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Atopic Dermatitis and Wound Management

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ABSTRACT
Wound treatment not only places a heavy strain on patients and their families, but it also substantially raises the cost of healthcare in a nation. Although there are several therapeutic options, they often lack perfection. Hydrogels, three-dimensional polymeric materials that may maintain structural integrity after rapidly expanding, are gaining attention due to their potential as topical wound therapy treatments, both in the form of films and as drug delivery vehicles. This interest is mostly driven by their unusual properties, such as high water content, biocompatibility, and flexibility. Drug delivery applications are especially well suited for hydrogels because they can be engineered to react to specific stimuli like pH, temperature, and light. In this article, we'll quickly go through the background and characteristics of hydrogels, assess how well they work for administering medications and healing wounds, and make some comparisons with other widely utilised drug delivery methods. Both the patients' and their families' financial burdens as well as the nation's healthcare system are significantly increased by the expense of wound care. Although there are many different therapy modalities accessible, they often fall short of providing the most efficient treatment. The potential of hydrogels, three-dimensional polymeric materials that can withstand substantial swelling without losing their structural integrity, to heal wounds has attracted a lot of interest. High water content, biocompatibility, and flexibility are just a few of their special characteristics that make them perfect drug delivery vehicles. They are accessible as films. Whether created synthetically or naturally, hydrogels may be precisely tailored to respond to certain triggers like pH, temperature, and light, making them ideally suited for drug delivery applications. In this review, we examine the origins and properties of hydrogels, consider how they might be used to treat wounds and distribute drugs, and compare them to other popular drug delivery methods.

I. INTRODUCTION

Human skin's complex construction serves two purposes: it protects the body's interior organs, which are both essential for existence, and functions as a powerful barrier against outside dangers. The skin is always at risk of injury, from physical trauma that might cut, shatter, or otherwise impair one or more skin layers to environmental variables like UV radiation.[1] Untreated skin wounds have the potential to become infected, which may exacerbate local tissue damage, cause systemic inflammation, and even result in life-threatening immunological reactions like sepsis. As a result, the host's general health is greatly influenced by the wound healing process.[2]

The growth and maturation of cells, cellular proliferation, inflammation, hemostasis of granulation tissue are only a few of the diverse but connected aspects of the complex and speedy process of wound healing. While certain animals, Mammals, including humans, have a hard time fully regenerating skin, even though fish and amphibians have shown this ability.[3] This is particularly true when the damage is extensive. Loss of skin apex structures like hair follicles and scarring, which are crucial for basic skin functions including feeling, are often side effects of human wound healing. There may be disruptions Despite the fact that the majority There are still certain factors that lead to chronic wounds, such as pressure ulcers, diabetic leg and foot ulcers, and infected wounds, even when wound healing conditions are effective in the sense that the process is complete and the dermal layers are restored.[4] This reinstates the skin's fundamental ability to retain moisture and keep infections at bay. Chronic wounds, or wounds that do not heal using the standard phases, remain inflamed, which puts an even greater strain on the patient, their family, and society as a whole. The yearly cost of treating chronic wounds is estimated to be over AUD$2.85 billion in Australia alone.[5]

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To treat wounds, a range of strategies are used, including bandages, dressings, surgical procedures, and precise medication administration using customised carriers (see [11] for a recent thorough assessment of wound therapy strategies).[6] Due to their outstanding qualities, such as biocompatibility, These tailored carriers in Because of their high water content and flexibility, hydrogels have drawn a lot of attention from the medical and pharmaceutical wound care sectors. In order to provide a clear overview of hydrogels and their applications, this research for administering medications and treating wounds, as well as their benefits over more traditional drug delivery methods.[7]

A Brief Research History of Hydrogels

Three-dimensional polymeric matrices called hydrogels have a strong attraction for water, which allows them to absorb water and expand without disintegrating .[8] A three-dimensional network of naturally occurring gums and hydrophilic polymers was first envisioned as a proto-hydrogel as early as 1894. However, Wichterle and Lim didn't characterise hydrogels using important characteristics like biocompatibility and a strong water-attracting nature until 1960.[9] Since then, the study of hydrogels has become more important, with almost exponential growth in publications beginning in the 1990s.[10] The development of hydrogels into the incredibly adaptable materials we have today is to blame for this rise in interest.[11]

