

Advanced trends in treatment of wounds

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There are a wide variety of dressing techniques available for the management of both acute and chronic wounds. The primary objective in both the cases is to achieve a healed wound. An ideal dressing material should accelerate wound healing and reduce loss of necessary fluids from the wound, and also help minimize pain and infection. The present trend is to promote the concept of moist wound healing. This article emphasizes on the importance of assessment of the wound, the volume of drainage fluid, amount of damage, presence of infection and location of wound for optimal wound healing.

Keywords: Advanced therapies, controlled drug delivery systems, modern dressings, wound healing.

WOUND healing is a moderately complex process which involves, among others, the engagement of a number of matrix elements¹. According to Mustoe², scars are clinically classified as immature, mature, hypertrophic and keloid scars. Hypertrophic and keloid scars are defaced and accompanied by severe pain, itching and tenderness. This eventually leads to low sleep arousal, depression, anxious behaviour and disrupts the daily activities of an individual. Various methods such as surgical management, laser therapy and pressure therapy have been employed in the treatment of these scars, but because of the various side effects and recurring chances associated with these methods, they are not popular³. The management of wounds and scars is still a big challenge for the scientists/medical practitioners⁴. Earlier lint, gauze and cotton wool were used for the purpose of wound healing. The main aim was to allow the evaporation of exudates, rendering it dry and to prevent the entry and production of harmful bacteria into the wound. However, according to recent research, the prevalence of a warm and moist environment accelerates the process of wound healing. A warm and moist environment required for wound healing includes good supply of oxygen and moisture for regeneration of cells in the tissues. The various factors that should be taken in consideration regarding management of wound healing are: the wound healing pathway, social factors, environmental factors, different types of wounds, nature as well as stage of the wounds, physico-chemical properties of the gauze used and general health conditions of the patients⁵. Based on the chemical and physical properties

of the drug molecules, a protective carrier can be dispensed. The carrier can be of a single phase or multiphase and protects the active component from chemical degradation.

Wound healing

Wound healing is a biological process. It generally deals with the phenomenon of tissue regeneration and growth. Wound healing follows an interconnected pathway which includes the participation of various cellular and matrix components. They work in conjunction in order to maintain and restore the damaged tissue^{6,7}. According to Schultz⁸, it consists of four stages that involve complex processes. The four stages are: coagulation, inflammation, cell proliferation and repair of matrix and epithelialization and remodelling of scar tissue. There is considerable overlap between the various stages, and the entire healing process can take months to complete, with full maturation often not achieved until a year after the wound was initiated⁹.

Wound dressings

The early wound dressings included application of animal fat, plant herbs and honey to the tissue. The Africans used various medicinal plants which not only helped in wound healing, but also had antibacterial properties¹⁰. *Guiera senegalensis*, a plant from Senegal and Nigeria used in wound healing was found to have antibacterial properties¹¹. According to researchers from Ghana, the extracts of *Spathodea campanulata* bark and *Commelina diffusa* herb were used traditionally for treating wounds. They showed antioxidant activity and antimicrobial activity against *Trichophyton* species¹². It was observed that plant extracts used for wound treatment contained microorganisms and various chemicals which have the potential to be harmful and cause irreversible complications such as aggravating the wounds. The aseptic procedures to be carried out in surgical practices led to remarkable improvement in the management of wound healing.

Modern wound dressings

The key characteristic of a modern dressing agent is to restore and maintain a moist environment which will accelerate the process of wound healing. The modern

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dressings are categorized according to the excipients, including alginates, hydrocolloids and hydrogels. They generally are in the form of thin films and sheets.

Hydrocolloid dressings: These consist of a combination of gel-forming agents (carboxymethylcellulose (CMC), gelatin and pectin), elastomers and adhesives. Examples of recent hydrocolloid dressings include Granuflex™ (Conva Tec, Hounslow, UK) and Tegaserb™ (3M Healthcare, Loughborough, UK). They generally occur as thin films or sheets, or as combination dressings. The hydrocolloids are impermeable to water in their general state, but when they absorb the exudate it results in the formation of a gel sheet. In the gel form they rapidly become permeable to air and water¹³. Unlike the traditional dry dressings, they do not cause pain on removal, maintain optimum moist environment, adhere to dry as well as moist sites and can be used in the management of both acute as well as chronic wounds¹⁴. A comparative study showed that a combination dressing is much more superior than a primary dressing. According to a trial, the efficacy achieved by the hydrocolloid was much better than that achieved by a paraffin gauze¹⁵. In another randomized trial, a comparison was made between a hydrocolloid dressing and a nonadherent dressing on patients suffering from lacerations and ulcers. It was observed that the time taken to heal was similar for both; however, patients with the hydrocolloid experienced less pain¹⁶. According to microscopic studies, alginate dressings adsorb all the harmful bacteria. The CMC dressings showed superior ability to encapsulate bacteria (*Pseudomonas aeruginosa* and *Staphylococcus aureus*)¹⁷.

