Universidade de Lisboa

Faculdade de Farmácia

Collagen as a wound healing material

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Monografia orientada pela Professora Assistente Katerina Tenorova da Universidade de Masaryk e coorientado pela Professora Doutora Liane Isabel Ferreira Moura, Investigadora Júnior da Faculdade de Farmácia da Universidade de Lisboa

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Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

Uma ferida é uma rutura na continuidade de uma estrutura corporal. A cicatrização de feridas é um processo fisiológico importante para manter a integridade da pele e pode incluir uma série previsível de eventos: exsudação, inflamação, proliferação/reparação e remodelação. É um processo dinâmico e complexo que requer um ambiente ideal para apoiar a recuperação. Com os avanços tecnológicos, mais de 3.000 produtos foram desenvolvidos para tratar diferentes tipos de feridas, visando vários estágios de cicatrização.

Os curativos têm como objetivo apoiar o leito da ferida e protegê-lo de fatores que possam retardar ou dificultar a cicatrização, como contaminação e perda de humidade, promovendo e agilizando o processo de cicatrização. Os materiais utilizados para criar curativos incluem polímeros naturais e sintéticos, bem como combinações destes, em diversas formas.

Uma das proteínas com maior relevância em termos de cicatrização é o colagénio, e como tal tem sido utilizado em vários tipos de pensos para feridas.

A cicatrização normal de feridas progride através das fases inflamatória, proliferativa e de remodelação em resposta à lesão tecidual. O colagénio, um componente importante da matriz extracelular, desempenha papéis essenciais na regulação destas fases de cicatrização, tanto na sua estrutura fibrilar nativa como como elementos solúveis no ambiente da ferida. As interrupções em qualquer uma destas fases podem deixar a ferida num estado crónico e sem cicatrização, muitas vezes exigindo intervenção para restaurar o progresso. Os principais fatores no ambiente adverso de uma ferida crônica incluem inflamação persistente, aumento da degradação dos componentes da MEC devido a metaloproteinases e outras enzimas elevadas e ativação inadequada de mediadores solúveis no processo de cicatrização. Dado o seu papel central na regulação destes processos, o colagénio tem sido utilizado como terapia adjuvante para apoiar a cura.

O corpo contém vários tipos de colágeno, incluindo os tipos I, II, III, IV e V, embora as fontes naturais de colágeno incluam plantas e animais marinhos. Suas propriedades físicas – como alta resistência à tração, aderência, elasticidade e capacidade de remodelação – desempenham um papel crucial na cicatrização de feridas. Formulações à base de colágeno, incluindo hidrogéis, esponjas, cremes, peptídeos e nano fibras compostas, são amplamente utilizadas na cicatrização de feridas e na engenharia de tecidos, servindo como principal linha de defesa.

Palavras-chave: Colagénio, ferida, cicatrização, curativos

Abstract

A wound is a break in the continuity of a body structure. Wound healing is an important physiological process to maintain the integrity of skin and may include a predictable series of events: exudation, inflammation, proliferation/repair, and remodeling. It is a dynamic, complex process that requires an optimal environment to support recovery. With technological advancements, over 3,000 products have been developed to treat different types of wounds by targeting various healing stages.

Wound dressings are intended to support the wound bed and safeguard it from factors that could delay or hinder healing, such as contamination and moisture loss, thus promoting and expediting the healing process. The materials used to create wound dressings include both natural and synthetic polymers, as well as combinations of these, in various forms.

One of the proteins with the greatest relevance in terms of healing is collagen, and as such it has been used in various types of wound dressings.

Normal wound healing progresses through the inflammatory, proliferative, and remodeling phases in response to tissue injury. Collagen, a major component of the extracellular matrix, plays essential roles in regulating these healing phases, both in its native fibrillar structure and as soluble elements in the wound environment. Disruptions in any of these phases can halt the wound in a chronic, non-healing state, often requiring intervention to restore progress. Key factors in the adverse environment of a chronic wound include persistent inflammation, increased breakdown of ECM components due to elevated metalloproteinases and other enzymes, and improper activation of soluble mediators in the healing process. Given its central role in regulating these processes, collagen has been employed as an adjunct therapy to support healing.

The body contains various types of collagen, including types I, II, III, IV, and V, though natural sources of collagen include plants and marine animals. Its physical properties—such as high tensile strength, adherence, elasticity, and remodeling capacity—play a crucial role in wound healing. Collagen-based formulations, including hydrogels, sponges, creams, peptides, and composite nanofibers, are widely used in wound healing and tissue engineering, serving as a primary line of defense.

Keywords: collagen, wound, healing, dressings

Abreviaturas

MMPs - Matrix Metalloproteinases

u-PA - urokinase Plasminogen Activator

t-PA - tissue Plasminogen Activator

ECM - Extracellular matrix

TIMPs - Tissue Inhibitors of Metalloproteinases

NSAIDs - Non-Steroidal Anti-inflammatory Drugs

COX-2 - Cyclooxygenase-2

CRP - C-reactive protein

CMC – Carboxymethylcellulose

EDTA - Ethylenediaminetetraacetic Acid

DFUs – Diabetic Foot Ulcers

PU - Polyurethane

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1 Wounds

Present in the daily life of all health systems, wounds continue to represent one of the biggest financial and health burdens in the world (1) making it essential to seek to know more and better ways to treat them.

1.1 Definition

Wounds can be defined as a break in normal tissue architecture (2) causing a disruption of anatomical structure and function of skin (3). These may result from numerous reasons such as: mutation affecting genes or chromosomes, trauma (heat, freezing, electricity, chemicals, radiation, or friction caused wounds), chronic wounds (diabetic foot ulcers, pressure ulcers, venous and arterial leg ulcers), or surgical interventions (3).

1.2 Types

Wounds can be classified according to two different criteria, the level of damage they involve or the time they take to heal. Taking the number of damaged skin layers, wound can be identified as: 1) superficial wounds where only the epidermal layer is affected; 2) partial-thickness wounds where both the epidermal and deeper layers are involved (these may also include damage to blood vessels, hair follicles, or sweat glands); and 3) full-thickness wounds, when wounds extend to the depth of the subcutaneous tissues (3)

If a categorization referring to the time of existence of the wound is used, wounds are commonly divided between acute or chronic based on their clinical presentation (4). Wounds that heal completely within twelve weeks with minimal scarring are referred as acute wounds, while those that take longer to heal—specifically, more than three months—and have a higher likelihood of recurring are called chronic wounds. This type refers to wounds that do not progress through the typical stages of healing and cannot be repaired in a structured or timely way.

Depending on the wound's appearance, they can be necrotic, sloughy, granulating, epithelializing or infected (5).

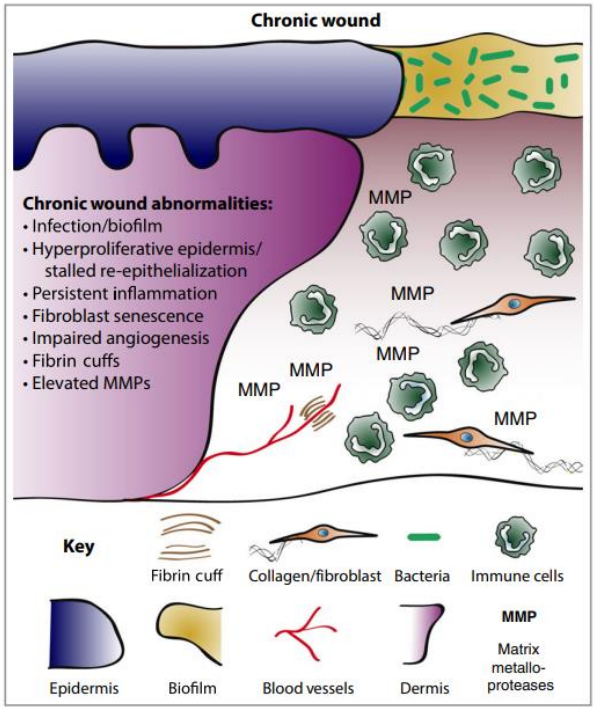


Figure 1 - Chronic Wound Biology

These are frequently infected and display a prolonged, abnormal inflammatory profile. Reepithelialization is delayed, although wound keratinocytes become hyperproliferative. Granulation tissue is compromised, failing to support healing, partly due to increased MMPs and inadequate fibroblast infiltration. Neoangiogenesis is limited, and fibrin cuffs around existing vessels restrict oxygen diffusion across the wound, resulting in a hypoxic environment.

1.3 Healing

Normal wound healing of acute wounds includes a predictable series of events: exudation, inflammation (resorptive and haemostasis phase), proliferation/repair, and remodeling (regeneration) (4).

