Innovare
Academic Sciences

Journal of Critical Reviews

ISSN- 2394-5125 Vol 2, Issue 2, 2015

Review Article

NOVEL DRUG DELIVERY STRATEGIES AND APPROACHES FOR WOUND HEALING MANAGEMENTS

FEDELIC ASHISH TOPPO, RAJESH SINGH PAWAR

Pharmacognosy and Phytochemistry Laboratory, Faculty of Pharmacy, VNS Group of Institutions, Neelbud, Bhopal, Madhya Pradesh, India 462044
Email: ashish_two@yahoo.co.in

Received: 05 Mar 2015 Revised and Accepted: 10 Apr 2015

ABSTRACT

New ideas on controlling the pharmacokinetics, pharmacodynamics, non specific toxicity, immunogenicity, biorecognition and efficiency of drugs have generated new strategies, often called as the drug delivery system. Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety, and efficacy. Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) from synthetic and natural bioactives such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes have been reported. The variety of dressings based on types of wounds and novel polymers used for the delivery of drugs to acute and chronic wound has resulted in a wide range of new products frequently introduced to target different aspects of the wound healing process. These include hydrocolloids, alginates, hydrogels, polyurethane, collagen, chitosan, pectin and hyaluronic acid. Nevertheless, nanofibers with their physicochemical properties and nanotopography display improvements in the fields of tissue engineering, wound therapy and drug delivery systems. At present, there are so many existing drug delivery technologies that a total compilation is not within the scope of this article. Yet an attempt is being made to compile some of the most successfully marketed drug delivery technologies. This review extends the information and hopes to give insight into past, present and future strategies and approaches for wound healing managements.

Keywords: Drug delivery systems, Novel drug delivery, Wound, Wound healing management.

INTRODUCTION

Novel drug delivery system is largely based on promoting the therapeutic effects of a drug and minimizing its toxic effects by increasing the amount and persistence of a drug in the vicinity of the target cell and reducing the drug exposure of non target cells [1]. Novel formulations are reported to have remarkable advantages over conventional which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. Development of novel drug delivery systems (NDDS) from synthetic and natural bioactives such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported. Nanoparticles and nanoformulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications [2].

The skin is a complex organ with three distinct histological layers: the epidermis, the dermis, and the hypodermis. Wound healing of healthy skin is an immediate restorative response to injury [3], and the process is dependent on unipotent and multipotent stem cells that reside in the basal layer of the epidermis, the hair follicle bulge, the sebaceous glands at the base of the hair follicle, the dermal papillae, and the dermis [4-6].

According to the Wound Healing Society, a wound is the result of 'disruption of normal anatomic structure and function [7]. Wound healing progresses through a series of interdependent and overlapping stages in which a variety of cellular and matrix components act together to reestablish the integrity of damaged tissue and replacement of lost tissue [8, 9]. The wound healing process has been reviewed and described by Schultz [10] as comprising five overlapping stages that involve complex biochemical and cellular processes. These are described as haemostasis, inflammation, migration, proliferation and maturation phases. In fact, Cooper [11] has argued for expanding the understanding of wounds beyond the cellular level to a molecular context as well. He emphasized the need to approach wound healing at multiple levels (cellular and molecular) to help improve wound treatment and management. In the developed countries, many sophisticated dressings are available to the wound care practitioners which are made from a wide range of materials including polyurethane, salts of alginic acid and other gel able polysaccharides such as starch and carboxymethylcellulose. These materials are combined to form products as diverse as films, foams, fibrous products, beads, hydrogels and hydrocolloid dressings [12] (table 1). The situation is totally different in the developing countries like ours where what is still commonly available to wound care provider are traditional agents such as sodium hypochlorite, hydrogen peroxide, cetrimide solution, chlorhexidine and others. These agents have been proven to be of limited efficacy and may also have an adverse effect upon the healing process [13] and therefore get out of favour [14]. Wound management methods depend on the healing process, the status and living environment of the patient, and the physical/chemical properties of the wound. Therefore, there is much attention given to the study of the physical characteristics and clinical role of available dressings with respect to each wound treatment phase and wound type [15, 16]. Wound related factors takes priority when considering choice of dressing for a particular wound. Therefore, we should always ask ourself, what type of wound are we dealing with? Is it a superficial, full thickness or cavity wound? Is the wound necrotic, sloughy, and granulating or epithelising? What about its characteristics, is it dry, moist, heavily exuding, malodorous, excessively painful or liable to bleed? What about the bacterial profile, is it sterile, colonized or infected? For example, a superficial, granulating or epithelising wound with minimal exudate should not be dressed with agents like hypochlorite solution or hydrogen peroxide. Rather, such wound may be dressed with sofra-tulle covered with saline soaked gauze or even dry gauze. In clinical practice, when considering dressings for an acute wound, the emphasis should be on prevention of infection and promotion of healing [17] whereas in chronic wound-healing, the control of wound infection is more important [18]. The aim of this study is to re-appraise the problem of limitation of wound dressing selection in the developing countries. We are still hoping to acquire newer agents for wound dressing, in the developing countries, we have

made an effort to discuss some characteristics needed to make us choose wisely from the limited variety of dressing materials to meet the needs of our wounds for efficient wound care. This is with the aim of sensitizing the wound care practitioner on the use of the commonly little available products based on the needs of a different wound or even the same wound throughout its healing course.