Alginate dressings: Alginate dressings are produced from a polysaccharide comprising guluronic and manuronic acid units. Alginate dressings occur either in the form of flexible fibres or as foams. They have high absorption capacity due to strong hydrophilic gel formation. They limit wound secretion and also minimize bacterial infection¹⁸. Examples are Sorbsan™ (Maersk, Suffolk, UK), Kaltostat™ (Conva Tec) and Tegagen™ (3M Healthcare). Comfeel Plus™ is an example of a combination dressing. The ions present in the alginate fibre are exchanged with those present in the exudate to form a protective layer¹⁹. This layer helps in the maintenance of an optimum environment required by the wound. The calcium ions present in the alginates provide the gelling property and also help in the production of a slow-degrading polymeric gel^{20,21}. According to a comparative study, the alginates show a higher residence time compared to hydrocolloid dressings²². According to a study, the calcium ions present in the alginates increase the proliferation of fibroblasts. The absence of calcium in wound fluid induces rapid resolution of alginate gel while the presence of a certain concentration of calcium prevents degradation of the gel for as long as one month^{23,24}. It has

been reported that alginate dressings cause the activation of human macrophages, which in turn produce the tumour necrosis factor- α (TNF α) that is required for wound healing²⁵. Alginate dressings proved successful in neurosurgery. The fibres arising from the alginate dressings are generally biodegradable²⁶. As they do not destroy granulation tissue while changing the dressing, they are painless and high on patient compliance. Because of their biodegradable property, they are also used in the production of alginate sutures. Alginate dressings require moisture; this can cause excessive dehydration and hence they are not used on dry wounds.

Hydrogel dressings: Hydrogel dressings are made from synthetic polymers such as poly(methacrylates) and polyvinylpyrrolidone. Examples are Nu-gel™ (Johnson & Johnson, Ascot, UK) and Purilon™ (Coloplast). Hydrogels can be either in the form of a gel or a film. The sheets entrap the water and form a crosslinking polymeric network. These sheets can be used for chronic as well as acute wound healing. When applied in the form of a gel, they require a secondary covering such as gauze and frequent change is required²⁷. When applied as a sheet, secondary dressing is not required. The sheets can also be cut into the shape of the wound as they are highly flexible in nature. The gels act as primary dressing and the sheets can be either primary or secondary dressing. Hydrogel dressings contain significantly large amounts of water and as a result they do not cause excessive absorption of the exudate. Hydrogels have low mechanical strength and hence can lead to accumulation of fluid and destruction of healthy tissues²⁸. This property makes them difficult to use and thus are low on patient compliance²⁹. Hydrogels are suitable for cleansing of dry, sloughy or necrotic wounds, are nonreactive with biological tissue, permeable to metabolites, are nonirritant, leave no residue, are malleable and improve re-epithelization of wounds³⁰.

Semi-permeable adhesive film dressings: The traditional film dressings were originally created from nylon derivatives supported in an adhesive polyethylene frame which provided them with an occlusion property. The disadvantages were that they had limited ability to absorb sufficient quantities of wound exudates, which led to oedema caused due to the presence of excessive fluids. This resulted in the destruction of skin cells and proliferation of bacterial cells and increase in the risk of infection and therefore required regular changing of the dressing as well as irrigation of the wound with saline in patients. Opsite™ (Smith and Nephew, Hull, UK) is a thin, semi-permeable film made from polyurethane and covered with hypoallergenic acrylic derivatives. It is more porous and permeable to water vapour and gases, but not permeable to the liquid from exudates³¹. The films generally are transparent, conform to contours and do not require additional taping. However, they are suitable only for

relatively shallow wounds because they are very thin. Other examples are Cutifilm™ (B.D.F. Medical, Milton Keynes, UK), Bioocclusive™ (Johnson & Johnson) and Tegaderm (3M Pharma).