- **Exudative phase:** After an injury, coagulation and hemostasis occur immediately at the wound site (6). Haemostasis is characterized by the creation of fibrin and the arrival of platelets, which together lead to the development of a clot. During this stage, platelets release various wound healing mediators a growth factors. These then activate macrophages and fibroblasts. Subsequent biological processes are regulated by the released mediators (growth factors) and by cytokines, which attract additional cellular components. Nowadays, more than 30 different cytokines have been identified, produced by macrophages, platelets, fibroblasts, epidermal cells, and neutrophil leukocytes. Neutrophils, the first cells to arrive at the injury site, clear away debris and bacteria to create a favourable environment for wound healing (7). The beginning of haemostasis

will occur with damage to the vascular endothelium and concludes with the formation and breakdown of a fibrin clot, a process that lasts for minutes.(2)

- **Inflammatory phase**: the next phase is the humoral and cellular inflammatory phase, which aims to establish an immune barrier against invading microorganisms(6). This process begins after haemostasis and may last between 3 to 5 days. During this phase, immune cells are recruited, while local tissue hypoxia and acidosis lead to reduced vasoconstriction and increased permeability of blood vessels (2). The degradation products of fibrin then trigger chemotaxis in the resorptive phase. Within just 24 to 48 hours, leukocytes and macrophages move into the wound area (inflammation). These cells can autolyze and eliminate non-viable tissue through fermentation processes. Overall, this results in an efficient system of phagocytosis, infection defense, and immune response.
- **Proliferation stage**: It is marked by fibroblast migration and the deposition of newly synthesized extracellular matrix, which replaces the temporary network of fibrin and fibronectin (6). Initiated by growth factor signalling during the inflammatory phase and can continue for up to two weeks. It consists on the epithelialization of the wound surface, the formation of new granulation tissue, and angiogenesis, which helps to partially fill the gap left by the injury. Between the third and seventh days, fibroblasts migrate into the area along with vascular proliferation during the proliferative phase. An essential feature of this phase is the development of granulation tissue, as epidermal cells extend into the wound from the edges, creating a visible, delicate border. These processes are regulated by various growth factors (cytokines). Fibroblasts produce a new extracellular matrix, while the newly formed capillaries supply essential oxygen for metabolism. The primary clot is broken down by components of the fibrinolysis system, including u-PA (urokinase plasminogen activator) and t-PA (tissue plasminogen activator). Various matrix metalloproteinases (MMPs) then remodel the extracellular matrix. It is crucial that these biological processes occur in a controlled manner, maintaining a balance between activating and inhibiting reactions. This intricate biological remodelling, involving the migration of fibroblasts and capillary sprouts into a structured extracellular matrix, requires a careful approach when changing dressings (2).
- **Remodelling phase:** Re-epithelization phase, as the final stage of wound healing, is responsible for developing new epithelium and forming the final scar tissue. The fourth and final phase can last from 1 to 2 years. During this process, remodelling occurs alongside fibroblast proliferation and involves the breakdown and reorganization of the

extracellular matrix (ECM), blood vessels, and granulation tissue. This phase may extend for up to a year. As collagen matures, the wound's resistance to tearing increases. Key features of this phase include epithelialization and scar formation. Throughout this time, remodelling and restructuring processes are continuously taking place. For instance, type III collagen is converted into type I collagen, which is characteristic of more mature wounds. The interactions between the extracellular matrix and the wound's cellular structures are regulated by transmembrane cell receptors (integrins) and cytokines.(2)

The outcome is a scar made up of organized collagen that has a tensile strength approximately 50–80% weaker than normal tissue (2). Wound healing, especially the formation of new epidermis, slows significantly with age. This appears to be linked to the cohesion of keratinocytes from eccrine sweat glands in older skin (8).

Wounds that do not progress through the typical phases and remain stuck in a dysregulated inflammatory state are classified as chronic wounds instead of acute ones. (9)

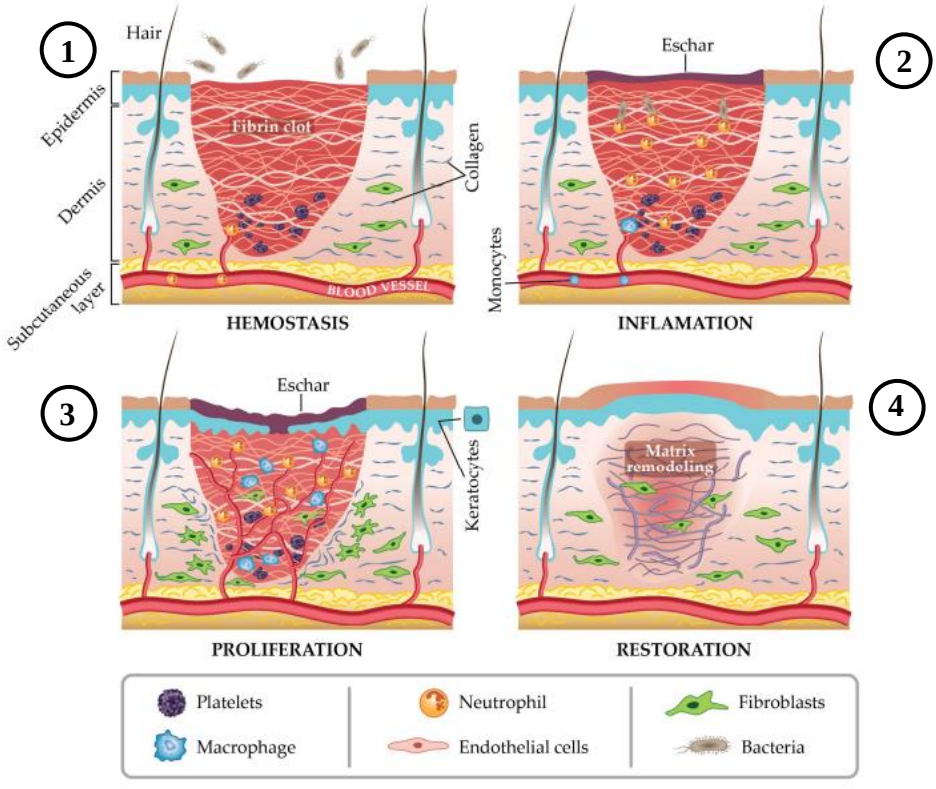


Figure 2 - The four stages of wound repair

1) Hemostasis: formation of a fibrin clot with arrival of platelets, macrophages and neutrophils;
2) Inflammation: creation of an eschar with the recruitment of immune cells;
3) Proliferation: fibroblasts and macrophages migrate into the area along with vascular proliferation;
4) Remodelling: fibroblast proliferation and creation of the extracellular matrix

1.4 Therapy

Wound treatment can be performed in some sequential steps resumed in two major phases (primary or secondary). The primary phase is based on the care taken initially, ensuring correct disinfection and that the wound is ready to heal without the need for more specific treatments. This secondary takes longer which may be due to increased wound size, the risk of infection or contamination, and can normally include a local stage with topical care and a systemic stage, based on the administration of medications with the aim of stopping the cascade of phases previously described, promoting healing. The selection of therapy and products is frequently determined by the experience of healthcare professionals, local guidelines and recommendations, as well as insights from evidence found in scientific research (10).

1.4.1 Primary wound healing

Primary intention wound healing refers to the straightforward process of healing non-infected wounds with well-approximated edges. This occurs when a healthcare professional closes the wound using surgical materials. Tissues brought together by surgical sutures or tapes with minimal tissue loss are described as healing by primary union or first intention (11). This approach allows the body to focus on healing a smaller area rather than the larger initial wound.

The most common complications of primary wound healing are infection and secondary bleeding. Infection typically reveals itself through classic symptoms such as heat, pain, redness, swelling, and loss of function. Wounds should be inspected at least once a day, and the chosen treatment should be regularly reassessed to ensure it remains appropriate(9).

Since a clean wound healing by primary intention closes relatively quickly due to fibrin crosslinking, gentle mechanical cleaning can begin after 24 hours (9). Factors such as comorbidities like diabetes mellitus, the use of immunosuppressive medication, increased skin tension at the closure site, or the formation of edema may require leaving the suture material in place for a longer period.

If the healing process is disrupted by local factors such as: oxygenation, infections, wound dehiscence, poor blood flow, or systemic factors like immunosuppression, secondary wound healing will occur. Other factors as age, stress, medications, obesity, smoking, alcohol consumption and nutrition can also affect the wound healing (12).

1.4.2 Secondary wound healing

This second phase includes a more local therapy phase, and it is essential that some points are considered, such as: moisture balance, oxygen balance, infection control, supporting strategies and tissue management.

Thus, providing a local wound therapy is based on many different factors and should consider, among other factors, the wound healing phases, exudate volumes and viscosities (10).