Three separate stages of the creation of a hydrogel are described by Buwalda and colleagues. Building on the fundamental idea of Wichterle and Lim, the first phase's goal was to create a very basic material with acceptable mechanical and swelling properties the 1970s marked the start of the second phase, saw the introduction of increasingly complicated hydrogels that could react in a customised manner to triggers like temperature and pH.[12] During the third and In the last stage of hydrogel production, supramolecular inclusion complexes with exceptional biocompatibility and flexibility were used. a supramolecular hydrogel that may be specifically designed to react to a range of different stimuli, such as temperature and pH or electrical fields, serves as an example, may be produced by a complex formed by Polyethylene Glycol (PEG) and -cyclodextrins. The third stage in the evolution of hydrogels gave birth to "smart hydrogels." These materials have a wide range of adaptable qualities and a variety of possible uses.[13]

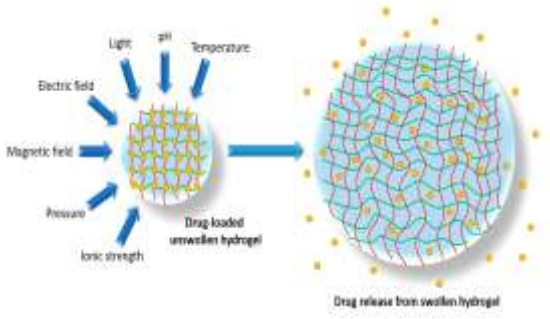

Fig 1. Swelling of a drug delivery

Hydrogel Classificatio

Hydrogels can be categorized based on several attributes, including their source (natural, artificial, or a mix of both), the nature of their side groups in polymers (ionic or non-ionic), the method of cross-linking (chemical or physical),14 and their receptivity to different chemical and physical stimuli, among other factors (as illustrated in Figure 2). In the subsequent two sections, we will provide a concise overview of hydrogel classifications and delve into their physical and mechanical characteristics.[15]

First, natural hydrogels, which are usually made comprises protein chains like collagen or polysaccharide chains like chitosan, cellulose, and hyaluronic acid, are distinguished into three main types. The second category is artificial hydrogels, which are made of polymers like Poly(acrylamide) with poly(ethylene glycol).Threeteenth, hybrid hydrogels, which combine synthetic and natural polymers. Hydrogels may be divided into two categories: natural and synthetic, each of which has benefits and cons.[17]

Natural Hydrogel

Since they are essential parts of the Extracellular Matrix (ECM), natural hydrogels are highly acclaimed for their remarkable biocompatibility.[18] Examples of such hydrogels include gels composed of hyaluronic acid, fibrin, and MatrigelTM, which was created from an extract of the basement membrane from Engelbrecht-Holm-Swarm (EHS) murine sarcoma cells. MatrigelTM, a popular natural hydrogel matrix, closely mimics the in vivo basement membrane since it contains type IV collagen, laminin, and nidogen.[19] Hydrogels known as fibrin gels have a long history of usage in promoting wound healing because they are made from the blood clotting proteins thrombin and fibrinogen. There are several applications for hyaluronic acid-based hydrogels in tissue engineering and

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regenerative medicine because they can adjust to different chemical, mechanical, and spatial signals.[20]

Natural hydrogels, although being very biocompatible, have drawbacks because of their organic origins. Since it may be difficult to regulate these factors across studies, the inherent natural variability between batches presents a problem.[21] Natural hydrogels' reliance on the original substance also limits their ability to be translated. Additionally, the origin of the hydrogel itself restricts the translational potential of natural hydrogels.[22]