Foam dressings: These dressings are made up of porous polyurethane foam or polyurethane foam film, and have adhesive borders. Foam dressings maintain an optimum moist environment with thermal insulation, good absorbent properties and are convenient to wear, making them patient compliant³². The porous structure of the dressings makes them flexible to use. They can be used for either partially thick or fully thick wounds. They can also be used for minimal, highly exuding wounds because of high absorbency. Foam dressings are also used in the treatment of granulating wounds³³. Due to their absorbency and insulation properties, they are used as primary wound dressings. They do not require secondary dressing. Examples of foam dressing are: Lyofoam1 (Conva Tec) and Allevyn1 (Smith and Nephew).

Biological dressings: These are also called as bioactive dressings. They are made from biological materials that play an active part in the wound healing process. Bioactive wound healing dressings also include tissue-engineered products. These technologies usually combine polymers such as collagen, hyaluronic acid, chitosan, alginates and elastin³⁴⁻³⁶. The advantages of biological dressings are that they are biodegradable and some of them play an active part in normal wound healing. They are also biocompatible, non-toxic and result in formation of new tissues^{37,38}. They are generally incorporated with antimicrobials and growth factors for better therapeutic activity. Collagen is the major structural protein of an organ. It helps in the migration of endothelial cells, activation of clotting factors, formation of fibroblasts and also plays a vital role in the appearance of the final scar. Collagen also plays a major role in wound healing³⁹. The matrix can be impregnated with a drug entity, thus acting as a reservoir for drug delivery. Hyaluronic acid is a glycosaminoglycan component of extracellular matrix with unique functions. It is biocompatible, biodegradable and lacks immunogenicity⁴⁰. Crosslinked hyaluronic acid hydrogel films have also been produced⁴¹. Hyaluronic acid-modified liposomes as bioadhesive carriers for delivering growth factors to wound sites have been studied⁴². A recent study of hyaluronic acid dressings found them to be efficacious in managing acute wounds⁴³. Chitosan leads to the acceleration of granulation during the proliferative stage of wound healing. Bioactive dressings are reported to be more superior to conventional and synthetic dressings⁴⁴.

Tissue-engineered skin substitutes: Both traditional and modern dressings cannot regenerate or replace the damaged and lost tissue. In advanced applications, 'smart'

polymers have been developed⁴⁵. Advancements in the fabrication of biomaterials and the culturing of skin cells have led to the development of a new generation of engineered skin substitutes⁴⁶. Such polymers replace lost tissue and also facilitate wound healing. The use of 'smart' polymers either in the natural biological form or semi-synthetic forms is reported to be able to mimic normal physiologic responses during wound healing^{47,48}. This can be of major help in tissue regeneration, particularly for chronic wounds that are difficult to heal. Tissue-engineered skin substitutes can be categorized as acellular and cell-containing matrices. Acellular matrices are produced either from synthetic collagen or in combination with hyaluronic acid⁴⁹. For example, Integra™ and Alloderm™. Collagen and glycosaminoglycans act as scaffolds onto which skin cells can be seeded for the growth of new tissues. They provide anatomic characteristics similar to that of the tissue (normal dermis) they replace⁵⁰. When introduced into the body they start degrading and leave behind a matrix of connective tissues having similar properties as that of the dermis. The effects of collagen on dermal wound healing and its combination with anti-microbial agents have been reported⁵¹. It was observed that it increased the formation of granulation tissue during wound healing. The disadvantages include high costs involved in the production of tissue-engineered skin substitutes, ethical issues regarding stem cultures, risk of infection and antigenicity⁵².

Controlled drug delivery to the wound

Hydrophilic polymers can be used as controlled release dressings because of several advantages. They are known to provide sustained release of the drug and they do not require change like the other dressings⁵³. Polymeric dressings which are synthetic, semisynthetic, bio-adhesive and of natural origin, have a good potential in topical infections as they increase the concentration of antibiotics locally without causing systemic toxicity⁵⁴. They can be easily washed-off once the action is exerted and are biodegradable⁵⁵. They are high on patient compliance.

