



Understanding the Benefits of Collagen-Based Wound Dressings for Chronic Wounds.

A scientific review of ColActive® Plus and ColActive® Plus Ag Dressings, with a Comparison to Other Collagen-based Wound Dressings (Promogran® and Promogran® Prisma).

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Why Some Wounds Won't Heal.

Hard-to-heal wounds have a higher than normal level of MMPs.

Proteases and Wound Healing

Elevated protease activity (EPA) can disrupt wound healing and can lead to chronic, difficult-to-heal wounds. Proteases are enzymes that usually digest proteins into smaller pieces, changing their structure and their function. Some proteases work by digesting only a specific protein, while others may work on a range of proteins. There are specific proteases that are present in wound beds which have key roles for healing, such as matrix metalloproteases (MMPs).¹

What are MMPs?

MMPs require a zinc atom to be active. They preferentially break down extracellular matrix (ECM) proteins such as collagen, elastin, and glycoproteins. The most studied MMPs for wound healing have been identified as MMP-1, MMP-2, MMP-8 and MMP-9. MMPs are essential for normal wound healing, they help to debride the wound bed, readying it for healing. In chronic wounds, the levels of MMPs are higher than those of acute wounds, which can quickly lead to wounds that fail to progress through the normal healing pathway.²

How do Dressings Modulate MMPs?

Currently, there are two methods in which wound dressings attempt to modulate MMP activity. The first is through the absorption of wound exudate, removing the MMPs from the wound bed into the dressing. The second is by binding proteases to the dressing or directly inactivating the MMPs.³ When clinicians are evaluating a wound bed and choosing what dressings to use, there are many questions that help to choose what combination of primary and secondary dressings should be applied: Does the dressing need to be antimicrobial? Will the dressings be used under compression? Does the patient have fragile skin? What are the levels of exudate? The status of the wound and the needs of the patient should be evaluated when choosing a method of care.

How Does Collagen Improve Healing?

“Collagen dressings act as a sacrificial substrate providing a wound with an alternate source of collagen that can be degraded by high levels of MMPs”

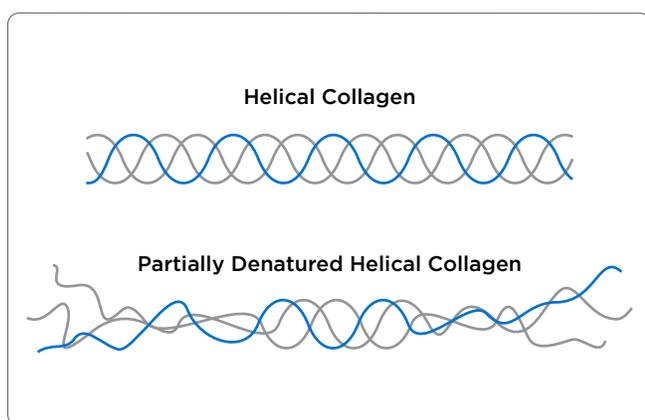


Figure 1

The Benefits of Collagen Dressings

Collagen dressings like ColActive® Plus and ColActive® Plus Ag provide multiple benefits to wound healing, particularly in difficult-to-heal wounds with EPA (elevated protease levels). As previously mentioned, hard-to-heal wounds have a higher than normal level of MMPs which can degrade the endogenous native collagen as its being produced – halting the healing process. Collagen dressings act as a sacrificial substrate providing a wound with an alternate source of collagen that can be degraded by high levels of MMPs, this allows the endogenous native collagen in the wound bed to continue with the normal healing pathway.⁴ Collagen dressings act in two ways to deactivate MMPs – absorption followed by chemical inactivation.

Apart from acting as a sacrificial substrate for MMPs, collagen dressings also provide a hydrophilic scaffold structure for cellular adhesion and mature collagen production, while simultaneously encouraging mobility of granulocytes, macrophages and fibroblasts, which are necessary for healing. All of these factors combine to improve healing times and the final appearance of the healed site.⁵

Efficacy of ColActive® Plus (Ag)

ColActive® Plus and ColActive® Plus Ag wound dressings transform into a soft gel sheet when in contact with wound exudates. The single use sterile dressings maintain a moist wound environment that aids in the formation of granulation tissue and epithelialization. In the case of ColActive® Plus Ag, the moistened dressing also activates the antimicrobial silver, eliminating colonization of bacteria within the dressing, protecting the wound bed from further risk of infection.

