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HYDROGEL FOR WOUND HEALING IN DIABETIC FOOT ULCER

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ABSTRACT

Diabetes-related foot ulcers are a common and significant global health concern. Hydrogel dressings are among the many types of dressings available to clinicians and patients, and they are an essential component of ulcer care. If left untreated, diabetic foot ulcers (DFU), a common and frequently incapacitating consequence of diabetes, can lead to lower limb amputations. Hydrogel dressings are made of three-dimensional networks of hydrophilic polymers, which have been demonstrated to have good fluid management, minimal toxicity, and excellent biocompatibility. They can absorb and retain considerable volumes of water. Moreover, hydrogels facilitate angiogenesis, migration, and proliferation of cells by generating a moist wound environment that aids in wound healing. We will go over the many ways that DFU hydrogels are prepared in detail and also go over the different kinds of hydrogels that are used in DFU research. We also summarize the most important discoveries, point out open issues, and provide a projection for this fascinating field's future growth. Diabetes-related wounds typically have high rates of amputation, recurrence, and mortality. As a result, managing these wounds has become an international responsibility. Diabetes wound care has been greatly aided by wound dressings, which have undergone constant innovation to acquire numerous remarkable qualities. With their significant moisture retention, biocompatibility, and therapeutic qualities, hydrogel dressings have emerged as one of the most appealing and promising types of wound dressings.

KEYWORDS: Diabetic Foot Ulcer (DFU), Hydrogel wound Dressings, Skin Tissue Engineering, Angiogenesis, Tissue Adhesive, Etc.

INTRODUCTION

Diabetes can cause diabetic foot ulcers (DFU), a common, crippling condition that can significantly increase morbidity and mortality.[1-3] It is estimated that 15% of people with diabetes have diabetic foot ulcers, which account for a large percentage of diabetes-related amputations.[4,5] Admittedly, DFU can cause serious side effects such infection, gangrene, or even amputation. Consequently, managing DFU is a difficult undertaking that frequently calls for a multidisciplinary strategy including numerous skilled medical experts skilled in various treatment modalities, such as wound debridement, off-loading, and wound dressings.[5,6]

DFU wound healing is a complicated process that includes multiple overlapping stages, such as renovation, proliferation, and inflammation. By generating a moist wound environment that encourages tissue regeneration, absorbs excess exudate, lowers inflammation, stops infection, and shields the wound from additional harm, wound dressings are essential to the care of diffuse focal wounds (DFU).[4,8,9] The choice of wound dressings for diabetic foot ulcers is typically based on the ulcer's severity and healing stage. However, the majority of existing wound dressings have significant drawbacks, including inadequate wound bed preparation, poor moisture management, limited antimicrobial activity, and insufficient capacity to stimulate healing. These deficiencies highlight the need for more sophisticated and potent wound dressings that can effectively address these pressing DFU concerns. Hydrogel dressings have shown great promise in the treatment of DFUs because of their superior moisture-retaining capabilities and biocompatibility.[13–15] Hydrogel dressings are made of networks of three-dimensional water-absorbing polymers that are able to retain a lot of water and keep the environment surrounding the wound moist. Through encouraging angiogenesis, lowering inflammation, and facilitating cell migration, this moist environment aids in the healing of wounds. Hydrogel dressings minimize the possibility of harm to the wound bed because they are non-adherent and offer a soft, painless removal process. Additionally, because they may include antibacterial compounds, they may serve as a barrier against bacterial infection.[13,15–17] Hydrogel dressings can also be customized to match the exact dimensions and form of the wound, and their qualities can be improved by combining them with different wound dressings. Hydrogel dressings have numerous advantages, but

they also have certain drawbacks, like the requirement for regular changes because they might get saturated with exudate and the possibility of the surrounding skin becoming macerated.[18,19]

Hydrogel therapy has been widely recognized as an effective wound management method, and various types of hydrogels are presently accessible. The best hydrogel therapies for chronic diabetic wounds are difficult to evaluate because the effectiveness of various compositions has not yet been determined and compared. Furthermore, hydrogels have potential applications in drug administration and wound healing optimization. We conducted a scoping study to define the existing use of hydrogels and find evidence for their safety and efficacy in the treatment of diabetic wounds.