Synthetic hydrogel

Given that they are manufactured matrices, synthetic hydrogels provide an alternative to natural hydrogels devoid of the limitations that natural hydrogels may incur due to their organic origins. Notable examples include Poly (Ethylene Glycol), commonly referred to as PEG, which stands as one of the synthetic hydrogel materials that is used the most commonly.[23] PEG is preferred for its biological inertness and potency in preventing cell attachment, protein adsorption, and bacterial adherence. With structures that can be accurately regulated, synthetic hydrogels have improved repeatability, enabling more flexibility in fine-tuning their chemical and mechanical properties.[24] Synthetic hydrogels often have more mechanical integrity; for example, a hydrogel made of slide-ring polymers may stretch more than 10 times its initial length. Nevertheless, it's essential to recognize that despite their engineered mimicry of biological tissues, synthetic hydrogels, originating from non-natural sources, may not offer the same level of biocompatibility. They often lack the capacity for self-healing seen in biological tissues.[25]

Hybride hydrogel

Hybrid hydrogels, belonging to the third hydrogel category, employ a combination of using both organic and synthetic polymers, combining their advantages.[26] This fusion facilitates the attainment of mechanical robustness akin to synthetic non-natural hydrogels, while still preserving the biocompatibility and recovery attributes characteristic based on organic hydrogels.[27] For instance, by adding cross-links using multi-armed PEG stars with esters on the termini, natural collagen or extracellular matrix-based hydrogels may be strengthened. These esters interact with the protein's amine residues to create a hybrid hydrogel that has the same biochemical cues as a natural hydrogel while also having a strong synthetic framework. Due to PEG's inert properties, biological signals are retained.[28]

The properties of Hydrogel

Physical properties

Given that hydrogels are polymeric matrices that swell when exposed to water, a hydrogel's usefulness is greatly influenced by the properties of the water it contains. The most polar and hydrophilic groups engage first with the water molecules when a dry hydrogel first absorbs water, becoming hydrated. This process is known as "primary bound water".[29] 'Secondary bound water' is created when the hydrophobic groups in these groups interact with water molecules after they have been hydrated. Total bound water is the term used to describe the mixture of primary and secondary bound water. Additional water is absorbed by the hydrogel due to osmotic pressures, but any further structural expansion is resisted by covalent or physical crosslinks, resulting in an equilibrium amount of swelling.[30] The centre areas of bigger pores or the gaps between network chains are thought to be where this extra water, known as "free" water, occupies.[31]

Mechanical Properties

The ability of hydrogels to modify their mechanical properties in accordance with particular needs accounts for a major portion of their adaptability in a variety of applications. For instance, heating may make the hydrogel structure less stiff, whilst increasing crosslinking can make it stiffer.[32] Additionally, by altering the degree of crosslinking in the hydrogel matrix, the pores inside a hydrogel's structure—which are in charge of absorbing extra water after it reaches a swelling equilibrium—can be made larger or smaller.[33] Traditional hydrogel constructions often become fragile when swelled, however new research shows that hydrogels' capacity to absorb large amounts of water does not always affect their toughness. The noteworthy adaptability of hydrogels' mechanical characteristics has sparked intense attention in the fields of medication delivery and wound healing.[34]

Hydrogels and Healing Wounds

As has previously been mentioned, wounds, particularly chronic wounds, have a significant negative impact on the patients, their families, and the economy. Wound dressings and topical medication formulations are only two of the treatments that may be used to treat wounds.35

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Jones and colleagues claim that the ideal wound dressing should be cosy, permit gaseous exchange, maintain high humidity at the site of the wound, allow for the removal of excess exudate, be able to keep the area free of debris and dangerous materials, be removable without causing further harm, be impermeable to bacteria, and only need to be changed infrequently.36 However, the majority of wound care techniques fall short of fulfilling each of these demands. For example, although bandages and dressings are useful in preventing wound infections, they also need to be changed often and are inefficient at reducing excessive exudate, maintaining a moist environment, or enabling trauma-free removal.37

However, hydrogel-based treatments provide a more alluring approach to wound healing. Because they are both mechanical and hydrophilic, they may retain a lot of water at the location of the wound, preventing the polymer from dissolving.38 It is simpler for bioactive compounds, such as antimicrobials and therapeutic drugs, to enter the wound thanks to the closely knit structure of hydrogel matrices, whereas bacterial penetration is effectively blocked.39 Additionally, compared to bandages, gauze, or non-hydrogel films, hydrogels have less of an adhesion to extremely hydrophilic surfaces like wounds. This considerably lowers the risk of injury brought on by dressing changes. These options attach to the wound because they are either low-adherent or inadequate for maintaining a constant moist environment.[40] The ability of hydrogels to Its most impressive characteristic may be its ability to reversibly absorb and release water in response to external conditions like temperature and light.[41]