Cells in the human body require a continuous supply of oxygen for nearly all metabolic processes that are essential to maintaining function and life. During wound healing, which involves heightened energy metabolism, the demand for oxygen is significantly greater compared to healthy skin. In the case of infected wounds, this demand increases even further. When oxygen is lacking in tissue, it is referred to as hypoxia. Hypoxia can result not only from reduced blood flow but also in nearly all types of chronic wounds due to the increased demands of cellular activity (13). If hypoxia persists, wound healing slows, and in more severe cases, progressive tissue loss may occur. Prolonged hypoxia leads to stagnation in the healing process. Oxygen can be applied to the wound surface either directly or indirectly, with various methods being used for its delivery (10).

The presence of microorganisms in wounds is natural and does not always disrupt the healing process or lead to infection. The purpose of applying further wound dressings must be to allow the immune status to ward off the bacteria already present, avoid further colonization from outside and thereby prevent infection (9). However, detecting infections in patients with chronic wounds can be clinically challenging. For effective local infection control, clinicians must understand the wound's infectious microenvironment. This includes identifying the types of bacteria involved, the nature of the infection (whether acute, chronic, localized, or spreading), as well as considering patient factors, such as immunosuppression. Topical antimicrobial therapy should be tailored to the individual needs of each patient. Delivering antiseptics locally may offer several advantages over systemic antibiotic treatments, making this is still a point of discussion and the focus of many studies (10).

The most widely used approach in wound therapy today focuses on therapeutic interactions with MMPs due to their imbalance in the microenvironment of chronic wounds. These are a group of zinc-dependent endopeptidases that catalyse the breakdown of peptide bonds, while their natural counterparts are tissue inhibitors of metalloproteinases (TIMPs). MMPs also perform various other functions, including the regulation of both physiological and pathological

processes playing key roles in angiogenesis, tumor growth, and act as signalling molecules, among other functions.

Another therapeutic approach involves the use of growth factors to promote wound healing in chronic wounds. Growth factors regulate a wide range of intracellular processes and are particularly vital for tissue development. In wound healing, their role in angiogenesis has been extensively studied. Growth factors currently used in wound treatment include platelet-derived growth factor, granulocyte-macrophage colony-stimulating factor, and epidermal growth factor. Additionally, some methods involve extracting growth factor-rich fractions from the patient's own blood for use in wound therapy (10).

Tissue management encompasses all local wound therapy measures that contribute to preparing the wound bed. The first step typically involves wound cleansing and debridement that refers to the removal of non-adherent materials using solutions. In addition to removing remnants of dressings, it often involves the atraumatic removal of dried wound exudates.

In chronic wounds, debridement refers to the removal of adherent dead tissue, crusts, or foreign bodies. The primary goals are to prevent or treat wound infections, reduce biofilm formation, improve the visibility and accessibility of the wound, and promote healing. Various methods are classified under mechanical debridement, where loosely adherent components are removed traumatically, often using cotton compresses or monofilament fibber pads (10).

Autolytic debridement activates the body’s own proteolytic enzymes and phagocytes to break down dead tissue (14). This process is supported by creating a moist wound environment, which facilitates autolysis, also promoting skin healing(10).

If physical and local treatments are insufficient to fully treat the wound, medications may be needed. Systemic agents generally fall into four main groups: penicillin, cephalosporins, aminoglycosides, and quinolones. Other commonly used drugs include clindamycin, metronidazole, and trimethoprim. Depending on the size and severity of the wound, oral analgesics may be recommended. Available options NSAIDs, metamizole, paracetamol, or COX-2 inhibitors (9).

Topical agents include antibiotics, antiseptics, and disinfectants. It is generally suggested that both antiseptics and disinfectants destroy microorganisms or limit their growth in the non-sporing or vegetative state. However, antiseptics are typically applied to living tissues, while disinfectants can be used on equipment and surfaces (15). Topical preparations can be divided into two categories based on their function. One group consists of antimicrobial lotions used to

irrigate or cleanse wounds, while the other group includes products like creams, ointments, and impregnated dressings, which are designed to remain in contact with the wound surface for an extended period, ideally until the next dressing change (16).

An open wound does not always require antibiotic treatment. If fever, leukocytosis, and elevated CRP persist, a detailed inspection or revision of the wound should be performed to assess the possibility of infection.

Systemic antibiotics may be considered a last resort when topical treatments have failed to promote wound healing (17).

2 Wound Dressings

Whether the wound is a small cut or a larger incision, proper care is crucial, and wound dressing is an essential part of this process.

When a wound is covered with a dressing, it is continuously exposed to proteinases, chemotactic factors, complement proteins, and growth factors, which would otherwise be lost if the wound were left uncovered (18). These dressings help speed up re-epithelialization, support collagen production, stimulate angiogenesis by inducing mild hypoxia in the wound bed, and lower the pH of the wound, which can reduce the risk of infection (19).

Thanks to advancements in technology, a wide variety of wound dressings and materials are now available to treat wounds effectively.

2.1 Characteristics

A few common themes visited when choosing among dressings are the depth of the wound, amount of exudate, chronicity, and the presence of infection. The ideal wound dressing possesses many crucial characteristics as such: provide and maintain a moist environment to promote autolytic debridement while controlling exudate and protecting the surrounding skin from potential maceration, enhance epidermal migration, promote angiogenesis and connective tissue synthesis, allow gas exchange between wounded tissue and environment, maintain an appropriate tissue temperature to improve the blood flow, provide protection against bacterial infection, must be sterile, must provide debridement action to enhance leucocytes migration and support the accumulation of enzyme, be non-toxic and non-allergic, should be nonadherent to the wound and easy to remove and help to minimize pain (19).

The selection of an appropriate dressing depends on the wound type and the healing phase and must respect the individual characteristics of each wound (20) and according to that suitable dressing material must be used. Finally, the dressing should be chosen to improve the patient's quality of life by optimizing patient compliance, minimizing cost, and allowing for maximal function.

2.2 Classification

Wound dressings can be divided into two large groups, traditional (made with basic components with the main objective to protect the wound) and modern (helps with wound healing, made of a lot of different materials).

2.2.1 Traditional wound dressing

Traditional wound dressings, such as gauze, lint, plasters, bandages (whether natural or synthetic), and cotton wool, are typically dry and serve as primary or secondary dressings to protect wounds from contamination. Gauze dressings, made from woven or non-woven fibbers like cotton, rayon, or polyester, offer some degree of protection against bacterial infections. Sterile gauze pads are often used to absorb exudates and fluids from an open wound, aided by the fibbers in the dressing (19). However, these dressings require frequent changes to prevent maceration of healthy tissue. Gauze dressings are also less cost-effective and due to excessive drainage, can become wet and adhere to the wound, causing pain when removed.

Bandages, made from natural cotton wool, cellulose, or synthetic polyamide materials, serve various purposes. For example, cotton bandages are used to secure light dressings, while high compression and short stretch compression bandages provide sustained pressure, particularly in the case of venous ulcers. Tulle dressings, which are commercially available and impregnated with paraffin, are suitable for treating superficial, clean wounds. In general, traditional dressings are recommended for clean, dry wounds with minimal exudate, or as secondary dressings (19). However, because these traditional dressings fail to maintain a moist environment for wound healing, they have largely been replaced by modern dressings with more advanced formulations.

2.2.2 Modern wound dressing

Modern wound dressings have been designed to support the healing process of the wound rather than simply covering it. These dressings focus on preventing dehydration and promoting tissue repair. With a wide variety of products available, the selection process can be quite challenging, as it depends on the type and cause of the wound. Typically, modern dressings are made from synthetic polymers and are categorized into passive, interactive, and bioactive products. Passive dressings, such as gauze and tulle, are non-occlusive and are used to cover the wound, allowing its underlying function to be restored. Interactive dressings, which are either semi-occlusive or occlusive, come in forms such as films, foams, hydrogels, and hydrocolloids (19).

2.2.2.1 Semi-permeable film dressings

Semipermeable film dressings are flexible, thin, and transparent, sheets of adherent polyurethane or copolyester covered with an adhesive layer that allows the dressing to adhere to the skin (21) and permits the transmission of water vapor, oxygen, and carbon dioxide from the wound. They also facilitate autolytic debridement of eschar and are impermeable to bacteria.

Initially, these films were created using nylon derivatives with adhesive polyethylene frames, making them occlusive. Early nylon-based film dressings were not suitable for heavily exuding wounds due to their limited absorption capacity, which could lead to maceration of both the wound and the surrounding healthy tissue(19). However, these dressings are highly elastic and flexible, allowing them to conform to various shapes without the need for additional taping. The transparent nature of the films also allows for wound inspection without removing the dressing. Therefore, these dressings are recommended for use on epithelializing wounds, superficial wounds, and shallow wounds with minimal exudate such as simple abrasions, minor burns, or lacerations (21).