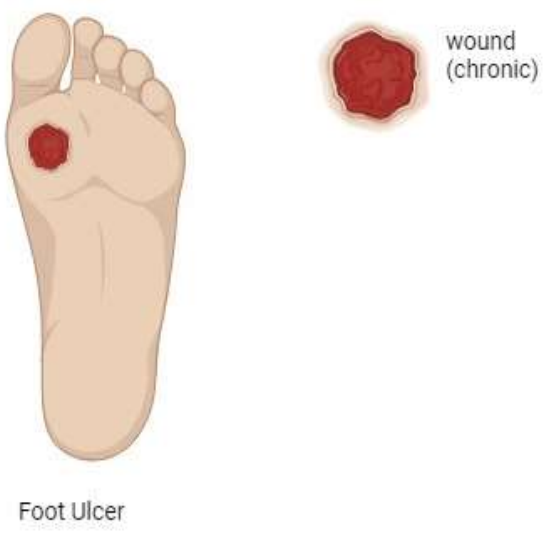

Figure No. 1: Figure showing Foot Ulcer.[1]

The typical healing process is interfered with in DFUs (Figure 1), resulting in diseases requiring ongoing care.[20] As a result, the diabetic patient's wide spectrum of metabolic dysfunction lead to inadequate lesion repair, which is mainly caused by decreased production of chemokines and pro-angiogenic growth factors. Furthermore, metalloproteinases (MMPs) are produced at a higher rate in chronic wounds, which leads to an abnormally prolonged inflammatory phase and inadequate re-epithelialization and remodeling. In certain cases, this excessive eroding of the extracellular matrix even induces senescence. Moreover, MMPs prevent growth factors from doing their job, which hinders angiogenesis and reduces tissue oxygenation, leaving the wound hypoxic and open for eternity. Consequently, pathogenic infections are more likely to occur in exposed wounds, and infections increase as a result of

hyperglycemia's impaired ability to stimulate phagocytosis. When all these elements come together, the patient's health problems get much worse.[18,19,21] Tissue engineering techniques have made it possible to create hydrogel-based systems that serve as scaffolds for healthy cell interactions and fill the wound with bioactive substances that encourage re-epithelialization, reduce inflammation, hasten healing, and enhance scar formation in response to this challenge.[22,23]

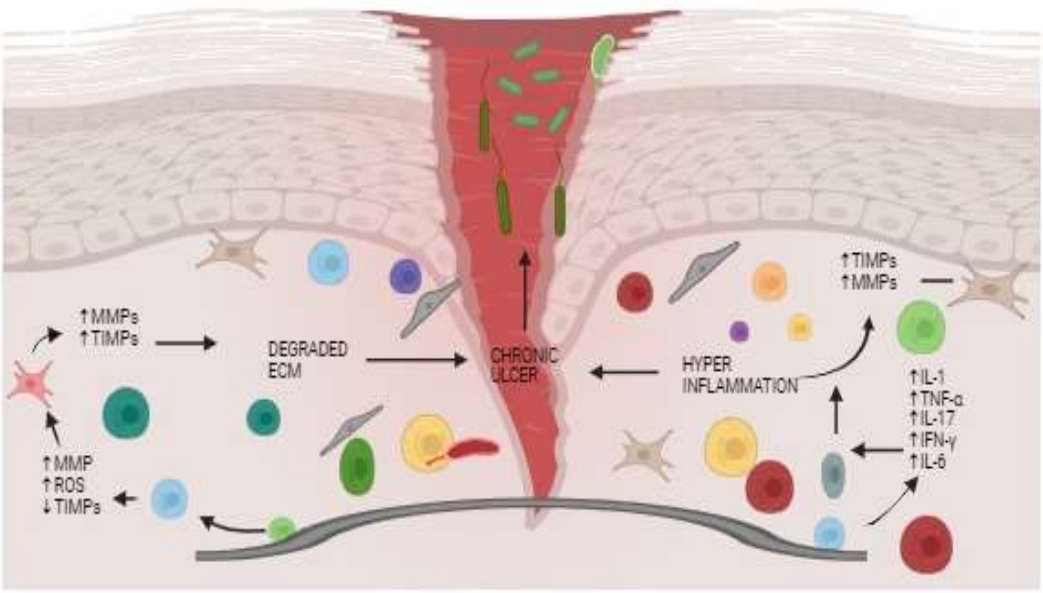

Figure No. 2: Figure showing Hyper inflammation in Chronic Ulcer.[2]

OBJECTIVE

To evaluate the impact of hydrogel wound dressings on the healing of diabetic foot ulcers in comparison to other dressings or no dressing at all.