Studies employing a variety of animal models have highlighted the potential of hydrogels in speeding up wound healing. It was revealed that a mouse model of diabetic ulcers temperature-sensitive hydrogel containing BSMC suppressed pro-inflammatory M1 macrophage production and greatly improved wound contraction and healing. In a mouse model of diabetic ulcers, discovered that an integrin-binding prosurvival peptide was present in Angiopoietin-1 hydrogel made of chitosan and collagen promotes faster wound healing. A poly(vinyl alcohol)/chitosan hydrogel containing bee venom accelerated wound healing in diabetes-related mice models and had an anti-inflammatory activity comparable to that of the commonly used nonsteroidal anti-inflammatory medication, diclofenac gel. Epithelialization, collagen production, and wound size were all dramatically raised by a bi-layered wound dressing made of a non-adhesive wax-coated silk fibroin fabric layer and a glutaraldehyde-crosslinked silk fibroin/gelatin bioactive layer in a full-thickness wound model, according to Kanokpanont and colleagues reduction compared to a clinically used wound dressing. In a different research, animals with full-thickness excision wounds treated with an ultrashort peptide hydrogel containing cysteine recovered more quickly than controls.[42]

Hydrogels containing medicinal substances have also shown promising outcomes. An thermosensitive hydrogel with continuous curcumin release treated a rat model of wound infection., for instance, healed wounds more quickly than gauze and shown antibacterial, qualities that are anti-nuclear and anti-oxidative.[43] A similar but improved tissue-targeting thermosensitive hydrogel filled with curcumin adhesion and sustained curcumin release promoted wound maturation and improved wound healing. Furthermore, in a mouse model, persistent administration using an alginate hydrogel vehicle to deliver the angiogenic chemokine stromal-derived factor-1 significantly decreased wound area and increased endothelial cell penetration into the wound bed. Simvastatin-chitosin microparticles placed into poly(vinyl alcohol) hydrogels at an ideal low dosage dramatically enhanced wound healing in rats when compared to controls.[44]

Because of their versatility, hydrogels provide ideal delivery vehicles for antibiotics used to treat infected wounds. Despite having a lengthy history of usage The reactivity of the silver broad-spectrum antibiotic in the treatment of illnesses has often made it difficult to incorporate silver into delivery systems. A soft agar hydrogel that has been loaded with silver was shown by Pinto et al. to be useful in treating skin and soft tissue infections, making it a more workable, stable, and controllable substance. Similar results were seen with Laçin's Due to its biodegradability, biocompatibility, and antibacterial qualities, 2,3-dialdehyde cellulose hydrogel loaded with chloramphenicol was a great candidate for wound healing. In comparison to a cellulose control, it displayed greater fibroblast adhesion and proliferation as well as sustained antibacterial properties.[45]

Beyond their efficacy, hydrogels' promise in wound healing goes beyond that of other methods in that they address issues like cost and usability. In addition to speeding up wound closure, a user-friendly delivery approach that avoided the

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high cost and handling challenges related with the application of thin sheets of living cellularized tissue, a favoured treatment technique, was revealed to be a hyaluronic acid-based hydrogel incorporating solubilized amnion membrane.[46]

Drug Delivery Using Hydrogels

Due to their unique qualities, hydrogels are gaining more and more attention as adaptable drug delivery vehicles. By changing how many cross-links are there in their matrix structure, their high porosity, which enables drug loading and release, may be further enhanced. As a result of controlling diffusion and swelling as well as computer programmes that react to environmental cues like pH or temperature, hydrogels have the unique benefit of maintaining drug delivery.[47]