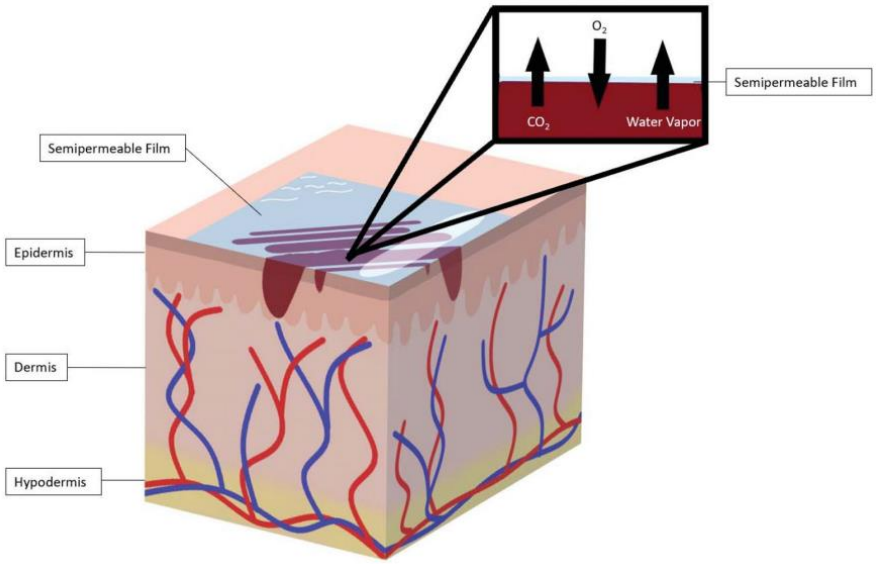


Figure 3 - Semi-permeable film dressings

Transparent wound dressings that block fluids but allow oxygen, carbon dioxide, and water vapor to pass between the wound and the surrounding environment (42).

2.2.2.2 Semi-permeable foam dressings

Foam dressings are composed of both hydrophobic and hydrophilic foam, often with adhesive borders, and can be made from porous polyurethane foam or polyaniline sponge-like polymer with a semi-occlusive hydrophobic backing. The outer hydrophobic layer protects against liquids while still allowing gas exchange and water vapor transmission. Silicone-based foam (silastic) moulds to the wound's shape, providing a custom fit. The foam's absorbent capacity varies based on the wound's thickness, making it ideal for wounds with moderate to heavy exudate. These dressings are available in both adhesive and non-adhesive forms, and they are commonly used for lower leg ulcers and granulating wounds. Foam dressings are typically used as primary dressings due to their high absorption and moisture vapor permeability, eliminating

the need for secondary dressings. However, a drawback is the need for frequent changes, and they are not suitable for dry wounds, scars, or those with low exudate, as they rely on wound moisture for healing (19).

Polyurethane-based semipermeable foams are widely used due to their excellent water absorption, good mechanical properties, and cost-effectiveness. However, their limited bioactivity and healing potential make them less effective for more complex wound healing situations (21).

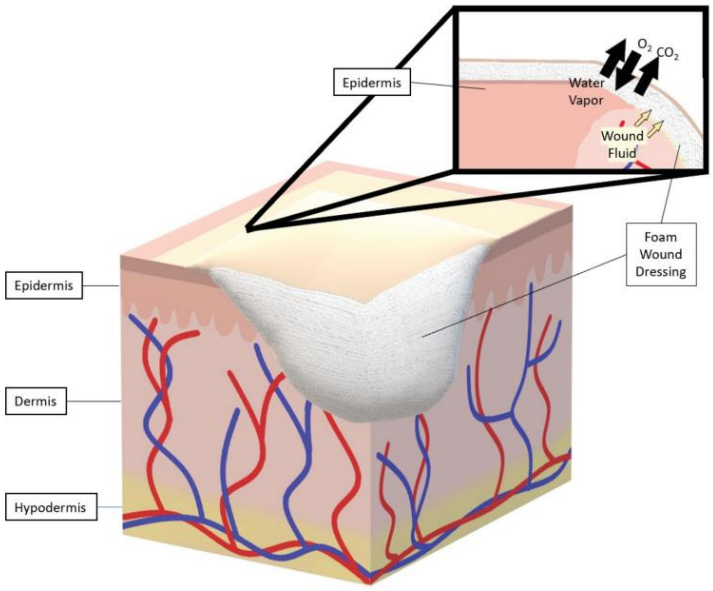


Figure 4 - Semi-permeable foam dressings

Foam wound dressings absorb blood and exudate while permitting the exchange of gases and water vapor between the wound bed and the surrounding environment (42).

2.2.2.3 Hydrogel dressing

Hydrogels are hydrophilic, insoluble materials made from synthetic polymers such as poly(methacrylates) and polyvinyl pyrrolidone. With a high-water content of 70-90%, hydrogels help maintain a moist environment, supporting granulation tissue and epithelial growth. Their soft and elastic properties make them easy to apply and remove without damaging the healed wound. Hydrogels also cool the wound by lowering its temperature, offering a soothing effect. They are commonly used for dry chronic wounds, necrotic wounds, pressure ulcers, and burns. These dressings are non-irritating, non-reactive with biological tissues, and allow the passage of metabolites (19). Several studies have shown that hydrogels are effective for treating chronic leg ulcers. However, a downside is the accumulation of exudate, which can lead to maceration and bacterial growth, often resulting in an unpleasant odour. Additionally,

the low mechanical strength of hydrogels makes them harder to handle. In some cases, hydrogels are used to deliver oxygen to a wound. Oxygen can be embedded in the dressing or released through a biochemical reaction in the hydrogel (10).

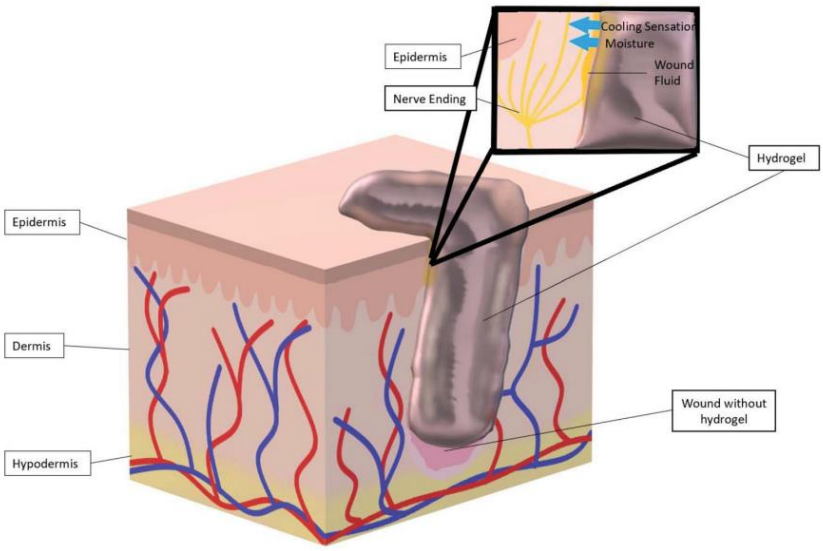


Figure 5 - Hydrogel dressing

Keep the wound moist and offer soothing relief through a cooling sensation(42).

2.2.2.4 Hydrocolloid dressing

Hydrocolloid dressings are among the most used interactive wound dressings, consisting of two layers: an inner colloidal layer and an outer waterproof layer. These dressings are made from a combination of gel-forming agents, such as carboxymethylcellulose, gelatin, and pectin, along with other materials like elastomers and adhesives. While they allow water vapor to pass through, they are impermeable to bacteria, offering protection and promoting debridement by absorbing wound exudates. Hydrocolloids are typically used on wounds with light to moderate exudate, such as pressure ulcers, minor burns, and traumatic injuries. They are also suitable for pediatric wound care since they can be removed without causing pain. When in contact with wound exudate, these dressings form a gel, creating a moist environment that protects granulation tissue by absorbing and trapping the exudate. However, hydrocolloids are not suitable for neuropathic ulcers or heavily exudating wounds, and they are often used as secondary dressings (19).