Hydrogels can promote angiogenesis by releasing growth factors, such as vascular endothelial growth factor and fibroblast growth factor. Additionally, some hydrogels have intrinsic antibacterial activity, which can prevent infections and improve wound healing.

MATERIALS

Pluronic®F127 (poloxamer-407, P_{407}, Mn = 12,600) was purchased from BASF Korea (Seoul, Korea). Hydrogenated soybean phospholipids (HSPC) and 1,2-ctadecanoyl-sn-glycero-3-phophocholine (DSPC) were both purchased from Avite Pharmaceutical Technology Co., Ltd. (Shanghai, China). Tert-butyl alcohol was purchased from XiLong Science Co., Ltd. HUVECs and NIH/3 T3 cells were provided by Shanghai Zhong Qiao Xin

Zhou biotechnology Co., Ltd.; DAF-FM DA was purchased from YEASEN (Shanghai, China); Growth.

Preparation

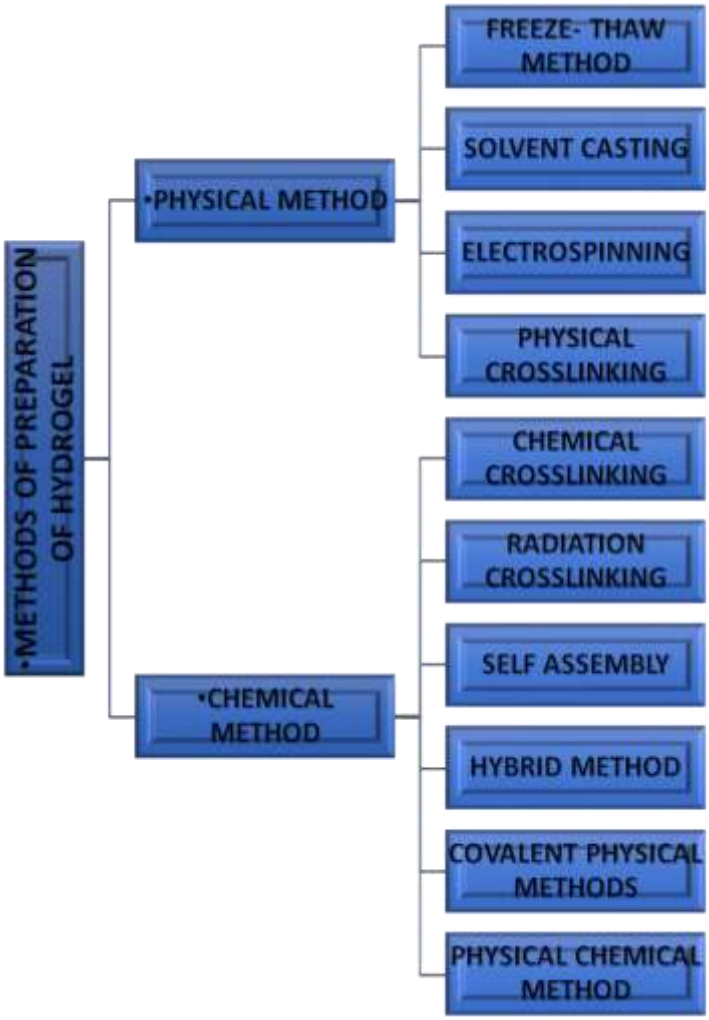

Figure No. 3: Method of Preparation of HYDROGEL.[3]

1. Physical Method

1.1 Freeze-Thaw Method

Freeze-thaw preparation is a physical technique that entails repeatedly freezing and thawing a polymer solution in order to prepare hydrogels. The production of the polymer solution, freezing the solution, and thawing the frozen solution are the general steps involved in the freeze-thaw process.[61] Ice crystals are created when the polymer solution is repeatedly frozen and thawed; these crystals serve as physical crosslinks between the polymer chains. It is through this physical crosslinking that a hydrogel with a three-dimensional network structure is created.