Hydrogels are effective delivery systems for proteins and peptides, especially those with short half-lives due to their flexibility. For instance, adding a medication to PEG may make it more difficult for the drug to pass through the kidneys, thus prolonging the drug's plasma half-life. Because it was difficult to evenly load hydrophobic medications into hydrogel matrices in the past, hydrogels were predominantly used to transport hydrophilic pharmaceuticals. To distribute both hydrophobic and hydrophilic chemicals, recent research have investigated hydrogels made up of networks of micelles that are only 200 nm in size and have hydrophilic shells and hydrophobic centres.[48]

In an oral administration simulation, Polo Fonseca and associates demonstrated that sodium diclofenac, an acidic, hydrophobic NSAID, could be delivered for up to 40 hours in a neutral solution using a polyurethane hydrogel and still achieve 80% cumulative release. For the site-specific delivery of the hydrophobic chemical curcumin, Pillai et al. developed a folic acid-conjugated cross-linked pH-sensitive hydrogel. Compared to a non-conjugated form of curcumin, this hydrogel enhanced cellular absorption. Deepa et al. exhibited pH-dependent continuous release of curcumin from an inverse emulsion-polymerized cross-linked hydrogel in an in vitro study, and they attained similar findings.[49]

Transdermal medication administration, a key method in the field of wound healing, has been the subject of several research investigating the use of hydrogel-based products. According to an in vitro study by Carafa et al., a topical hydrogel with drug-loaded niosomes (non-ionic surfactant vesicular structures) covered by the polysaccharides locust bean gum and xanthan. The drug-loaded niosomes were released from the hydrogel system later, over a longer period of time[50]. It was discovered that a solid hydrogel's transdermal delivery of diclofenac over a 24-hour period outperformed that of any other diclofenac formulation known to science, a solid hydrogel structure with the integration of temperature-responsive nanogels enabling temperature-dependent sustained release.[51]

Coated polyester non-woven supports with To create composite membranes, use a linear poly(2-hydroxyethyl methacrylate) (pHEMA) solution. Depending on the conditions used during preparation, these membranes may be produced to provide permeation fluxes for nitroglycerin ranging from 4 to 68 g/cm2 per hour. It was simpler to release both when bovine serum albumin (BSA) and PEG copolymerized to create high water content hydrogels, soluble and hydrophobic components were released from a 2.4 mm thick hydrogel disc. The scientists also demonstrated that when PEG molecular weight increases, the hydrogel becomes more porous.[52]

In contrast to the commercially available ProtopicTM control, a tacrolimus ointment, In mice with imiquimod-induced psoriasis, showed that the poorly soluble psoriasis drug tacrolimus was delivered to the skin at double the rate by a methoxy PEG hexyl-substituted poly(lactic acid) composite hydrogel. Betamethasone corticosteroid delivery using a hydrogel-thickened microemulsion system dipropionate was reported to suppress inflammation by 72.11% in a rat hind paw edoema model of psoriasis, in contrast to a 43.96% inhibition by a commercial gel.[53]

Hydrogels used as medicine delivery systems have also shown promise in improving the skin's aesthetic qualities. According to Kwankaew et al., Skin hyperpigmentation was significantly decreased by a patch of a weakly soluble heartwood extract of Artocarpus altilis that contains the melanogenesis inhibitor artocarpin.[54]

Comparing Other Drug-Delivery Vehicles with Hydrogels

Topical pharmaceutical distribution, patient tolerability, and treatment efficacy are just a few of the variables that may be strongly impacted by the choice of delivery system. Additionally, the visual attractiveness of these vehicles is essential for maintaining patient adherence; patients are naturally discouraged by formulations that are difficult to apply or painful after administration.

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Patients are more willing to use creams and lotions because they are less greasy than occlusive options, which increases compliance. They promote surface evaporation, which has the cooling effect, and are easy to wipe off the skin. However, they could leave behind mucilaginous residue on the surfaces of the wounds and need chemical preservatives, which might slow the healing process. Additionally, they often have a poorer capability for hydrating the epidermis than occlusive vehicles do.[55]

The occlusive barrier formed by ointments, which are commonly paraffin-based, over wounds improves Percutaneous drug absorption and skin hydration. Due to their occlusive, water-free nature, they provide longer contact periods than creams or lotions and protect the skin from watery irritants. Additionally, the danger of hypersensitivity is decreased by the absence of preservatives. However, ointments are sometimes oily and difficult to wash off, which can impair patient compliance. They lack the ability to cool via surface evaporation, which might be uncomfortable. Additionally, ointments stop excessive exudate from escaping, which might lead to the maceration of good skin.[56]

