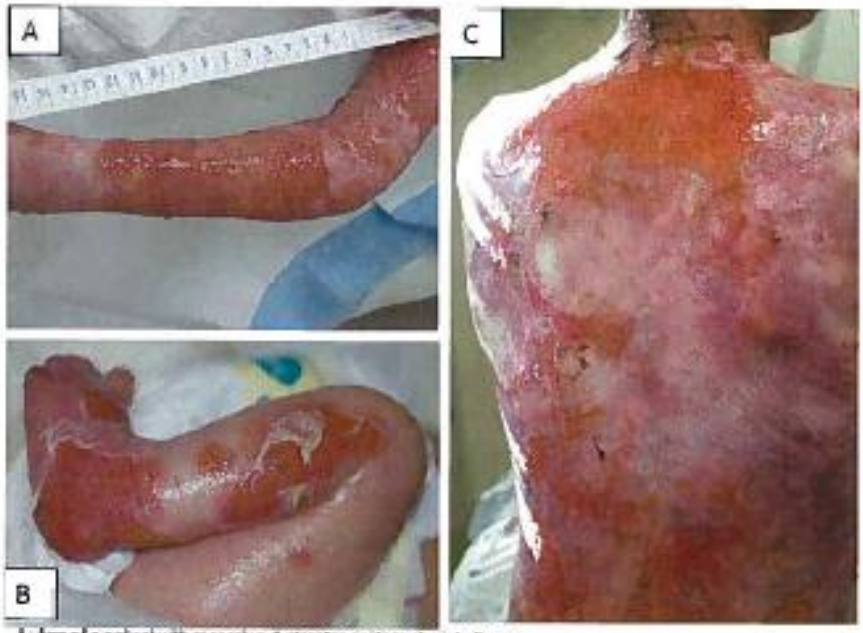


A: Arm of a patient with recessive dystrophic epidermolysis bullosa
B: Leg of a newborn with epidermolysis bullosa
C: Back of an 18-year-old with recessive dystrophic epidermolysis bullosa.

Figure 2: Chronic wound in a patient with epidermolysis bullosa. This wound was present for over 6 months, before being treated with Helicoll:

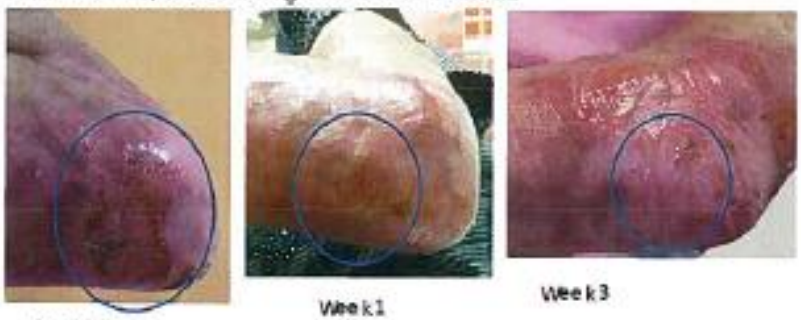


In our study, only two wounds are selected to receive Helicoll, in order to provide a quantitative assessment as well as a within-subject control wound. Four subjects who have completed the study have requested to receive Helicoll outside of the study to treat their other wounds. However, this has been complicated by the fact that this product lacks a unique Q41xx HCPCS code, creating significant barriers for insurance authorizations and/or approvals. Generally, our patients are in government programs such as Medi-Cal, Medicaid, Medicare, and/or California Children's Services and cannot afford to pay for this dressing without assistance from



A. Arm of a patient with recessive dystrophic epidermolysis bullosa
B. Leg of a newborn with epidermolysis bullosa
C. Back of an 18-year-old with recessive dystrophic epidermolysis bullosa.

Figure 2: Chronic wound in a patient with epidermolysis bullosa. This wound was present for over 6 months, before being treated with Helicoll:



In our study, only two wounds are selected to receive Helicoll, in order to provide a quantitative assessment as well as a within-subject control wound. Four subjects who have completed the study have requested to receive Helicoll outside of the study to treat their other wounds. However, this has been complicated by the fact that this product lacks a unique Q41xx HCPCS code, creating significant barriers for insurance authorizations and/or approvals. Generally, our patients are in government programs such as Medi-Cal, Medicaid, Medicare, and/or California Children's Services and cannot afford to pay for this dressing without assistance from

insurance or these government programs. Wound dressings for patients with epidermolysis bullosa routinely cost caregivers $5,000 per month.

I strongly endorse the efforts made by EnColl for Helicoll to receive a unique Q41xx code and an appropriate reimbursement rate. Approving Encoll's request will allow patients who are otherwise administratively isolated from Helicoll to use the product and benefit from it.

I would request that your office expedite EnColl's application. Most importantly, approving this request will result in access to this product for our patients, which will heal their chronic wounds, giving them some relief from their life-long suffering.

Thank you for your time and attention to this matter.

Sincerely yours,

Alfred T. Lane, M.D.