A physical method called "freeze-thaw preparation" is used to create hydrogels by periodically freezing and thawing a polymer solution. The general steps in the freeze-thaw process are creating the polymer solution, freezing the solution, and thawing the frozen solution.[61] When the polymer solution is repeatedly frozen and thawed, ice crystals are formed; these crystals act as physical crosslinks between the polymer chains. A hydrogel with a three-dimensional network structure is produced by this physical crosslinking.

1.2 Solvent Casting

A physical method for creating hydrogels is called "solvent casting," which entails pouring a polymer solution into a mold, letting the solvent evaporate to create a hydrogel, and then, for some kinds of hydrogel, going through additional crosslinking.[64] Hydrogels with a thin film or sheet-like morphology that are easily applied to the wound site are frequently made using this technique.

By varying the concentration of the polymer solution and the casting conditions, solvent casting is a straightforward and adaptable technique for creating hydrogels that may be used to create hydrogels with precise characteristics like thickness, porosity, and mechanical strength.[53] Hydrogels can be made with this technique from a variety of polymers, including synthetic and natural polymers like PVA and PEG as well as natural polymers like collagen and chitosan.

1.3 ELECROSPINNING

A high voltage is given to a polymer melt or solution during the electrospinning process, causing a fine jet of polymer fibers to emerge. These fibers are then collected on a collector to form a fibrous hydrogel substance. The production of the polymer solution, the electrospinning of the solution, and the gathering of the fibers on a collector are among the crucial processes in the process.[65,66]

A variety of polymers, including synthetic, natural, and hybrid polymers, can be utilized to create hydrogels by the electrospinning method. The hydrogel fibers can then be changed to include additional components, including pharmaceuticals or nanoparticles.

1.4 PHYSICAL CROSSLINKING

Another technique that's frequently utilized to prepare hydrogels for use as wound dressings is physical crosslinking. Physical crosslinking does not require the application of a

crosslinking agent, in contrast to chemical crosslinking. Rather, in order to create a stable three-dimensional structure, physical crosslinking depends on non-covalent interactions between the polymer chains in the hydrogel network.

2. CHEMICAL METHODS

2.1 Chemical Crosslinking

Hydrogels are frequently prepared via chemical crosslinking for use as wound dressings. In order to create a stable, three-dimensional structure, this approach links the polymer chains in the hydrogel network using a crosslinking agent.[43,70] There are several ways to do chemical crosslinking, including as ionically induced crosslinking, covalent bonding, and physical adsorption.

2.2 Radiation crosslinking

Another promising material for use as wound dressings is radiation crosslinked hydrogel. This plan uses high-energy radiation, such electron beams or gamma rays, to cause the polymer chains in the hydrogel network to crosslink.[60] High-energy radiation enters the hydrogel matrix during radiation crosslinking, interacts with the polymer chains, and creates free radicals.[74] A stable, crosslinked hydrogel is the end product of these free radicals' subsequent reactions with nearby polymer chains, which create covalent bonds. The polymer concentration and radiation dose can be changed to modify the degree of crosslinking.

Many hydrogels, such as poly (vinyl alcohol), chitosan, and gelatin-based hydrogels, have been prepared for use as wound dressings using radiation crosslinking.[76] These crosslinked hydrogels are potential options for wound healing applications since they have shown good mechanical and biocompatibility qualities.

Furthermore, upon crosslinking, leftover radiation may remain in the hydrogel and create possible health hazards. For this reason, it's critical to monitor the radiation dosage closely and make sure the hydrogel is completely cleaned and sterilised following the crosslinking process.

2.3 Self-assembly method

A novel technique for producing hydrogels for use as wound dressings is self-assembly. This process is predicated on the hydrogel's constituent parts, such as peptides or polymers,

spontaneously organizing into a stable three-dimensional structure via non-covalent interactions.

(A) - Supramolecular assembly

A self-assembling hydrogel that is enzyme-reinforced and injectable for the treatment of diabetic wounds. Insulin-loaded self-assembled aldehyde Pluronic F127 micelles and ε-polylysine (EPL)-coated MnO2 nanosheets underwent a reversible Schiff-based reaction to create the injectable multifunctional hydrogel. This hydrogel breaks down the large ROS (H2O2) into O2, shielding fibroblasts from oxidative damage. Together, the positively charged EPL and the pointed MnO2 nanosheets that resemble nanoknifes enhance wound healing in vivo, expedite hemostasis, and provide effective antibacterial activity. Used by permission.[77] American Chemical Society (ACS) Copyright 2020.