Wound healing managements

Effective wound management depends on understanding a number of different factors such as the type of wound being treated, the healing process, patient conditions in terms of health (e. g. diabetes), environment and social setting, and the physical chemical properties of the available dressings [19]. It is important therefore, that different dressings be evaluated and tested in terms of their physical properties and clinical performance for a given type of wound and the stage of wound healing, before being considered for routine use.

Several factors apart from the choice of wound dressings need to be considered to ensure successful wound healing. In the case of chronic wounds, underlying factors such as disease, drug therapy and patient circumstance must all be reviewed and addressed before a particular wound dressing is applied. Table 1 [20] describes factors to be considered in the choice of wound dressings based on their performance characteristics (functions) [21-23]. In the past, traditional dressings (table 2) such as natural or synthetic bandages, cotton wool, lint and gauzes all with varying degrees of absorbency were used for the management of wounds. Their primary function was to keep the wound dry by allowing evaporation of wound exudates and preventing entry of harmful bacteria into the wound. Modern dressings are based on the concept of creating an optimum environment to allow epithelial cells to move unimpeded, for the treatment of wounds. Such optimum conditions include a moist environment around the wound, effective oxygen circulation to aid regenerating cells and tissues and a low bacterial load. Other factors which have contributed to the wide range of wound dressings include the different type of wound (e. g. acute, chronic, exuding and dry wounds, etc.) and the fact that no single dressing is suitable for the management of all wounds. In addition, the wound healing process has several different phases that cannot be targeted by any particular dressing.

The use of topical pharmaceutical agents in the form of solutions, creams, ointments and incorporated drugs i.e. active compounds and the dressings (novel polymer systems) play an active role in the wound healing process either directly or indirectly as cleansing or de briding agents for removing necrotic tissue, antimicrobials which prevent or treat infection or growth agents (factors) to aid tissue regeneration and also possess antiseptic and antibacterial actions. Some dressings such as gauze and saline are useful for the initials stages of wound healing for absorbing blood and exudates, cleansing and debridement. Other dressings provide a moist environment during the latter stages of wound healing, whilst some medicated dressings and biomaterials can take active part in all the stages of wound healing. In most cases, a combination of dressings is needed in order to achieve complete wound healing in a reasonable time. Wound healing formulations (dressings) and novel technologies developed to date focus on one or more of these aspects of the natural healing process [24] that are summarized briefly in table 3.

Most modern dressings are made from polymers which can serve as vehicles for the release and delivery of drugs to wound sites. The polymeric dressings employed for controlled drug delivery to wounds include hydrogels such as poly (lactide-co-glycolide) [25] poly (vinyl pyrrolidone) [26], poly (vinyl alcohol) [23] and poly (hydroxyalkylmethacrylates) [37-39] polyurethane-foam [40-44], hydrocolloid [45] and alginate dressings [46-49]. Other polymeric dressings reported for drug delivery to wounds comprise novel formulations prepared from polymeric biomaterials such as hyaluronic acid [50, 51], collagen [52, 53] and chitosan [54-57]. Synthetic polymers employed as swellable dressings for controlled drug delivery include silicone gel sheets [58], lactic acid [59]. Some of these novel polymeric dressings for drug delivery exist as patents [60-65]. Composite dressings comprising both synthetic and naturally occurring polymers have also been reported for controlled drug delivery to wound sites [66, 67]. Sustained release tissue engineered polymeric scaffolds for controlled delivery of growth factors and genetic material to wound sites has also been reported [68, 69]. The modern dressings for drug delivery to wounds may be applied in the form of gels, films and foams whilst the novel polymeric dressings produced in the form of films and porous sponges such as freeze-dried wafers or discs [70-77] or as tissue engineered polymeric scaffolds [70, 78](table 4) (fig. 1).