Solid lipid nanoparticles: These are novel drug delivery systems which are known to minimize all the shortcomings observed by the drugs. They are nanoplatelets or nanospheres which are made up from lipids solid at room and body temperature, such as glycerol behenate (Compritol®), glycerol palmitostearate (Precirol®) or tristearin glyceride. Nanoparticles are ultra small and controllable size, highly reactive and high-functioning structures. Drug loading can not only increase skin penetration rate, but also aid in the epidermal drug targeting. It has been reported that solid liquid nanoparticles impregnated with podophyllotoxin (POD) provide a strong localization of POD in the epidermis⁵⁶. It possesses good tolerability and

stability, scaling-up feasibility, the ability to incorporate hydrophobic/hydrophilic drugs and can be used on damaged or inflamed skin. It is non-irritant and non-toxic. However, dispersion observed low viscosity properties and a zero yield value, making it inconvenient for topical use⁵⁷.

Liposomes: These are spherical structures having an aqueous phase inside and covered with several concentric lipid layers outside⁵⁸. The recent advanced types of liposomes reported are niosomes, ethosomes and highly flexible transfersomes. Niosomes are chemically stable and cheap compared to conventional liposomes^{59,60}. A combination of ethanol, phospholipid and water comprises the ethosomal system⁶¹. A dynamic interaction between ethosomes and the stratum corneum enhances skin permeation⁶². Transfersomes that follow the transepidermal water activity gradient in the skin can enhance the transdermal bioavailability of drugs. Vogt *et al.*⁶³ observed that polyvinyl pyrrolidone–iodine impregnated in a new liposome hydrogel formulation could be applied topically to patients with meshed skin grafts after burns. According to Yang⁶⁴, the topical treatment of liposome-encapsulated hydroxycamptothecin significantly reduced epidural scar. The other advantages were that liposomes could increase the hydrolysis half-life, drugs could be slowly and continuously released from the liposome and provide sustained effect, and liposome formation could decrease the toxicity of free drugs.

Microemulsions: These form spontaneously without high shear equipment. The active agents are solubilized and thus penetrate the skin rapidly. Increasing thermodynamic activity and the presence of (co-)surfactants enhance penetration and improve the occlusive nature. This improves skin penetration to variable degrees⁶⁵. Kitagawa⁶⁶ reported that genistein containing microemulsion could prevent UV irradiation-induced erythema formation. However, in order to stabilize the nanodroplets, it has been observed that the use of a higher concentration of a co-surfactant and surfactant is mandatory. Microemulsion is an ideal medium for topical drug delivery. The advantages of using microemulsions are their ideal thermodynamic properties and stable nature, they are easily formed, have low viscosity with Newtonian behaviour, high surface area and small droplet size. The microemulsion droplets have greater chance to adhere to membranes and to transport bioactive molecules in a controlled fashion.

Microsponges: The microsphere delivery system (MDS) is a polymeric microsphere system uniquely fulfilling these requirements of topical controlled drug delivery systems. MDS is a highly cross-linked, porous, polymeric microsphere system that can entrap and adsorb active drugs and then release them into the skin. After some-

time, due to the contact generated, a response occurs⁶⁷. Microsponges which consist of non-collapsible structures with porous surface through active ingredients are released in a controlled manner⁶⁸. The microsphere particles have open structures and the active agent is free to move until equilibrium is reached when the vehicle becomes saturated. When the product is applied onto the skin, the active drug present in the vehicles will be absorbed into the skin. Gradually the vehicle gets depleted; this leads to unsaturation and causes disturbances to maintain an equilibrium. This will start a flow of the active agent from the microsphere particle into the vehicle and from it, to the skin, until the vehicle is either dried or absorbed. The microsphere particles that are present on the surface of the skin layer – stratum corneum will constantly continue the action of releasing the drug into the skin. Hence a sustained release is observed. The microsphere technology can also be used to formulate a combination of drugs that are incompatible with each other. Formulations can be developed with otherwise incompatible ingredients with prolonged stability without use of preservatives.