In order to create stable and well-organized structures, supramolecular assembly makes advantage of non-covalent interactions like hydrophobic, electrostatic, and hydrogen bonding interactions.[43] Typically, low molecular weight substances that enable self-assembly into a network, like peptides or tiny organic molecules, make up supramolecular hydrogels.

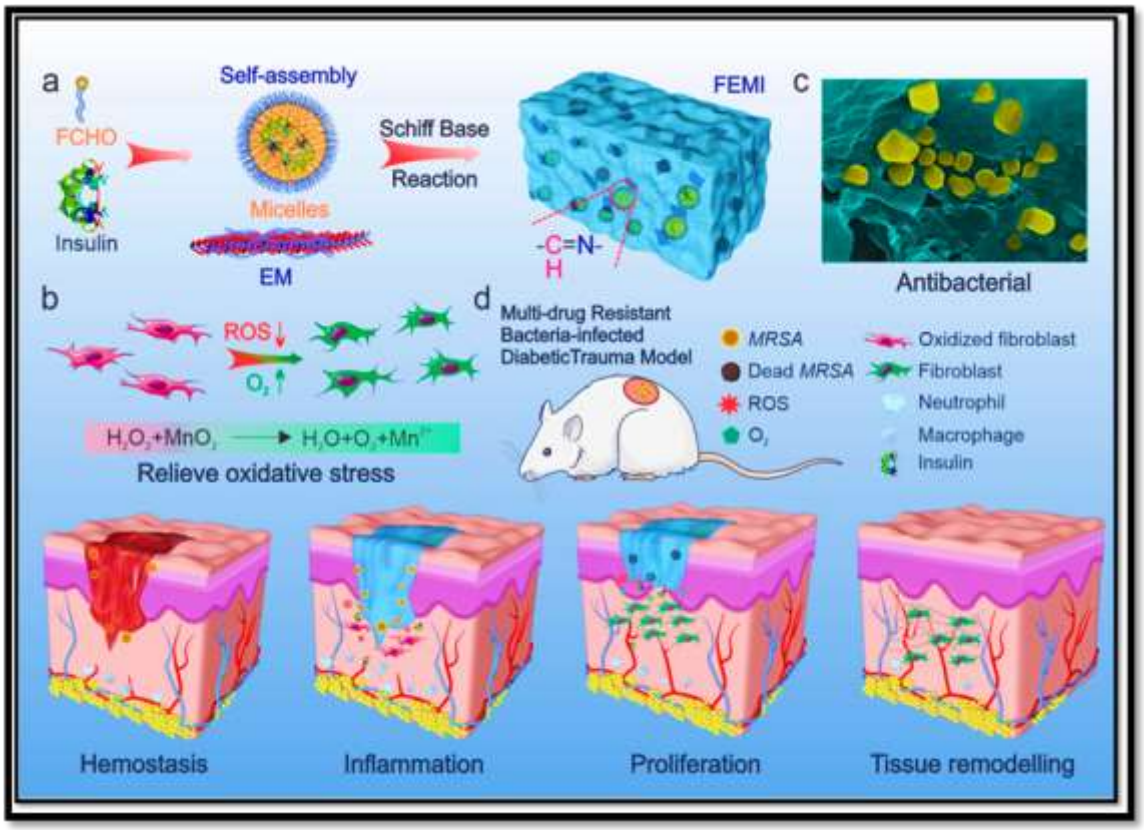

Figure No. 4: Tissue Remodelling.[4]

(B)- Phase Separation

Phase separation, sometimes known as coacervation, is the process of dividing a polymer solution into two independent phases: a solvent-rich dilute phase and a polymer-rich dense phase.[78,79] Using physical or chemical crosslinking agents, the polymer-rich phase can create a stable, crosslinked hydrogel structure.

Self-assembled hydrogels provide a number of benefits over conventional crosslinking techniques. These hydrogels can be made with easy, low-cost methods, and they are frequently designed to have particular biological characteristics, such improved cell adherence or regulated drug release. Specifically, self-assembled hydrogels have been applied to various wound dressings. Self-assembling peptide hydrogels, for instance, have been demonstrated to facilitate tissue regeneration by supplying a wet environment that encourages cell adhesion and proliferation, as well as wound healing.