Bioengineered skin substitutes, both biosynthetic skin substitutes and cultured autologous engineered skin, are available to provide temporary or permanent coverage, with the advantages of availability in large quantities and negligible risk of infection or immunologic issues. With advances in burn resuscitation and critical care management, more patients with significant body surface area burns are surviving, leading to the issue of coverage of large wounds. Autograft is currently the preferred option, but in many instances there is an insufficient amount of tissue available for grafting, or the patient's condition precludes the use of autograft. Allografts and xenografts can provide a temporary coverage option, but they come with issues regarding rejection, and possible disease transfer, availability, as well as cultural and ethical considerations. Biobrane is a temporary dressing composed of knitted nylon mesh bonded to a thin silicone membrane and coated with porcine polypeptides [79]. It is used in clean superficial and middermal depth burns or as coverage for donor sites in split-thickness skin grafting. Trans Cyte is a biosynthetic dressing of a semipermeable silicone membrane on a nylon mesh coated with porcine collagen and newborn human fibroblast cells [79]. It is used as a dressing in superficial burns that do not require skin grafting, or as a temporary cover for excised burns prior to grafting. Dermagraft contains neonatal fibroblasts on a bioabsorbable polyglactin mesh. The fibroblasts produce dermal collagen, glycosaminoglycans, growth factors, and fibronectin to support wound healing [80]. It is a temporary or permanent cover used for excised burn wounds as well as venous ulcers and pressure ulcers [79]. Results show it to be comparable to allograft for wound infection, healing time, exudates, and graft take, with higher patient satisfaction [81, 82]. Apligraf is composed of an epidermal layer of allogeneic neonatal keratinocytes and fibroblasts from neonatal foreskin on bilayered type I bovine collagen [79, 83] that is used as an adjunct covering to autograft, providing accelerated healing times [80]. It is also used alone in chronic wound ulcers, showing increased healing times when compared to controls [84]. Integra is a semibiologic bilayered dressing composed of a matrix of type I bovine collagen, chondroitin-6-sulfate, a glycosaminoglycan from shark cartilage, under a temporary silicone epidermal sheet [79, 85]. The pore size (70–200 μm) is designed to allow migration of the patient's own endothelial cells and fibroblasts. As the wound heals, the silicone sheet is removed and a thin autograft is grafted onto the neodermis to complete the wound coverage.

Recently, the method of delivering growth factors from outside the body using a drug delivery system is being researched for the treatment of chronic wounds [86]. Growth factors stimulate mainly fibroblasts and keratinocytes via transmembrane glycoproteins [87]. The development of modern wound dressings, which mimic exactly the missing matrix, is the most comprehensible approach for the treatment of non-healing wounds. For the aforementioned reasons, nanofibers can be used as efficient natural extracellular matrix (ECM) analogues. After the application onto the wound, cells will take the latter as if synthesized by themselves and consequently oriented chemotaxis, adhesion, differentiation and cell growth will be stimulated as well as the formation and deposition of a provisional matrix and re-epithelialization [88-90].

Future strategies and approaches

The goal of wound healing management need not always be a more rapid healing, but rather can also encompass a reduction in pain or improved quality of life. With the development of various results, including the complete healing, little pain when attaching and detaching the wound dressing, etc, there will no doubt be significant crossover in wound dressing that leads to better, safer, and more integrated original tissue. The primary wound treatment method has been changing from the dry method in the 1900s and the wet

method in the 1970s to the drug delivery system (DDS) method today. In the past, the dry dressings were used where the wound was disinfected and a crust was formed which would come off when the wound was healed. Nowadays, the wet dressings are used frequently; these dressings maintain the wetness of the wound site, accelerate the recovery speed, minimize scarring, and do not cause the formation of a crust [91]. In addition, the wet dressing has a significant amount of contact with the wound site so that it results in little secondary damage and prevents pathogens and foreign substances from entering the wound.

As technology and engineering processes become increasingly sophisticated, it seems ideal to have composite dressings which combine the different characteristics of current technologies. This will aid in targeting the many aspects of the complex wound healing process, to ensure effective, complete wound healing and shorter healing times for chronic wounds (and other difficult to heal wounds). It may also be expedient to employ individualized therapeutic approaches for treating specific wound types and individuals using emerging tissue engineering technologies. Such advanced approaches can help treat chronic wounds in a clinically efficient manner. One can only anticipate that further development of biocompatible scaffolds will result in a range of sophisticated dressings that will be capable of facilitating migration and proliferation through the controlled release of cytokines and growth factors, in response to biomarkers present in the wound environment, while impeding infection and relieving pain. Each wound arises from a unique cause, be it a particular trauma or underlying condition on a unique patient. This requires a range of dressings to ensure optimal healing conditions for all wounds and, ultimately, a suite of sophisticated dressings that possess all of the features of an 'ideal dressing' while catering to the individual.

More recently the hyperbaric oxygen therapy in diabetics with chronic foot ulcers (HODFU) study was completed [92, 93]. This suggests that in addition to immediate assistance in healing, hyperbaric oxygen also has a role in long-term wound improvement, perhaps as the full effects of neovascularization are realized. Negative pressure wound devices are relatively new in wound care treatment, and their indications are continually expanding to encompass aspects of wound management that previously had very few options. With the advent of biosynthetics and tissue engineering, skin substitutes are being created that not only provide novel effective temporary coverage of wounds, but are also changing the paradigm of wound management. By supporting the wound with growth factors and biologic substances, we can help augment or modulate the wound healing process itself. There may be many unexplored polymeric dressings with idealised properties required for the effective and sustained delivery of therapeutic agents to chronic wounds and it is hoped that this article can provide a key to this knowledge.