Elite Orthopaedics & Sports Medicine, LLC

Dr. ChandraSekhar Sompalli

July 24, 2013

To Whom It May Concern:

I am writing this letter in support of Encoll's efforts on obtaining HCPCS coding for their acellular dermal replacement product, Helicoll. I am a practicing orthopedic surgeon in Oak Brook, IL who has used the product now for a number of years. Helicoll is very beneficial on all patients upon which I have applied the product. I would be able to apply the product on more patients once assigned an HCPCS code and the product is approved for reimbursement.

In my clinics I have used a number of previously available the wound care products. The clinical results from the use of Helicoll have been positive in comparison with these other products. Additionally it is my experience that using Helicoll reduces the overall expense in the treatment of wounds seen in my practice. Helicoll has proven to be a lower cost option and gives consistently positive results for my patients.

It is my understanding that Encoll is applying for a unique HCPCS Q code. This will benefit my patients who need the unique benefits of Helicoll: rapid growth of granulation tissue in the wound bed, reduced pain for split thickness skin grafts and burns, lower costs due to both the accelerated healing and the need to apply Helicoll typically one time.

Not having an assigned Q Code is affecting my ability to treat my patients with Helicoll; both at the expense of the patient and with increase costs to the health care system. I fully support and urge that a Q Code be assigned as quickly as possible.

Feel free to contact me if I can be of any further support ssompalli@gmail.com

Sincerely;

Dr. Chandra Sekhar Sompalli

Current and Past Hospital Affiliations:
Saint Anthony Hospital, Chicago, Illinois 60623
Holy Cross Hospital, Chicago, Illinois 60629
Perry Memorial Hospital, Princeton, Illinois 61356
Pekin Hospital, Pekin, Illinois 61554
St. Margarets Hospital, Spring Valley, Illinois 61362
Mendota Community Hospital, Mendota, IL 61342

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Associate, American College of Foot and Ankle Surgeons

FOOT & ANKLE CENTER OF NEBRASKA

Reconstructive Foot and Ankle Surgery
Arthroscopic and Endoscopic Surgery
Treatment of Foot & Ankle Fractures
Correction of Bunion Deformities
Sports Medicine
Children's Conditions
Diabetic Foot Care

July 2, 2013

To whom it may concern

I have utilized Helicoll for wound care for approximately 1 year. I have found that the product does an excellent job accelerating granulation formation especially with the use of negative pressure wound therapy (NPWT). Helicoll significantly reduces the duration of NPWT, saving money in both device rental and cost for home nursing. I have also used Helicoll on split thickness skin graft harvest sites. The product decreases pain at the harvest site and speeds healing. The use of this product increases patient's post-operative satisfaction.

The lack of a billable Q-code has limited my ability to use Helicoll to the detriment of the patient and at an increase cost to the health care system. I strongly urge you to provide a Q-code for the device as soon as possible. Feel free to contact me for case studies or further details.

Sincerely,

Robert Greenhagen, DPM

WOUND CARE
EDUCATION INSTITUTE®

To whom it may concern,

I am writing to inform you of my complete support of Encoll's efforts to modify the HCPCS code for their acellular dermal replacement product, Helicoll. I have been a wound care professional and educator for over 20 years, and currently have my own wound care education company called Wound Care Education Institute (WCEI).

I have utilized and dealt with almost all of the various wound care products on the market. From a clinical perspective as well as a financial perspective, Helicoll is certainly unique. It is an effective product, as the science behind the patents and manufacturing process make it a unique Type 1 Collagen skin substitute. If you combine the clinical outcomes with the price points this product sells for in the marketplace, you have a product that must have its own unique Q code as soon as possible. This also provides a less expensive option for patients and facilities to utilize rendering positive outcomes.

As a clinician, Helicoll addresses several key areas for patients with wounds:

- Totally safe for all age groups
- Shelf life is 3 years at room temperature
- Many times Helicoll is applied only once
- Once its place in the wound bed, the growth of granulation tissue is accelerated
- Reduces pain for split thickness grafts

MCT Medical Solutions, the exclusive distributor of Helicoll for Encoll, has been a good partner to WCEI. The purpose of my company is to educate clinicians that are interested in increasing their knowledge on wound care and best practices and many go on to sit for a National Certification Exam the "WCC" (Wound Care Certified). We have trained over 14,000+ licensed professionals in wound care who are now certified. During product education and application of various wound care products, Helicoll has always generated much positive interest and feedback amongst all who learn about the product and use it in the field.

Please consider Encoll's request for a timely HCPCS Q code assignment for Helicoll. This will most certainly positively benefit patients who need the product, as well as our healthcare system as a whole that benefits from clinically cost-effective technologies and innovative products.

Thank you for your attention to this important endeavor, and to my request to expedite a Q code for Helicoll.

Sincerely,

Nancy Morgan

Nancy Morgan RN, BSN, MBA, WOC, WCC, CWCMS, DWC, OMS
Owner/Clinical Instructor
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