2.4 Hybrid methods

Hydrogels are prepared using hybrid procedures, which combine physical and chemical techniques. Hybrid techniques can be applied to get hydrogels with better qualities and get around the drawbacks of single techniques.

2.5 Covalent physical hybridization

Covalent physical hybridization is a technique that combines the benefits of physical crosslinking techniques, which serve as a secondary function, and covalent crosslinking techniques, which play a key role, in the preparation of hydrogels for use as wound dressings.[82] In this technique, physical crosslinking agents like thermally or ionically reversible crosslinkers are combined with covalent crosslinking agents/methods like radiation or chemical crosslinkers. When both kinds of crosslinking agents are used together, hydrogels with better wound-healing capabilities can be produced.

Covalent crosslinkers create permanent crosslinking points that stabilize the hydrogel structure, while physical crosslinkers provide transient crosslinking points that keep the polymer chains together in covalent physical hybridization. It is possible to create hydrogels with enhanced mechanical characteristics, stability, and response to external stimuli by combining the two types of crosslinking agents.

For usage in wound dressing applications, covalent physical hybridization has been employed to create a range of hydrogels, such as chitosan- and poly(N-isopropyl acrylamide)-based hydrogels. When compared to hydrogels made just via chemical or physical crosslinking, these hydrogels have shown better mechanical qualities and biocompatibility. Creating hydrogels by combining chemical crosslinkers like genipin or glutaraldehyde with reversible physical crosslinkers like β-cyclodextrin is a further instance of covalent physical hybridization. Using this technique, the chemical crosslinkers create long-lasting covalent crosslinks between the polymer chains, while the β-cyclodextrin creates transient physical crosslinks by forming inclusion complexes with the hydrophobic groups on the polymer chains.[83]

All things considered, covalent physical hybridization presents a viable method for creating hydrogels with enhanced qualities for use as wound dressings. To guarantee that the produced hydrogel has the appropriate qualities for its intended purpose, careful optimization of the crosslinking agents and conditions is required.

2.6 Physical chemical hybridization

The physical-chemical hybridization method combines chemical and physical crosslinking techniques to generate hydrogels. Physical crosslinkers are used in physical-chemical hybridization prepared hydrogels, which differ from those made using covalent physical hybridization. Their primary function is to provide temporary crosslinking points that hold polymer chains together, while their secondary role is to form permanent crosslinking points that stabilize the hydrogel structure.[84] Even though covalent physical hybridization and physical chemical hybridization are just slightly different from one another, the hydrogels produced using each technique typically have very different characteristics.

This technique has been used to create a number of hydrogels, such as chitosan and gelatin-based hydrogels, for use as wound dressings. When compared to hydrogels made just via chemical or physical crosslinking, these hydrogels have shown better mechanical qualities and biocompatibility. For instance, specific hydrogels have been created by combining a chemical crosslinker, such as N, N′-methylene bisacrylamide (MBAA), with a pH-sensitive physical crosslinker, like poly (acrylic acid) (PAA). In this work, the chemical crosslinker creates long-lasting covalent crosslinks between the polymer chains, while the PAA, via its pH-sensitive swelling activity, generates transient physical crosslinks.[85] A viable method for

creating hydrogels with better qualities for use as wound dressings is physical-chemical hybridization.

Explanation and Intervention

Diabetic foot ulcers are generally treated with wound dressings, infection control, debridement (removing dead cell material from the wound surface), pressure relief (or off-loading) by resting the foot or using special footwear or shoe inserts (or both). Additional basic approaches to treating diabetic foot ulcers include: educating patients; optimizing blood glucose control; correcting arterial insufficiency when feasible; and performing surgical procedures (debridement, pus drainage, revascularization, amputation).

In order to shield the wound and encourage healing, dressings are frequently used in wound care procedures. A dressing's classification is often determined by the primary component utilized. According to the BNF (2010), the perfect wound dressing should include a number of characteristics, such as:

The dressing's capacity to absorb and confine exudate without leaking or causing strike-through; the absence of particulate contaminants left in the wound by the dressing
Its thermal insulation;
Its permeability to water and bacteria;
The prevention of wound trauma during dressing removal;
The frequency of dressing changes; the pain relief and comfort it provides.