Table 1: Desirable characteristics and clinical significance for wound healing

Desirable characteristics	Clinical significance for wound healing
Debridement (wound cleansing)	Enhances migration of leucocytes into the wound bed and supports the accumulation of enzymes. Necrotic tissue, foreign bodies and particles prolong the inflammatory phase and serve as a medium for bacterial growth
Provide or maintain a moist wound environment	Prevents desiccation and cell death, enhances epidermal migration, promotes angiogenesis and connective tissue synthesis and supports autolysis by rehydration of desiccated tissue
Absorption. Removal of blood and excess exudate	In chronic wounds, there is excess exudate containing tissue degrading enzymes that block the proliferation and activity of cell and break down extracellular matrix materials and growth factors, thus delaying wound healing.
Gaseous exchange (water vapour and air)	Permeability to water vapour controls the management of exudate. Low tissue oxygen levels stimulate angiogenesis. Raised tissue oxygen stimulates epithelialisation and fibroblasts
Prevent infection: Protect the wound from bacterial invasion	Infection prolongs the inflammatory phase and delays collagen synthesis, inhibits epidermal migration and induces additional tissue damage. Infected wounds can give an unpleasant odour.
Provision of thermal insulation	Normal tissue temperature improves the blood flow to the wound bed and enhances epidermal migration
Low adherence. Protects the wound from trauma	Adherent dressings may be painful and difficult to remove and cause further tissue damage
Cost effective low frequency of dressing change	Dressing comparisons based on treatment costs rather than unit or pack costs should be made (cost-benefit-ratio). Although many dressings are more expensive than traditional materials, the more rapid response to treatment may save considerably on total cost

Table 2: Traditional wound dressings in the world market

Dressing material	Brand name	Manufacturer
Paraffin gauze dressing containing 0.5% chlorhexidine acetate	Bactigras	Smith & Nephew
Paraffin gauze dressing	Jelonet	Smith & Nephew
Petrolatum gauze	Xeroform	Chesebrough-Pond's Inc.
Petrolatum gauze containing 3% bismuth tribromophenate	Xeroform	Chesebrough-Pond's Inc.
Scarlet Red dressing	Scarlet Red	Chesebrough-Pond's Inc.
Sterile hydrogel dressing	2nd skin®	Spenco
Highly absorbent cotton wool pad	Gamgee® pad	3M
Highly absorbent rayon/cellulose blend sandwiched with a layer of antishear high density polyethylene	Exu Dry Dressing	Smith & Nephew
Absorbent cotton pad	Telfa "Ouchless" Nonadherent Dressings	Kendall (Covidien)

Source: Sezer AD *et.al.* 2011

Table 3: Advances in wound healing managements

S. No.	Dressings	Managements
1	Protective dressings	
	Gauze	Inexpensive; Traumatic removal, lateral bacterial migration.
	Bandage	Readily available; Cheap; accessible; Efficacy to retain and absorb exudates varies; need to be changed regularly to prevent maceration.
	Impregnated gauze	Nonadherent; Preserves moisture; May not prevent maceration.

2	Honey dressing	Antimicrobial, antifungal, deodorizing, anti-inflammatory, maintains moist environment; As a topical treatment, it rapidly dilutes and requires frequent dressings to maintain efficacy.
3	**Antimicrobial dressings**	
	Antibacterial ointments	Needs to reapply often to maintain moisture
	Iodine based	Absorbent; Antiseptic, only small amounts of free iodine released into wound site; not for use with thyroid; through cytotoxic action against fibroblasts, keratinocytes and leukocytes; only suitable for short-term use.
	Silver based	Antibacterial action well established; broad spectrum; Possible systemic toxicity currently being investigated; Effectiveness varies between products.
4	**Autolytic debridement**	
	Films	Occlusive; allows exchange of gasses
	Hydrocolloids	Provides a moist, hypoxic wound environment; Not for exudative or infected wounds
	Hydrogels	Can provide moisture to dry wounds as well as absorb excess exudates depending; Atraumatic when used correctly; Facilitates autolysis of necrotic tissue, and does not support bacterial growth.
5	**Chemical debridement**	
	Papain/urea	Availability issues in US
	Collagenase	Selective debridement
6	**Absorbent dressings**	
	Foams	Can be cut to any shape, thermally insulating, provides moist interface, absorbs excess exudate, impregnable; Absorbs moderate exudates; Not suitable for dry wounds.
	Hydrogels	Rehydrates to soften dry wounds; Only suitable for low exuding wounds or dry wounds. Can cause maceration in heavily exuding wounds, can shift from dry to wet gangrene in exuding ischaemic ulcers.; Absorbs minimal exudate
	Hydrofibers	Absorbs heavy exudate
	Alginates	Absorbs heavy exudates; They are unsuitable for dry wounds or dry hardened necrotic tissue.
7	**Soft Silicone**	Prevents maceration of the surrounding tissue, atraumatic removal with nonadherence to the wound site, suitable for wide range of wound types, can be used for difficult wound sites, can be left for up to 10 days, can be impregnated with silver. Used in conjunction with secondary absorbent dressing, requires contact with the wound site.
8	**Scaffolds**	
	Scaffold–natural material (Alloderm)	Biocompatible, degradable, and is low in antigenicity; Collagen may enable the transmission of infectious agents and thus requires vigorous disinfection protocols
	Scaffold–Synthetic material (Integra)	Variety of methods of construction, electrospun scaffolds stimulate cellular adhesion. Polylactides degrade to lactic acid ensuring limited host immune response. Localised production of lactic acid may affect the efficacy of some proteins in the local environment.