There is sound scientific evidence which indicates EDTA (ethylenediaminetetraacetic acid), CMC (carboxymethyl cellulose) and alginate, enhance both the performance and the clinical efficacy of Covalon's Collagen Wound Dressings.

Covalon's collagen wound dressings have been used successfully on millions of patients over the past 10 years. The unique mechanisms of action in ColActive® Plus (Ag) is a result of Covalon's patented manufacturing process that produces a crosslinked matrix of collagen containing both native-like triple helical and denatured random coil configurations of collagen chains (Figure 1). The partial unwinding of the collagen triple helix in ColActive® Plus (Ag) dressings exposes a greater proportion of the polypeptide sequence to potential interactions with wound site components, improving healing capacity.⁶

How Can ColActive® Plus (Ag) Help?

“EDTA allows ColActive® Plus to specifically deactivate MMPs”

Why do ColActive® Plus (Ag) dressings contain EDTA?

ColActive® Plus and ColActive® Plus Ag dressings contain ethylenediaminetetraacetic acid, simply known as EDTA. Chronic wounds are often associated with an enzymatic imbalance. They have significantly elevated levels of a family of proteases known as matrix metalloproteinases (MMPs). The high levels of MMPs, often referred to as Elevated Protease Activity (EPA), result in the destruction and degradation of components of the extracellular matrix (ECM) and impaired wound healing.⁷

Therefore, it is ideal to inhibit the activity of these proteases in order to develop an environment ideal for wound healing. The presence of EDTA allows the dressings to specifically deactivate MMPs through the mechanism described below.

How does EDTA inhibit the activity of MMPs?

MMPs are a family of zinc-dependent endoproteinases that modulate cell-matrix interactions through degradation and re-modelling of ECM proteins and are critical for normal development and function of organisms.⁸ MMPs require zinc ions to be active.

EDTA is a metal ion chelator that has a strong binding capacity for divalent metal ions, such as iron, calcium, and zinc.⁹ EDTA preferentially binds with zinc ions and when enough EDTA is available in the presence of excess MMPs the EDTA can strip the zinc ions from the active site of the enzymes, rendering them inactive.⁹ EDTA's ability to bind to zinc ions, a necessary co-factor for MMPs, allows for specific deactivation of the proteases, which are often responsible for the chronic nature of wounds that are out of balance.

What Do Other Collagen Dressings Do?

How do other collagen dressings try to control MMPs?

Other collagen dressings available in the market attempt to reduce MMP activity through modes of action different from those of ColActive® Plus and ColActive® Plus Ag (Figure 2). For instance, some products like Promogran® and Promogran Prisma® contain high concentrations (45%) of oxidized regenerated cellulose (ORC) to hydrolyze and deactivate MMPs. It has been shown that high concentrations of ORC can reduce the pH to levels as low as 3.6 in plasma, well below physiological pH.⁹ This low pH is thought to inhibit bacterial growth, while stimulating cell migration and growth, however, a pH level this low can immediately denature plasma proteins and damage growth factors and various cell types that are required for normal wound healing.¹⁰

What is CMC?

CMC is another important component of ColActive® Plus (Ag) dressings. CMC is a water soluble polymer derived from cellulose. CMC allows ColActive® Plus and ColActive® Plus Ag to be highly absorptive and conformable to virtually any geometry once the dressing is fully hydrated.

Carbohydrate polymers, including CMC, are used extensively in biomedical and pharmaceutical applications due to their biocompatibility and biodegradability.¹¹

Another example of a carbohydrate polymer used in healthcare is oxidized regenerated cellulose (ORC), which is found in wound dressings such as Promogran® and Promogran Prisma®, as well as the hemostat Surgicel™ (Ethicon™). The chemical formula of ORC is virtually identical to CMC as both have been derivatized to contain carboxyl groups.

In contrast, however the lower concentrations of CMC in ColActive® Plus and ColActive® Plus Ag dressings does not lead to harsh and potentially damaging low pH conditions in the wound bed as demonstrated by the complete absence of any FDA-reported adverse events (related to pain or otherwise).