While minimising some of its disadvantages, hydrogels may provide the benefits of creams, lotions, and ointments. Draelos found that both researchers and patients thought the hydrogel product worked better in a brief split-body, double-blind, randomised study comparing the effects of a cream vehicle vs. a hydrogel vehicle on 80 adults, adolescents, and children with contact dermatitis.[57]

This led to a significant improvement in contact dermatitis symptoms and indicators as compared to the cream-based treatment. Sabale and colleagues found that a microemulsion-based hydrogel maintained similar While enhancing the solubility and skin permeability of the commonly used antifungal drug bifonazole. a commercially available bifonazole cream while reducing skin irritation and antifungal activity.[58] An hydrogel formulation containing desonide was judged to be simple to use by patients with atopic dermatitis, according to a participant preference research by Trookman et al., pleasant, calming, quick to disappear, and not drying, oily, or glossy on the skin. Individuals evaluated the desonide hydrogel's absorbability and absence of greasiness as much higher than those of the ointment. Similar results were obtained by Yentzer et al. Desonide treatment was studied for four weeks in individuals with mild to severe atopic dermatitis, who discovered that a hydrogel formulation consistently earned superior ratings in all categories.[59] Additionally, patients were more compliant with the treatment plan and It has been shown that the hydrogel formulation is more efficient than other vehicles in a shorter period of time. The findings imply that using ointments as the first line of therapy for atopic dermatitis may be ineffective. Compared to a moisturising lotion, a hydrogel formulation substantially increased skin hydration in a tiny, single-center exploratory investigation using split-body randomization. Transepidermal water loss (TEWL) was unaffected by the hydrogel, but TEWL was elevated by the lotion. A hydrogel preparation with 0.1% mometasone furoate was discovered to was not only more moisturising than a lotion containing 0.1% mometasone furoate, but it was also bioequivalent.[30] The hydrogel caused a large 43% drop in TEWL after 2 hours after application, and that decrease persisted significantly at 29% after 24 hours. After 24 hours, skin moisture considerably enhanced by 38% over baseline. This raised the anticipation of increased patient adherence to hydrogel application regimens, combined with preference experiments using a desonide hydrogel. a hydrogel containing 1% hydrocortisone and modelled after the popular DermAidTM line has just been created.[59] As long as the active component level is the same, hydrocortisone's formulation independence in terms of effectiveness and safety provides for adaptability in the management of mild atopic dermatitis and related conditions. Although Franz Cell methodology-based comparative diffusion testing revealed variations in permeation across 1% hydrocortisone solutions, the physiochemical characteristics determining release rates may not always have an influence on therapeutic equivalence or bioequivalence. When hydrocortisone is applied topically, it has been shown that the stratum corneum retains it; Therefore, the drug's diffusion from this reservoir often serves as the rate-controlling step. These findings, the abundance of information on the effectiveness of hydrocortisone, and DermAidTM 1% Hydrogel's bioequivalence to other 1% hydrocortisone formulations make it a more flexible, patient-friendly approach for managing moderate atopic dermatitis and associated ailments.[60]

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II. CONCLUSION

We provide a concise introduction of hydrogels and their many uses in this extensive analysis, including both wound treatment and medication delivery for ailments including atopic dermatitis. We also provide a succinct comparison of the benefits compared to the traditional drug delivery techniques of creams, lotions, and ointments, of hydrogel vehicles.

In the field of wound treatment, hydrogels have extraordinary potential and have the ability to overcome a number of drawbacks that are often connected to more conventional wound care techniques like bandaging and dressings. They are the perfect option for medication administration because to their great biocompatibility, user-friendliness, extraordinary adaptability, and programmability. Hydrogels have shown to be at least bioequivalent to traditional drug delivery methods and often more effective. They routinely get better user acceptance scores, which may greatly improve patient compliance. These appealing qualities, together with the ongoing advances in hydrogel research, place hydrogels as the top option for managing wounds and delivering drugs.