Source: Murphy PS *et. al.*2012*;* Daunton C *et. al.*2012

Table 4: Novel drug delivery approaches for wound healing managements

S. No.	Company/Products	Descriptions
1	**Activa Healthcare**	**Absorbent Dressings**
	Flivasorb®	These dressings are indicated for highly exuding wounds and/or as a secondary dressing.
	Molnlycke	*__QIPP TIP__-Where possible use dressing pads before using super absorbent dressings.
	Mextra superabsorbent	
2	**ConvaTec**	**Activated Charcoal Dressings**
	Carboflex®	Indications for use include malodorous exuding wounds such as fungating and/or malignant wounds and also infected wounds. *__QIPP TIP__-Charcoal becomes rapidly deactivated once it becomes wet.
3	**ConvaTec**	**Alginate Dressings**
	Kaltostat®	Suitable for a wide range of wound types including cavities, granulating and, sloughy wounds with moderate-to-high levels of exudate. Kaltostat is especially useful for haemostasis in bleeding wounds. Caution is needed as blood clots can adhere to the wound surface. *__QIPP TIP__-Alginate dressing needs to be cut approximately to the size of the wound as the exudate will transfer laterally.
	Kaltostat® Rope	
4	**Smith and Nephew**	**Anti-Microbial-Cadexomer Iodine Dressings**
	Iodoflex®	Cadexomer iodine is recommended for infected wounds. It should not be used in children, pregnant or lactating women or people with renal impairment or thyroid disorders or those receiving Lithium treatment. Maximum single 50g and 150g weekly application. ***QIPP TIP–** If wound not improving to treatment after 4 weeks treatment refer to tissue viability service
5	**Advancis**	**Anti-Microbial-Honey Dressings**
	Activon Tulle®	Beneficial in the management of chronic wounds, including the reduction of odour, anti-inflammatory activity and the stimulation of healing. Should not be used on patients with allergy to bee stings or bee products or in patients with extreme sensitivity to honey. *__QIPP TIP–__Monitor blood glucose for patients who have diabetes.
	Algivon®	
	Actilite®	
	Activon® Tube	
6	**Activa Healthcare**	**Anti-Microbial-PHMB Dressings**
	Suprasorb® X+PHMB Rope	This dressing is an antimicrobial hydrobalance wound dressing. It is suitable for use in a wide variety of wounds such as leg ulcers, pressure ulcer etc. *__QIPP TIP–__It is used to reduce the wound bioburden. If no improvement after 4 weeks use refer to tissue viability service
7	**Smith and Nephew**	**Anti-Microbial Dressings–Silver Dressings**
	Acticoat®	Should be reviewed regularly: weekly and long term use should be avoided. Where there are