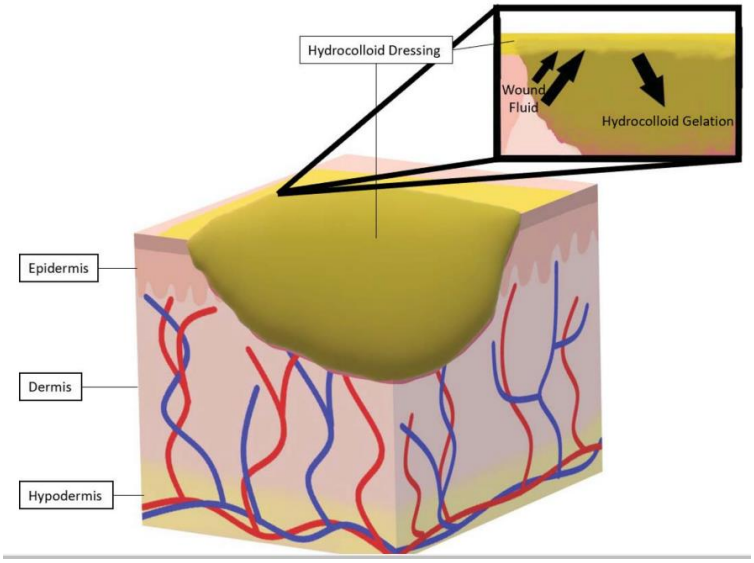


Figure 6 – Hydrocolloids

Hydrocolloid dressings are generally opaque and create a moist environment for the wound by forming a gel when they come into contact with wound fluids like blood and exudate (42).

2.2.2.5 Alginate dressing

Alginate dressings are made from sodium and calcium salts derived from seaweed, which contain mannuronic and guluronic acid units. These dressings are highly absorbent and biodegradable, and their absorption capacity comes from the formation of a strong hydrophilic gel that helps to control wound exudate and to reduce bacterial contamination. Alginate enhances the hydrophilic character of wound dressing materials to create the necessary moist wound environment and improve the ability of skin healing of the wound (21). While some studies suggest alginates may inhibit keratinocyte migration, others indicate they can speed up the healing process by stimulating macrophages to release TNF-α, which triggers the inflammatory response. When applied to a wound, the ions in alginate interact with blood to form a protective layer. Alginate dressings are best suited for wounds with moderate to heavy exudate but are not recommended for dry wounds, third-degree burns, or severe wounds with exposed bone. They also require a secondary dressing to prevent the wound from drying out, which could delay the healing process (19).

2.2.2.6 Bioactive wound dressings

Bioactive dressings are a modern type of wound dressing made from biomaterials that play a key role in the healing process. Known for their biocompatibility, biodegradability, and non-

toxic properties, these dressings are typically derived from natural tissues or synthetic sources like collagen, hyaluronic acid, chitosan, alginate, and elastin (22). These polymers can be used individually or in combination, depending on the wound's nature. Sometimes, bioactive dressings are enhanced with growth factors and antimicrobials to accelerate healing. Collagen, for instance, is a well-researched structural protein that promotes fibroblast formation and endothelial cell migration when it comes into contact with the wound. Hyaluronic acid, another important component of the ECM, is biocompatible, biodegradable, and lacks immunogenicity, similar to collagen. Chitosan aids in forming granulation tissue during the wound healing process (19).

2.2.2.7 Medicated dressings

Medicated dressings infused with drugs play a crucial role in the healing process by directly or indirectly assisting with the removal of necrotic tissue. This is achieved using cleaning or debriding agents for dead tissue, as well as antimicrobials that help prevent infection and promote tissue regeneration. Some compounds incorporated into these dressings include antimicrobial agents, growth factors, and enzymes. Silver-impregnated dressings, like fibrous hydrocolloids, polyurethane foam films, and silicone gels, are also popular due to their antimicrobial properties. Iodine-based antiseptic dressings work by disrupting bacterial cell function through oxidative degradation of proteins, effectively combating pathogens. However, prolonged use of iodine can cause skin irritation and staining (19).

The primary function of antimicrobials is to prevent or treat infections, particularly in cases as diabetic foot ulcers (DFUs), where wound dressings are a critical component in the treatment. To improve DFU management, clinicians recognize the importance of dressings that support quicker healing, inhibit bacterial growth, and promote overall recovery(23). Studies have demonstrated that silver dressings can be effective for DFUs, as silver ion dressings have been shown to eliminate bacteria, create a favourable healing environment, hydrate and soften dead tissue, and cleanse the wound while releasing silver ions (24).

The normal tissue repair process is driven by growth factors naturally present in the body, but in chronic wounds, these growth factors and cells can become trapped in the wound bed, hindering healing. Applying external growth factors has been shown to significantly aid the healing process. Among these, platelet-derived growth factor is the most used, as it encourages the recruitment and proliferation of cells and promotes angiogenesis (19).

2.2.2.8 Composite dressing

Composite dressings are highly versatile and suitable for both partial and full-thickness wounds. These dressings are made up of multiple layers, each serving a distinct purpose. Typically, composite dressings have three layers. Some also feature an adhesive border made from non-woven fabric tape or transparent film. They can be used as either a primary or secondary dressing for a variety of wounds, and they may be combined with topical medications. The outermost layer acts as a barrier against infection, the middle layer contains an absorptive material that helps maintain a moist environment and supports autolytic debridement, while the innermost layer is non-adherent to prevent sticking to delicate, newly formed granulation tissue (19). However, composite dressings tend to be less flexible and are generally more expensive.

For dry wounds, hydrogels can be used to add moisture. However, wounds with excessive exudate, such as venous leg ulcers or ulcers caused by edema, require different solutions. In these cases, products like alginates, gelling fibers, or foam dressings are suitable. For wounds with heavy exudate, superabsorbent dressings or negative pressure wound therapy may be more effective. Beyond selecting the right primary dressing, the secondary dressing also plays a critical role in absorbing excess exudate as needed (19).

3 Collagen

Collagen has been immensely valuable to humanity in numerous applications. As the most abundant protein found in animals (5), it is the primary ingredient in products such as leather, adhesives, gelatin for both food and pharmaceutical capsules, as well as strings for musical instruments and tennis rackets. Few other proteins have offered such wide-ranging practical uses. (25).

Collagen is also the primary structural element of the ECM and the most prevalent protein in the human body. It plays a crucial role in supporting connective tissues like tendons, ligaments, skin, and bones, while also participating in key physiological functions like wound healing and scar formation. Since collagen is vital throughout all stages of wound repair, it is widely utilized in wound care as well as in fields such as food, cosmetics, medicine, and tissue engineering (20). This protein can be sourced from various origins, which can affect both its quality and cost.

3.1 Structure, properties and types

Collagen constitutes about one-third of the protein in humans and approximately three-quarters of the dry weight of skin. Currently, 29 different types of collagen have been identified, all of which display a triple-helical tertiary structure. Types I, II, III, V, and XI have fibrillar quaternary structures, making them critical for various biological and medical applications(26).

3.1.1 Collagen Structure

Collagen molecules are made up of three polypeptide chains, with sizes ranging from 662 to 3,152 amino acids. These three chains can either be identical, forming homotrimers, or different, forming heterotrimers. In fibril-forming collagens, the chains align in a parallel fashion and coil into a left-handed polyproline II-type helix, which then twists into a right-handed triple helix. This helical structure is stabilized by several molecular interactions, including interstrand hydrogen bonds and intrastrain $n \rightarrow \pi^*$ interactions(27).

Collagen's stability is further enhanced by the repeating Gly-X-Y sequence in its amino acids, where X and Y are frequently proline and 4-hydroxyproline, respectively. These repetitive sequences are essential for the formation of the triple helix. The small glycine residues allow the chains to pack tightly together, while proline and hydroxyproline provide structural rigidity.

In types I, II, III, and V/X collagens, 3-hydroxyproline residues have been identified as key elements in supramolecular assembly formation (27).

Although the triple helix is rigid and rod-like, certain imperfections and interruptions in the Gly-X-Y pattern, especially in collagen IV, introduce flexibility to the structure. These imperfections consist of one to three amino acid residues, while interruptions can be as long as 21 to 26 residues. This flexibility allows collagen to function effectively in various biological roles, including molecular recognition and elasticity in tissues.

3.1.2 Role of Collagen in the Body

Collagen plays a vital role in providing structural and mechanical support in animal tissues, bones, and basement membranes. Each polypeptide chain within the collagen triple helix contains approximately 1,000 amino acids, which are essential for its stability and function. In animals, individual collagen triple helices, known as tropocollagen, aggregate to form macroscopic fibers and networks. These fibers are crucial for the mechanical integrity of tissues, giving skin its elasticity and strength, while also contributing to bone structure (28).

3.1.3 Fibrillar Collagen and Tissue Support

The collagen family consists of 29 distinct types, formed from around 25 different polypeptide chains that assemble in diverse combinations. Though homotrimeric triple helices exist, heterotrimeric forms are more common, particularly in biological tissues. Collagen types I, II, III, V, and XI, which form fibrils, are essential for tissue integrity. These fibril-forming collagens possess long sections of homologous sequences, which are important for wound healing and tissue engineering. Among these, type I collagen is the most abundant in animals and the most used in medical applications, particularly for its biocompatibility and effectiveness in wound repair (28).