Simple dressings for wound contact Low-adherence dressings and materials for wound contact are often cotton pads applied directly onto the wound. They can be medicated (containing povidone iodine or chlorhexidine, for example) or non-medicated (paraffin gauze dressing). Examples include BP 1993, Xeroform (Covidien) dressing, which is a non-adherent petrolatum blend over fine mesh gauze containing 3% bismuth tribromo-phenate, and paraffin gauze dressing.

Absorbent Dressing

Absorbent dressings can be used topically on wounds that are actively shedding fluid, or they can be utilized as secondary absorbent layers.

Sophisticated bandages Hydrogel sheets and amorphous dressings are composed of up to 96% water and cross-linked insoluble polymers, such as starch or carboxymethylcellulose.

Depending on the moisture content of the wound, these dressings are intended to rehydrate the wound or absorb wound exudate. They come in three different forms: beads, amorphous hydrogel, or flat sheets.

Permeable Film and Membrane Dressing

Permeable to water vapour and oxygen but not to water or microorganisms. It is also called as vapour film dressing.

Vapour-permeable coverings and coatings help preserve delicate granulation tissue and provide a wet wound bed. They permit oxygen and water vapor to pass through, but not liquid water or microorganisms. They also permit wound observation to occur without interfering with the wound's ongoing healing process. They work well on wounds with little exudate.

Soft polymer dressings

Dressing includes soft silicon polymer that held in a non-adherent film.

They are moderately absorbents.

Hydrocolloid dressings

These are occlusive dressings that typically consist of a hydrocolloid matrix adhered to a foam backing or vapour-permeable membrane. This matrix creates a gel upon contact with the wound surface, creating a moist environment**.** Examples are: Granuflex and NU DERM (Systagenix).) and NU DERM (Systagenix).

Foam Dressing

Often made of hydrophilic polyurethane foam, which is intended to absorb wound exudate and keep the wound surface moist. There are other variations of foam dressings that are silicone-coated for non-traumatic removal, or that contain extra absorbent materials like viscose and acrylate fibres or particles of superabsorbent polyacrylate.

Alginate Dressings

Extremely absorbent; they can be mixed with collagen and are available as calcium sodium alginate or calcium alginate. When the alginate comes into touch with the wound surface, it turns into a gel that can be removed with a dressing or washed away with sterile saline. A supplementary viscose pad bond improves absorbency.

The soft, non-woven fibres of an alginate dressing are made of a polysaccharide that resembles cellulose and is obtained from the calcium salts found in seaweed.[26] They are very absorbent, non-adherent, hydrophilic, and biodegradable. This type of dressing forms a hydrophilic gel as a consequence of the production of a soluble sodium salt upon contact between wound exudate and its insoluble calcium alginate.

Examples are: Algiderm (Bard); Algisite (Smith & Nephew); Algisorb (Calgon-Vestal, St Louis, MO); Algosteril (Johnson & Johnson Medical); Kaltostat (ConvaTec); Curasorb (The Kendall Company); Carasorb (Carrington Lab); Dermacea (Sherwood Medical Co, St Louis, MO)

Iodine -Impregnated Dressings

Release free iodine in response to wound exudate; this process is believed to function as an antibacterial for wounds. One instance is Iodozyme.

Silver-impregnated dressings

Due to its antibacterial property silver ion is used in treatment of infected wound. (e.g. silver foam, silver hydrocolloid etc).

Specialist dressings

Protease-modulating matrix dressings: modify the proteolytic enzyme activity in long-term wounds.

When choosing the appropriate course of therapy for a patient, doctors are faced with a variety of dressing options, some of which vary even within the categories mentioned above, making evidence-based decision-making challenging. A variety of therapies were reported in a UK survey conducted to ascertain the methods used to debride diabetic foot ulcers (Smith 2003).

Regarding clothing choice, it's probable that a similar situation applies. Despite the lack of evidence supporting either of these dressing types, a study of diabetes specialist nurses revealed that low/non-adherent dressings, hydrocolloids, and alginate dressings were the most commonly used for all types of wounds (Fiskin1996). But in recent years, a number of novel dressing options have been introduced and actively marketed. Nowadays, several dressings are marketed as dressing treatment choices that decrease infection and may thus also assist healing. One such element is silver. As more advanced technology is used for wound care,

clinicians must understand the effectiveness of these very costly dressings in comparison to more conventional dressings.

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