	Acticoat® 7 Acticoat® Absorbent Acticoat® Flex 3 Acticoat® Flex 7	large amounts of exudate present an absorbent silver dressing should be used. Not compatible with saline. ***QIPP TIP-**Not recommended for routine use in chronic venous leg ulcers, uncomplicated ulcers, acute wounds. Dressing should be changed every 3-7 days. If wound does not improve refer to tissue viability service
8	**3M Health Care** Tegaderm® **Smith and Nephew** IV 3000 Adhesive IV Film dressing Peripheral lines PICC Line For Central Lines	**Film Dressings** Suitable for shallow wounds and can be used as a secondary dressing, they protects newly epithelialising wounds from trauma. Additionally they can be used to protect skin from exposure to friction. Care needs to be taken while removing dressings and many have a specific method to break the adhesive bond to ensure a non-traumatic removal.
9	**Smith and Nephew** Allevyn® Adhesive Sacral Allevyn® Gentle Border Heel Allevyn® Gentle Border Lite Allevyn® Gentle Allevyn® Non Adhesive **Coloplast** Biatain® Adhesive Biatain® Non Adhesive Biatain® Silicone	**Foam Dressings** Foams can be used on a variety of wounds including pressure ulcers, leg ulcers, burns, surgical wounds, etc. as a primary or secondary dressing. They are available in adhesive bordered format, although some are non-bordered and some are more suitable for delicate or problematic skin. Foams are best suited for exuding wounds and are not recommended for dry superficial wounds. ***QIPP TIP-**Consider the size of the wound when selecting shaped dressings such as heel or sacral as it may be better to use a 10 cm X 10 cm dressing if the wound is small
10	**Coloplast** Comfeel Plus Ulcer Sacral Contour **ConvaTec** DuoDERM® Extra Thin	**Hydrocolloids** Comfeel is often used to debride necrotic tissue. Duoderm is used to protect fragile skin or as secondary dressing. Can be used on a variety of wounds including pressure ulcers, leg ulcers, surgical wounds and minor burns. They can be used in granulating wounds and they can aid in the rehydration and debridement of dry, sloughy and necrotic wounds. ***QIPP TIP-**Avoid bordered hydrocolloids as these do not always adhere and may require more frequent changing due to increase exudate levels.
11	**ConvaTec** Aquacel® Extra Aquacel® Aquacel® Foam Adhesive Aquacel® Foam non adhesive	**Hydrofiber® Technology** Suitable for use in a wide variety of wound types including leg ulcers and pressure ulcers with moderate to high levels of exudate. The dressing absorbs and locks away large amounts of exudate and reduces the likelihood of peri-lesion maceration or excoriation. ***QIPP TIP-**Please ensure that you request Aquacel and not Aquacel AG as this contains silver and is not on formulary
12	**Systagenix Wound Management** Nu-Gel® **Smith and Nephew** Intrasite® Intrasite® Conformable	**Hydrogel** These can be used on dry and sloughy wounds and are good at hydrating dry wounds by providing a moist wound environment. They have been shown to reduce pain.***QIPP Tip-**Hydrogels possess a high water content and should not be used in highly exuding wounds.
13	**Paul Hartman Ltd** Atrauman **Systagenix Wound Management** Adaptic Touch	**Wound Contact Layer** Primary dressings used for low exuding, granulating wounds. Suitable for use under compression bandaging systems. Adaptic Touch can be used on superficial burns to prevent trauma to the wound bed and make dressing changes less painful
14	**Activa Health Care** Activa Leg Ulcer Hosiery Kit **Medi UK** Mediven Ulcer Kit Standard Mediven Ulcer Kit Petite	**Leg Ulcer Hosiery Kits** Hosiery kits allow for cost effective treatment of small venous leg ulcers. This allows patients to self-manage where possible. Kits are less bulky than bandages, which may improve comfort and mobility
15	**Smith & Nephew** Sheet Strips Heel Sacrum/ankle wrap	**Aderma Dermal Pads** Polymer gel-shaped pad that redistributes pressure while protecting and padding bony prominences used for pressure ulcer prevention. ***QIPP TIP–**These pads are washable and reusable.
16	**Activa Health Care** Debrisoft®	**Active Debridement Pad** A soft pad of monofilament polyester fibres intended as a rapid, highly effective and safe debridement method for the removal of loose soft slough in superficial wounds and the surrounding skin. ***QIPP TIP–**Consider using in shallow pressure ulcers with light covering of soft slough prior to pressure ulcer grading.
17	**Smith & Nephew** Renasys® G with Soft Port Gauze Dressing Kit Renasys® F with Soft Port Foam Dressing Kit Renasys® Go Canister Kit Renasys® Y Connector	**Negative Pressure Wound Therapy (NPWT)** This is used for the management of large wounds such as cavity wounds with high exudate. Equipment should be requested from the Integrated Community Equipment Store. Please contact the Tissue Viability Service for support and advice.
18	**3M Health Care** Tegaderm® Matrix **Systagenix Wound Management** Promogram®	**Protease Modulators** Chronic wound healing is characterised by a protracted inflammatory phase as a result of altered biochemistry where elevated levels of proteases are found. The consequences of this distorted biochemical profile is that tissue degrading enzymes matrix metalloproteases (MMPs) interfere with protein synthesis and denature growth factors. These dressings are

	Promogram® Prisma	designed to interact with the wound and modulate protease activity.
19	**Biomond** BioBag®	**Larvae Therapy** A Biosurgical treatment for the debridement of wounds. The larvae are sealed within a dressing which is a finely woven net pouch containing a small piece, or pieces of foam, which aid the growth of the larvae. The larvae remain sealed within the dressing throughout the treatment.
20	**Smith & Nephew** PICO®	**PICO** Indicated for a range of wound types including chronic wounds, incision sites, acute wounds, traumatic wounds, sub-acute and dehisced wounds, partial-thickness burns, ulcers (such as diabetic or pressure), flaps and grafts, dermal substitutes.* **QIPP TIP–**Due to the large cost of these dressings. This treatment is only to be prescribed following assessment by The Tissue Viability Service.