3.1.4 Biochemical Properties of Collagen

Collagen belongs to a broader group of substances known as biopolymers, which include proteins that provide structural support in living organisms. Collagen stability depends on a combination of intra- and intermolecular forces, predominantly hydrogen bonds. Electrostatic interactions, such as those between lysine and aspartate residues, also play an important role in the collagen structure. As collagen matures, it becomes highly crosslinked, which significantly

reduces its solubility. This crosslinking also impacts its mechanical strength and resistance to degradation (28).

3.1.5 Thermal Stability of Collagen

Hydrogen bonds, dipole-dipole interactions, and electrostatic forces in collagen can be disrupted by heat. The temperature at which collagen denatures depends largely on the degree of crosslinking between its molecules. However, other factors, including water content and pH, also influence collagen's thermal stability. The water content in collagen-rich tissues is particularly important as it directly affects the molecular dynamics and structural properties of the collagen fibers (29). Hydrated collagen shows considerable stability, and the behaviour of water molecules within the collagen matrix is crucial for the functional and structural integrity of collagenous tissues.

The denaturation temperature of collagen is highly dependent on the extent of crosslinking. In mature collagen fibers, this temperature is higher compared to collagen derived from younger tissues. In solution, the unfolding temperature of fibrous collagen types only slightly differs from body temperature. However, once the collagen molecules aggregate into fibers, their thermal stability significantly increases.

Another factor affecting collagen’s thermal stability is the presence of hydroxyproline. Collagens with higher hydroxyproline content exhibit greater thermal stability. For instance, fish collagen, which has a lower hydroxyproline content compared to mammalian collagen, is more susceptible to thermal degradation(30). This sensitivity to temperature has significant implications for the processing and use of collagen in biomaterials, as certain collagen-based products cannot be exposed to high temperatures without risking denaturation (26).

3.1.6 Physical Properties of Collagen

Collagen possesses a range of physical properties that make it highly useful in various industries. These properties can be divided into two main categories. The first involves properties related to gelling behaviour, such as gel formation, thickening, and water-binding capacity. The second category includes properties associated with surface behaviour, such as the ability to form and stabilize emulsions and foams, as well as its adhesion, cohesion, and film-forming capacities (31).

Due to its ability to form a stable gel matrix, collagen is used in both medical and non-medical fields. In medicine, this ability is exploited to create scaffolds for tissue regeneration. In food science, collagen's gelling properties improve the texture and structure of food products, making it a key ingredient in products like gelatin.

Collagen's interaction with water is another crucial factor in its behaviour. In its hydrated form, collagen exhibits remarkable flexibility and strength, and the water molecules in collagen fibers play a significant role in stabilizing the triple-helical structure. In the absence of sufficient water, the collagen fibers lose their mechanical properties, becoming brittle and prone to degradation (29).

Collagen is a versatile and essential biopolymer, providing both structural and mechanical support in animal tissues. Its triple-helical structure, reinforced by hydrogen bonds and electrostatic interactions, gives collagen its characteristic strength and flexibility. Collagen's remarkable stability, particularly in its fibril-forming types, makes it indispensable for biological and medical applications (32). Its use in wound healing, tissue engineering, and other biomedical fields has made collagen an important focus of research and development. However, its thermal sensitivity, particularly in certain collagen types like fish collagen, poses challenges in high-temperature applications. Despite these limitations, collagen continues to be a valuable resource in both biological research and industrial applications.

Collagen-based biomaterials can also be used for a wide range of purposes beyond wound healing and tissue engineering. These include the formation of films, the stabilization of emulsions and foams, and providing protective colloid functions. Collagen is also utilized in the food industry, particularly for its gelling properties and ability to improve the texture and consistency of food products.

3.1.7 Applications of Collagen in Medicine and Biotechnology

Type I collagen, which is found in skin, tendons, and bones, is the most prevalent and widely studied type of collagen. It is also the form most frequently used in medical applications, particularly in the fields of tissue engineering and wound healing. Collagen's biocompatibility, structural integrity, and ability to promote cell adhesion and growth make it a prime candidate for creating scaffolds in tissue regeneration. Its unique properties, such as its ability to form gels, bind water, and provide mechanical support, are highly beneficial in these applications.

3.2 Collagen in wound healing

In a healing wound, collagen is produced by cells namely fibroblasts and gradually forms intricate structures. The type, amount, and organization of collagen change throughout the healing process, which determines the strength of the repaired skin. Collagen III is the first to be synthesized in the early phases of wound healing, and as healing progresses, it is replaced by collagen I, the main collagen in the skin. During granulation tissue formation, collagen is initially deposited in a random manner but is later reinforced through covalent cross-linking facilitated by the enzyme lysyl oxidase. This process matures the collagen, aligning it to restore the skin's tensile strength. Collagen continues to remodel for months after the wound closes, eventually restoring about 80–85% of the original tissue strength, if the healing process proceeds smoothly. In the skin, the most common fibrillar collagens are types I, III, and V, followed by fibril-associated types such as XII, XIV, XVI, and VI. Non-fibrillar collagens, like types IV and XVIII, are found in the skin's basement membrane (14).

In response to an injury, collagen triggers platelet activation and aggregation, leading to the formation of a fibrin clot at the wound site. During the inflammatory phase of wound healing, the activation of immune cells results in the release of proinflammatory cytokines, which influence the migration of fibroblasts, as well as epithelial and endothelial cells. Fibroblasts play a key role in depositing collagen. At the same time, the breakdown of collagen produces fragments that stimulate fibroblast proliferation and the release of growth factors, promoting angiogenesis and re-epithelialization. The remodelling of the ECM (a balance between new matrix production and matrix metalloproteinase activity) dictates the restoration of tensile strength.

Collagen applied as adjunct therapy in wound healing could promote healing potentially by acting as:

- A decoy/sink for the raging MMPs and other enzymes in the wound thereby abating inflammation and restoring progression into the reparative stages;
- A substrate aiding in the migration of key cellular components of wound healing;
- A promoter of a proangiogenic, anti-inflammatory environment to resolve the injury towards healing

Degradation of collagen is important for the physiological remodelling of connective tissues during wound healing. Extracellular degradation of collagen fibers is mediated by MMPs and can be thought of as a multistep process (33).

3.3 Preparation of Collagen-Based Materials

Natural collagen-based biomaterials can be classified into two categories based on the extent of their purification: de-cellularized collagen matrices that maintain the original tissue properties and ECM structure; and more refined scaffolds prepared via extraction, purification, and collagen polymerization. De-cellularizing collagen entails a combination of physical (snap freezing or high pressure), chemical (acid or alkali treatment, chelation with EDTA, or treatment with detergents or solutions of high osmolarity), and enzymatic (digestion with trypsin) methods to produce the biomaterial. Collagen in this form is used often as sutures, cardiac valves, and ligamentary prostheses. Generating collagen-based scaffolds involves processing collagen solutions with other biomolecules, such as elastin, glycosaminoglycans, and chitosan. Different applications require different formulations. Production of such biomaterials requires the extraction and purification of collagen from natural tissues. The dissolution of collagen is, however, impeded by the low solubility of natural collagen due to its covalent cross-links. Natural collagen is insoluble in organic solvents but can dissolve in aqueous solutions, depending on the extant cross-linking (25).

Collagen is usually obtained by extraction from natural sources, for example, several animal tissues, or by recombinant protein production systems including yeast, bacteria, mammalian cells, insects or plants, or artificial fibrils that mimic collagen characteristics. Collagen is a material which can be cost-efficiently obtained from leather solid waste because the collagen fibre is the main component of leather. Such collagen presents excellent biocompatibility and biodegradability. However, studies have shown that the direct use of collagen fibre as an adsorbent material shows certain disadvantages as low adsorption capacity, poor selectivity, or inability to resist high temperatures. Collagen fibre modifications with metal ions, tannin, hyperbranched polymers, and aldehydes etc. have been shown. The functional and bioactive properties of collagen depend on its sources, method of its extraction and purification.

Bovine as well as pig collagen have been widely applied. However, due to the risk of bovine spongiform encephalopathy and transmissible spongiform encephalopath development, the practical use of such collagen is limited. Collagen extraction from fish skin and/or scales is a safer alternative. Collagen obtained from young tissues is soluble at the acidic pH and dispersible in water, and it thus generates collagen liquids that are used as distinct biopolymer precursors for materials development. In recent years, especially in cosmetic applications,

mammalian collagen has been successfully replaced with fish collagen. The one obtained from fish skin and scales can also be used for scaffold preparation, wound healing, and for pharmaceutical preparations (26).

3.4 Collagen modifications

Collagen-based materials are commonly used in biomedical applications, but they have some limitations, such as low thermal stability, weak mechanical strength, and susceptibility to enzymatic degradation. As a result, collagen must be modified before use.