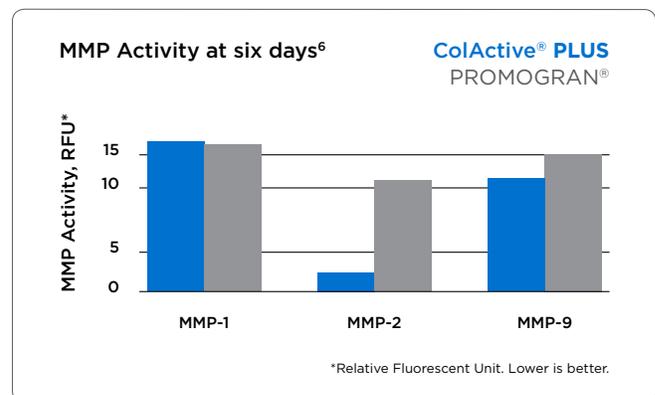


Figure 2

How Do CMC & Alginate Help?

“CMC allows ColActive Plus (Ag) to be highly absorptive and conformable. Alginate encourages fluid absorption while removing exudate away”

How does CMC help wounds heal?

There are several processes that must occur to create an optimal wound bed for healing. In difficult to heal wounds, it has been frequently stated that both an optimal moisture balance must be maintained, and that excess MMPs must be removed to transition the wound into a healing phase.^{12,13} CMC possesses properties that satisfy both requirements.

The dual hydrophilic and hydrophobic nature of CMC allows it to bind exudate into the center of the fiber and to sequester any “corrosive” wound fluid, while also creating a breathable moist wound environment. CMC is capable of binding to the glycoproteins on cell surfaces, allowing absorption and sequestration of inflammatory cells, particularly neutrophils, hastening re-epithelialization.¹⁴

Although both the ColActive® Plus (Ag) and Promogran® (Prisma®) dressings contain cellulose, it was shown in a study by Walker et al.¹³, that CMC (from Aquacel® Ag, ConvaTec) was more effective in reducing MMP-2 levels in the wound bed than dressings with ORC. The two dressings performed similarly when it came to lowering levels of MMP-9 in the wound bed, out-performing Acticoat™ (Smith & Nephew) and Silvercel™ (Systagenix).

The above studies demonstrate the effectiveness of CMC in a wound dressing and clearly illustrates why Covalon Technologies Ltd., the makers of ColActive® Plus, have developed dressings using CMC: so as to better sequester MMPs and therefore promote healing. The presence of CMC in ColActive® Plus (Ag) aids in the maintenance of a moist wound site and assists in the removal of excess MMPs.

Why do ColActive® Plus (Ag) dressings contain Alginate?

Alginate encourages fluid absorption while removing exudate away from the wound bed to induce granulation tissue formation.^{15,16}

Alginate has an inherent capability to induce hemostasis, which permits control of minor bleeding.¹⁷ This can promote the formation and deposition of a new provisional ECM by secreting collagen and fibronectin.¹⁸ (Table 1)

	Partially Denatured Collagen	EDTA	CMC	Alginate
ColActive® Plus	✓	✓	✓	✓
Promogran®	—	—	—	—

Table 1

Conclusion

“Covalon’s collagen wound dressings have been used *successfully* on millions of patients over the past 10 years”

ColActive® Plus and ColActive® Plus Ag have been used on millions of patients. ColActive® Plus and ColActive® Plus Ag distinguish themselves through the use of carboxymethyl cellulose, EDTA and alginate. To date, there are no reports of adverse events associated with the use of the ColActive® products. ColActive® Plus and ColActive® Plus Ag are designed to absorb fluids forming a soft gel sheet that conforms to the wound site, providing a breathable, moist healing environment. The gelled dressing promotes motility of important cellular elements for healing. This results in the formation of granulation tissue and epithelialization. In the case of ColActive® Plus Ag, the moistened dressing also activates the antimicrobial silver, eliminating colonization of bacteria within the dressing, protecting the wound bed from further risk of infection.

There is sound scientific evidence which indicates EDTA (ethylenediaminetetraacetic acid), CMC (carboxymethyl cellulose) and alginate, enhance both the performance and the clinical efficacy of ColActive® Plus - Collagen Matrix Dressings.

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