ELFT Formulary Development 2014, Wound Dressing Formulary NHS foundation trust East London 2014, ***QIPP TIP**-Quality Innovation, Productivity and Prevention tips

Fig. 1(a): A typical hydrocolloid dressing, (Tegasorb™). It combines moisture vapour permeability with absorbency, conformability and its transparency allows for wound observation
Source: Boateng JS. *et al.* 2007

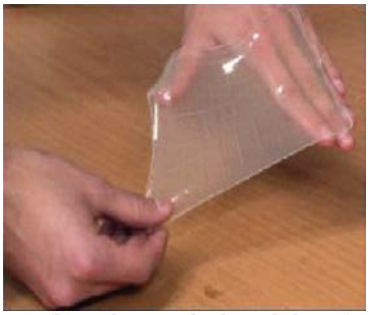

Fig. 1(b): Polymeric hydrogel sheet for wound dressing. It does not need a secondary dressing and due to their flexible nature, can be cut to fit around the wound
Source: Boateng JS. *et al.* 2007

Fig. 1(c): Lyofoam® Max is designed for the management of moderately to highly exuding wounds. Its high absorbency and fluid handling capacity combined with the reduced risk of maceration
Source:http://www.klinemedicalsupply.com/Wound-Care

Fig. 1(d): Application of Kalypto forefoot wound dressing.
Source: http://www.diamondrx.com

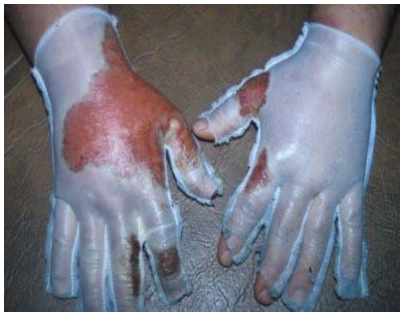

Fig. 1(e): Pictured here are biosynthetic wound dressing gloves.
Source: Wounds 15(1):4-9, 2003. © 2003 Health Management Publications, Inc

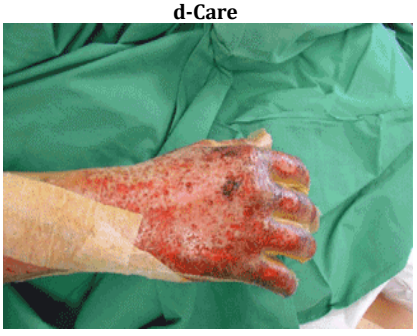

Fig. 1(f): Management of superficial partial thickness burns with Biobrane (15/3 denier nylon fibers)
Source: Greenwood JE. *et al.* 2009

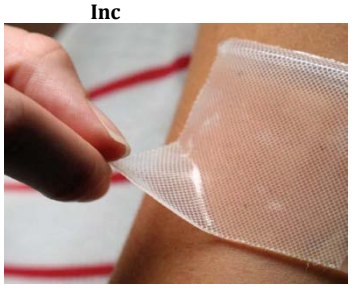

Fig. 1(g): A transdermal adhesive is suitable for use in drug-delivery and combination devices. Offered as part of a company's drug-delivery silicone family, DDR-1370 is a traditional pressure-sensitive adhesive (PSA), while DDR-4355 is a strong-tack silicone gel. Can be used in wound-care applications for dispensing pharmaceutical ingredients such as antibiotics, anti-inflammatory drugs, or antimicrobials. Source: www.nusil.com

Fig. 1: Medicated dressings for drug delivery in wound healing managements

CONCLUSION

This article has considered many classes of wound dressings including topical pharmaceutical agents, traditional wound dressings and modern dressings such as hydrocolloids, alginates, hydrogels, polyurethane film and foam and novel biomaterials such as collagen, chitosan and hyaluronic acid used directly or as tissue engineered matrices for skin replacement. Polymeric dressings

designed as vehicles to deliver therapeutic agents directly to the surface of wounds have also been discussed. These include alginates, chitosan, pectin and hyaluronic acid as polymers of natural origin; collagen sponges and other hydrogel materials; artificial skin grafts and tissue engineered products. The mechanism(s) for the controlled delivery of drugs from polymeric dressings were also considered and the requirement for the development of novel dressings with improved residence on the wound site (prolonged delivery) was also solicited.

Effective dressings should have properties and delivery characteristics that are optimised for specific wound types with minimum or no inconvenience to the patient and at reasonable cost. To achieve such objectives, manipulation of the physical characteristics of the identified systems is necessary. Newer products are currently being used to replace or augment various substrates in the wound healing cascade. Faced with the prospect of increased prevalence of antibiotic-resistant pathogens, and the diminished effectiveness of current therapies, careful consideration of treatment options is now important. With the abundance of available products, the goal is to find the most appropriate modality or combination of modalities to optimize healing. This article extends the information and hopes to give insight into past, present and future treatment strategies and approaches for wound healing management.