Advanced therapies

Low-level laser therapy

It was observed that using light of low intensity, no thermal effect was generated but biological, chemical and physical effects could be generated. Low-level laser, when given at appropriate doses, causes stimulation of cell function. This is important for the healing process. The mechanism of the healing process is tissue biostimulation. Increase in ATP production and activation of mast cell, fibroblasts and lymphocyte causes anti-inflammatory and analgesia in patients^{69,70}. The factors which affect the action of the laser are: duration of action, type of laser used and area exposed to the laser. The parameters should be maintained in order to obtain an efficacious treatment⁷¹. According to Kolárová *et al.*⁷², by the application of laser of high intensities for fraction of seconds, it reached up to 19 mm of depth in the dermis. It was observed that the laser was absorbed even by the adjacent tissues; hence it was necessary to provide targeted therapy. Application of a low-intensity (640–940 nm) laser having penetration power that is low provides good therapeutic action⁷³.

Hyperbaric oxygen therapy

This is defined as the process where the entire body of a patient is compressed with approximately 1.4 atmospheres of pure oxygen having absolute pressure⁷⁴. A single session or compression involves using 2 atm of pure oxygen having absolute pressure. The average session of

Table 1. List of products available in the market

Product	Type	Component	Use
Biobrane™ (Hickham/Bertek Pharmaceuticals, Sugar Land, TX)	Biosynthetic skin substitute	Silicone, nylon mesh, porcine collagen type I	To cover extensive partial thickness burns and donor sites
Epicel™ (Genzyme Biosurgery, Cambridge, MA)	Epidermal skin substitute	Cultured autologous human keratinocytes	Permanent coverage for superficial and partial thickness burns
Integra™ (Integra LifeScience, Plainsborough, NJ)	Artificial skin	Collagen/chondroitin-6 sulphate matrix overlaid with a thin silicone sheet	Immediate permanent coverage for surgically excised full-thickness burns; reconstructive surgery
Apligraf™ (Organogenesis, Canton, MA)	Epidermal and dermal skin substitutes	Bovine type-I collagen mixed with a suspension of dermal fibroblasts	Non-healing diabetic foot ulcer and venous leg ulcer
Alloderm™ (Lifecell Corporation, Branchberg, NJ)	Acellular dermal graft	Normal human dermis with all the cellular material removed	Intended to permanently cover full-thickness burns and deep ulcers; reconstructive surgery
TranCyte™ (Advanced Tissue Sciences)	Human fibroblast- derived skin sub- stitute (synthetic epider+mis)	Polyglycolic acid/polylactic acid, extracellular matrix proteins derived from allogenic human fibroblasts and collagen	To cover surgically excised full thickness burns and non-excised partial thickness burns

a compression is 90 min for wound healing. Compressions generally take place in chambers which can be monoplace or multiplace. In monoplace chambers only the patient can enter inside the chamber and attain 100% oxygen, while the attendant waits outside when the compression session commences. In multiplace chambers, 2–10 patients can be accommodated. Unlike the monoplace chambers, multiplace chambers have two attenders – one inside and one outside. Inside the chamber, well-secured hoods present above the head and neck allow the passage of 100% oxygen at a certain depth⁷⁵. Both types of chambers can be used for critical care and the medical staff provide entire coverage for patients who are severely ill. Hyperbaric oxygen therapy caters to wound healing and salvaged limbs.

Negative-pressure wound devices

Negative-pressure wounds devices (NPWDs) are now being used to treat acute wounds. NPWDs are used for patients suffering from serious injuries, such as large soft-tissue injuries and wounds with compromised tissue. Ideally, muscle or any tissue having a soft texture should be kept between the structure and the resultant sponge, but if this is not possible Vaseline or silicone mesh should be used⁷⁶. This leads to closing of the wounds in patients who are critical, allowing the focus on stabilization of the patient for later definitive reconstruction, with flaps⁷⁷. To allow a simpler reconstruction, many NPWDs have gained temporary use in treating complex wounds. The optimization of the medical status of the patient helps in promoting the healing of both acute and chronic wounds.

Conclusion

Wound management has made rapid advances over the last 25 years and clear guidelines focusing on the principles of effective wound-bed preparation are available. The plethora of wound care products in the market has resulted in practitioners' using different types of products in combination, which may make the treatment expensive. However, even if a dressing is expensive, it promotes rapid wound healing, thus leading to the desired clinical results, both patients and clinicians would opt for it. The field of wound care is ever expanding with advances in technology. While there is no superior substitute, the new products can help in the following ways: (i) prophylaxis against barriers to healing, (ii) augmentation of wound healing factors, (iii) bridging time to definitive repair and (iv) optimization of wound reconstruction. Recent wound healing products and modalities increase the armamentarium of the health professional to address all aspects of wound care.

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