Crosslinking methods are particularly significant for collagen-based biomaterials, in contrast to acellular collagen matrices that have already undergone in vivo polymerization, these can be crosslinked to improve their mechanical strength and resistance to enzymatic degradation, making them more suitable for implantation. Crosslinking reactions work by modifying the amine and carboxyl groups within collagen molecules to form covalent bonds. Various techniques have been developed for crosslinking collagen scaffolds, categorized into three main types: physical, chemical, and enzymatic crosslinking (34).

Various crosslinking methods can enhance its properties, including physical, chemical, and biochemical modifications. Another effective approach is blending collagen with other biomaterials to create collagen-based composites. However, each crosslinking method offers its own set of benefits as well as drawbacks (35).

The proteolytic resistance and high tensile strength of natural collagen are primarily due to its covalent cross-links. However, when these links are damaged during extraction or over time, reconstituted collagen becomes weaker and may break down when handled or subjected to pressure from surrounding tissues in the body. To address this, new cross-links have been introduced to control the degradation rate and in vivo absorption. *In vitro* cross-linking of collagen usually involves utilizing its amino and carboxyl groups to create new covalent bonds. (25).

The properties of collagen-based materials can be significantly enhanced through appropriate chemical modifications. Over the past three decades, there has been growing interest in creating new materials by blending two or more polymers, either natural, synthetic, or a combination of both. These blends can lead to the development of a new class of materials with superior mechanical properties and biocompatibility compared to single-polymer materials. When synthetic and natural polymers are combined, they are referred to as bio-artificial or

biosynthetic materials. These blends can be created by melt mixing or dissolving both polymers in a common solvent.

One promising approach for solid-phase polymer modification involves applying high pressure and shear deformation to the polymer blend. However, biopolymers like proteins may undergo denaturation or degradation when exposed to high pressure and temperature. In a solution-based biopolymer blend, interactions occur not only between the polymers but also with the solvent through hydrogen bonds. The interaction between two or more biopolymers is known as miscibility, which plays a crucial role in determining the properties of the blend. Common interactions in such blends include hydrogen bonding, ionic, dipole, pi-electron interactions, and charge-transfer complexes (36).

Miscibility is key to the final properties of the blend and can be evaluated through optical homogeneity and other chemical and physical methods. Various biopolymers, such as carrageenan, chitosan, cellulose, sodium alginate, and starch, can be blended with synthetic polymers like polyvinyl alcohol or polyethyleneimine (37). These blends have potential applications in fields such as drug delivery, tissue engineering, wound healing, and gene therapy.

Collagen is a valuable biopolymer for creating polymer blends. Numerous studies have explored collagen's combination with both synthetic and natural polymers, especially chitosan, which is widely used to create biomaterials. Such biopolymer blends also have uses in packaging materials and cosmetics as rheology modifiers. Collagen can be combined with chitosan, elastin, keratin, silk fibroin, or hyaluronic acid, showing promise for biomedical and cosmetic applications like artificial skin, bone, membranes, hydrogels, and other innovative products (26).

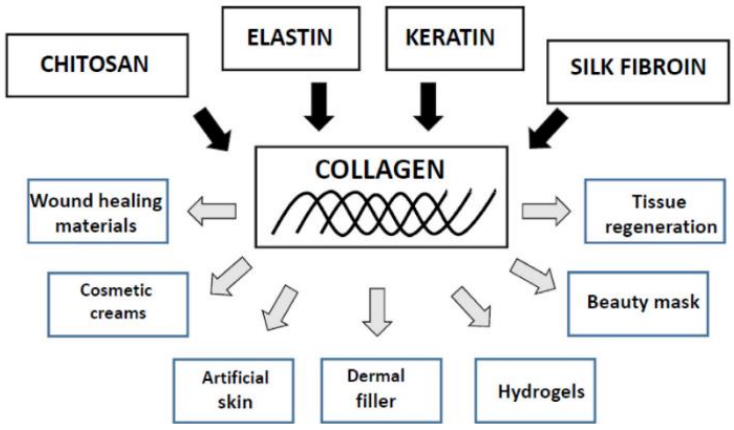


Figure 7 - Biopolymers and purposes of blends

Some biopolymers can be used for preparation the blends with collagen and lead for lots of different potencial uses having more relevance in areas such as cosmetics

3.5 Collagens wound dressings

Collagen films have been utilized in wound healing and tissue engineering, primarily acting as a protective barrier. Films with a thickness of approximately 0.1–0.5 mm can be created by casting collagen solutions and air-drying them, similar to the process used for ophthalmological shields. Another benefit of these films is that those made from biodegradable materials, such as telopeptide-free reconstituted collagen, exhibit a gradual release of encapsulated drugs. These drug-loaded films are easy to sterilize and become flexible after hydration, without losing their mechanical strength (28).

Collagen wound dressings could be presented in different forms such as sponges, powders, and hydrogels. This protein also possesses remarkable film-forming abilities, and collagen films are widely used as edible coatings in the food industry. Their application is restricted by their relatively weak mechanical properties and the difficulty in handling them after they become wet from contact with wound exudate (20).

Natural collagen has been widely used for surgical repairs due to its low antigenicity and natural compatibility with most body tissues. Collagen-based wound dressings are practical, easy to remodel, and readily available, making them ideal for medical use. These properties have also enabled the creation of innovative surgical adhesives made from porcine collagen and poly (glutamic acid), which have been utilized to prevent air leakage from damaged lungs (38). The absorption rate of these adhesives can be adjusted by modifying the collagen content. Collagen-based dressings have a long history of use in treating burn wounds and ulcers, offering a practical and cost-effective alternative to growth factor and cell-based treatments for deep wounds. Various formulations have been developed, including a novel powdered form made from avian collagen, which accelerates the healing of chronic wounds by promoting cellular recruitment, initiating the inflammation phase, and supporting new tissue formation(39).

Some collagen dressings have been designed with a semi-occlusive polymer film on their outer layer. These films protect against bacterial invasion and additional mechanical damage while ensuring appropriate air and moisture exchange. They also help minimize wound contraction and scarring, promoting faster epithelialization. (25)

A wide range of collagen-based formulations, including amorphous gels, sheets, or powders, are also available as wound dressings. These are often combined with other agents, such as silver for its antimicrobial properties, or enhancers like EDTA, CMC, or alginate. Collagen in the form of sponges or fleece has been tested as a cell-free matrix, showing potential in

promoting new tissue formation in preliminary studies. Particulate or powdered collagen, which has minimal covalent cross-linking, is biologically active and functions as a signalling molecule upon application.

Collagen membranes are used in various applications, including wound dressings, dural repairs, reinforcement of damaged tissues, and guided tissue regeneration. In diabetic db/db mice, wound healing has been enhanced by a sustained release of human growth hormone encapsulated in collagen films (40). Similarly, films made from collagen–poly (vinyl alcohol) blends and crosslinked with glutaraldehyde vapors have been tested as a delivery system for recombinant human growth hormone (28).

Collagen is also utilized as a surface coating to improve moisture retention and encourage cell adhesion within scaffolds or matrices(39). Maintaining moisture in the wound bed is crucial for healing, and collagen helps achieve this by retaining water.

Additionally, a combination of collagen with another polymer, such as an atelocollagen grafted onto ozone oxidized surface of polyurethane films enhances fibroblast attachment, promotes their proliferation, and supports long-term survival. Creating PU surfaces through ozone oxidation offers benefits, including the straightforward and uniform addition of functional groups like peroxide, which primarily forms covalent bonds with collagen amino groups. This process allows for the gradual degradation of grafted type I atelocollagen, significantly improving fibroblast attachment and growth on PU surfaces. The grafted collagen establishes a supportive biological environment, enhancing cellular activity within the hybrid biomaterials. (41).

3.6 Collagen/Carboxymethylcellulose films

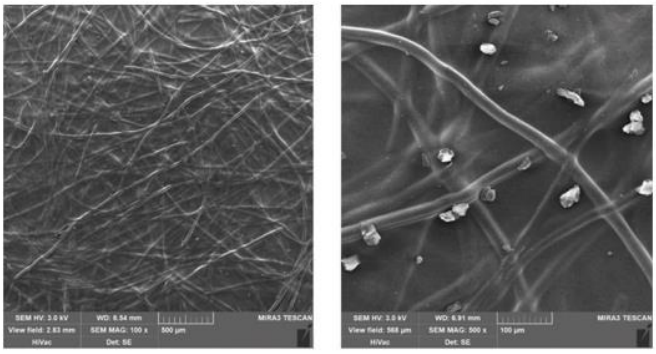
To enhance the properties of collagen films for wound dressings, improvements are needed. One approach is crosslinking, but another option is to combine collagen with materials that can improve the performance of the resulting dressing.

Carboxymethylcellulose (CMC) is a cellulose derivative with carboxymethyl groups attached to the hydroxyl groups along the cellulose backbone. It is produced through a two-step process involving the alkalization of cellulose, followed by carboxymethylation using chloroacetic acid. It is a non-toxic, biocompatible, low antigenicity, biodegradable and non-immunogenic polymer that is hydrophilic and quickly forms a gel in water. It is commonly used in wound dressings such as hydrocolloids, hydrogels, and hydrofibers (42). CMC, a cellulose derivative

commonly used in medicine, pharmaceuticals, cosmetics, and tissue engineering, is one such material.

Although CMC has excellent film-forming capabilities, films made from this polymer are not yet widely used in clinical practice. Recent research has explored CMC films as potential wound dressings, including blends with polymers like chitosan, gelatin, and polyvinyl alcohol (43). These modern dressings have shown satisfactory properties for wound care applications. Another promising approach is the creation of a film dressing by blending collagen with carboxymethylcellulose (20).

1)



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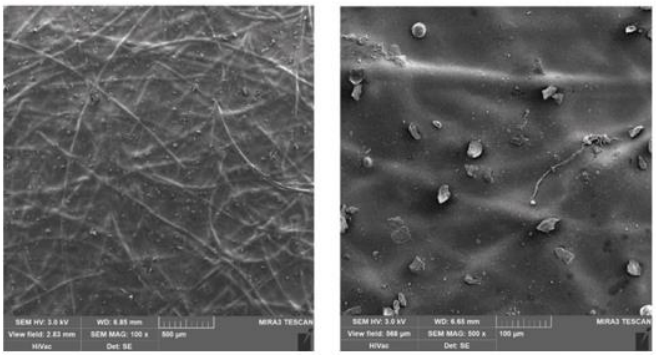

Figure 8 - Microscopic appearance of films

SEM images revealed the presence of fibers resulting from the use of partially substituted CMC. The microfibrillar structure is more prominent in CMC films (image 1) than in blend films due to the presence of collagen (image 2). Microfibrous CMC enhances the strength and improves the mechanical properties of the resulting film wound dressing

According to this new study (20), the microfibrillar structure of CMC enhanced the mechanical durability of the films needed for practical wound application. All samples met the standards for mass content uniformity and maintained an acidic or neutral pH, even after 24 hours on an artificial wound model. Unlike CMC films, blend films showed a lower absorption capacity but greater mechanical durability, even when wet. As such, it is possible to confirm that combining collagen and CMC can improve the properties of the resulting film wound dressing (20).

Conclusion

When selecting wound care products for individual patients, it is essential to carefully consider both personal and economic factors. Knowledge of available wound dressings, their correct applications, and potential side effects is essential for effective wound management. Addressing each patient's unique needs and abilities through a shared decision-making process is crucial, and the selected products must be accessible and suitable for the patient's specific type of care. Traditional dressings often fall short in performance, so researchers have recently focused on innovative dressings, enhancing their biocompatibility and environmental sustainability. An ideal dressing should have some specific characteristics as establish and maintain a moist environment that fosters autolytic debridement, controls exudate, and safeguards the surrounding skin from maceration. The mechanical properties depend on factors such as the chosen polymer, solvent, solution pH, plasticizers, and blending process. Synthetic polymers often exhibit superior mechanical strength compared to natural ones but generally have lower adherence, absorption, and permeability. As a result, combinations of synthetic and natural materials, along with various modifications, have been developed.

Collagen, the most abundant protein in the human body, is crucial for all stages of wound healing as it stimulates cell migration and new tissue formation. Collagen dressings enhance healing by promoting the deposition of new collagen and recruiting cells like macrophages and fibroblasts. Depending on their delivery system, these dressings can either retain moisture or absorb excess fluid. Typically derived from bovine, avian, or porcine sources, collagen dressings are flexible, non-toxic, biodegradable, and have low immunogenicity. They are effective for treating full and partial thickness wounds with minimal to moderate exudate, available in forms such as gels, matrices, and freeze-dried composites.

While no universal dressing exists yet, ongoing research focuses on customizing materials and formulations to meet specific wound care needs, with collagen being a particularly valuable component in various dressing types.

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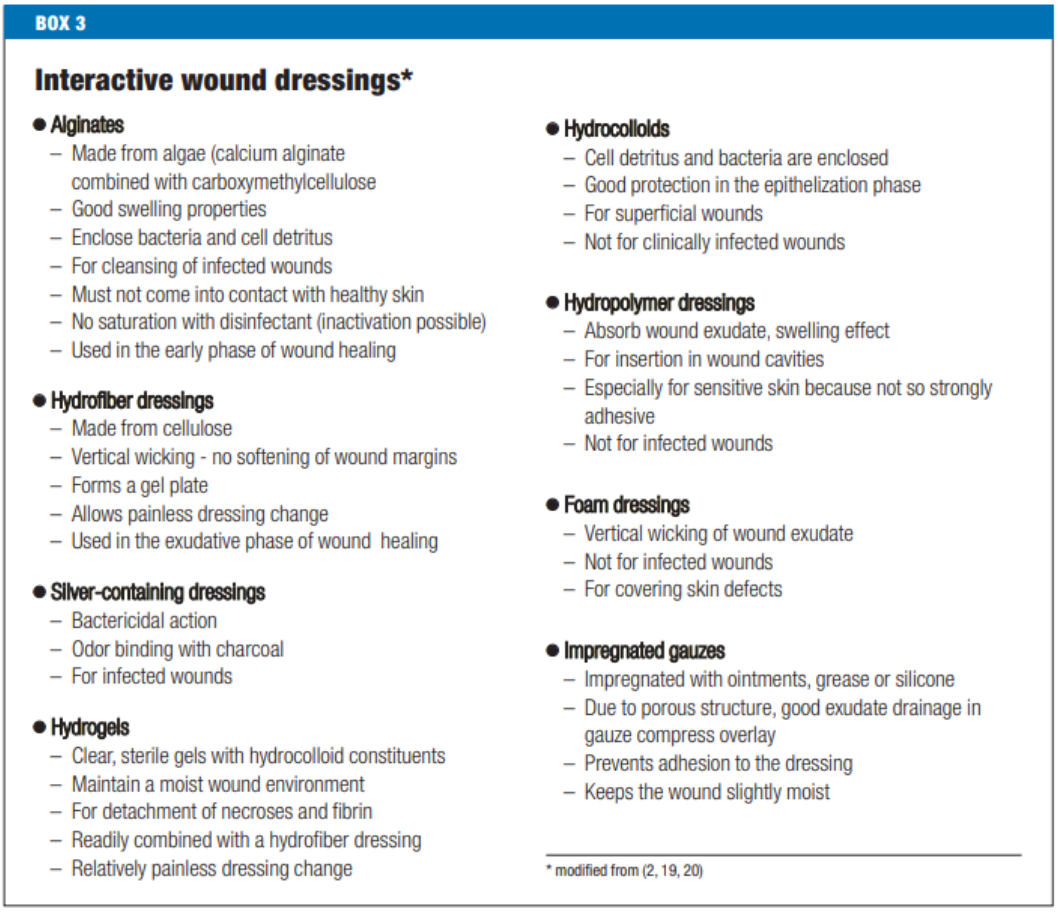
Attachments

A1. Wound dressings advantages



BOX 3

Interactive wound dressings*

- **Alginates**
  - Made from algae (calcium alginate combined with carboxymethylcellulose
  - Good swelling properties
  - Enclose bacteria and cell detritus
  - For cleansing of infected wounds
  - Must not come into contact with healthy skin
  - No saturation with disinfectant (inactivation possible)
  - Used in the early phase of wound healing
- **Hydrofiber dressings**
  - Made from cellulose
  - Vertical wicking - no softening of wound margins
  - Forms a gel plate
  - Allows painless dressing change
  - Used in the exudative phase of wound healing
- **Silver-containing dressings**
  - Bactericidal action
  - Odor binding with charcoal
  - For infected wounds
- **Hydrogels**
  - Clear, sterile gels with hydrocolloid constituents
  - Maintain a moist wound environment
  - For detachment of necroses and fibrin
  - Readily combined with a hydrofiber dressing
  - Relatively painless dressing change
- **Hydrocolloids**
  - Cell detritus and bacteria are enclosed
  - Good protection in the epithelization phase
  - For superficial wounds
  - Not for clinically infected wounds
- **Hydropolymer dressings**
  - Absorb wound exudate, swelling effect
  - For insertion in wound cavities
  - Especially for sensitive skin because not so strongly adhesive
  - Not for infected wounds
- **Foam dressings**
  - Vertical wicking of wound exudate
  - Not for infected wounds
  - For covering skin defects
- **Impregnated gauzes**
  - Impregnated with ointments, grease or silicone
  - Due to porous structure, good exudate drainage in gauze compress overlay
  - Prevents adhesion to the dressing
  - Keeps the wound slightly moist

* modified from (2, 19, 20)