ACKNOWLEDGEMENT

I gratefully acknowledge the encouragement and guidance given to me by Dr R. S. Pawar, Associate Professor, VNS group of institutions, Bhopal MP and grateful to Indian council of medical research for providing financial support as ICMR-SRF.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Charman WN, Chan HK, Finnin BC, Charman SA. Drug delivery: a key factor in realising the full therapeutic potential of drugs. Drug Dev Res 1999;46:316-27.
2. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based microand nanoparticles in drug delivery. J Control Release 100;5-28:2004.
3. Clark RA. Cutaneous tissue repair: basic biologic considerations. J Am Acad Dermatol 1985;13:701–25.
4. Wong DJ, Chang HY. Skin tissue engineering in stembook [Internet]. Cambridge, MA: Harvard Stem Cell Institute; 2008.
5. Jahoda CA, Reynolds AJ. Hair follicle dermal sheath cells: Unsung participants in wound healing. Lancet 2001;358:1445–8.
6. Sellheyer K, Krahl D. Skin mesenchymal stem cells: Prospects for clinical dermatology. J Am Acad Dermatol 2010;63:859–65.
7. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Percoraro ER, Rodeheaver G, *et al*. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 1994;130:489-93.
8. Rothe M, Falanga V. Growth factors, their biology and promise in dermatologic diseases and tissue repair. Arch Dermatol 1989;125:1390-8.
9. Shakespeare P. Burn wound healing and skin substitutes. Burns 2001;27:517-22.
10. Schultz GS. Molecular regulations of wound healing. In: Bryant RA. editor. Acute and chronic wounds: Nursing management. 2nd edition. St. Louis, MO: Mosby; 1999. p. 413-29.
11. Cooper DM. Burn wound healing: New standings. Nursing Practice Forum 1999;10:74-86.
12. Evans H. A treatment of last resort. Nursing Times 1997;93:62-5.
13. Moore D. Hypochlorites: A review of the evidence. J Wound Care 1992;1:44-53.
14. Poon VK, Burd A. *In vitro* cytotoxicity of silver: implication for clinical wound care. Burns 2004;30:140-7.
15. Kotek R. Recent advances in polymer fibers. Polymer Rev 2008;48:221.
16. Knighton DR, Ciresi KF, Fiegel VD. Classification and treatment of chronic non-healing wounds. Ann Surg 1986;204:322.
17. Burd A, Kwok CH, Hung SC, Chan HS, Gu H, Lam WK, *et al*. A comparative study of the cytotoxicity of silver-based dressing in monolayer cell, tissue explant and animal model. Wound Rep Regen 2007;15:94-104.
18. Rahman GA, Adigun IA, Yusuf IF, Ofoegbu CKP. Wound dressing where there is limitation of choice. Nigerian J Surgery 2006;8(3-4):151-4.
19. Morgan DA. Wounds-What should a dressing formulary include? Hosp Pharm 2002;9:261–6.
20. Eccleston GM. Wound dressings. In: Aulton ME. editor. Pharmaceutics: The science of dosage form design. 3rd edition. UK: Churchill Livingstone; 2007. p. 264-71.
21. The annual uk drug tariff. 1988 (Nov), 1998 (May). The Stationary Office. London, UK: The UK Drug Tariff; 2007.
22. Rothe M, Falanga V. Growth factors, their biology and promise in dermatologic disease and tissue repair. Arch Dermatol 1989;125:1390-8.
23. Thomas S. Wounds and wound healing. In: Wound management and dressings. 1st edition. London: Pharmaceutical Press; 1990. p. 1–14.
24. Debra JB, Cheri O. Wound healing: Technological innovations and market overview. 1998;2:1-185.
25. Katti DS, Robinson KW, Ko FK, Laurencin CT. Bioresobable nanofiber-based systems for wound healing and drug delivery: Optimisation of fabrication parameters. J Biomed Mater Res Part B 2004;70:286-96.
26. Hoffman AS. Hydrogels for biomedical applications. Adv Drug Delivery Rev 2002;43:3-12.
27. Kietzmann M, Braun M. Effects of the zinc oxide and cod liver oil containing ointment Zincojecol in an animal model of wound healing. Dtsch Tierarztl Wochenschr 2006;113:331-4.
28. Thorn RM, Greenman J, Austin A. An *in vitro* study of antimicrobial activity and efficacy of iodine-generating hydrogel dressings. J Wound Care 2006;15:305-10.
29. Tsou TL, Tang ST, Huang YC, Wu JR, Young JJ, Wang HJ. Poly (2-hydroxyethyl methacrylate) wound dressing containing ciprofloxacin and its drug release studies. J Mater Sci Mater Med 2002;16:95–100.
30. Blanco MD, Garcia O, Gomez C, Sastre RL, Teijon JM. *In-vivo* drug delivery of 5-fluorouracil using poly (2-hydroxyethyl methacrylate-co-acrylamide) hydrogels. J Pharm Pharmacol 2000;52:1319-25.
31. Blanco MD, Trigo RM, Garcia O, Teijon JM. Controlled release of cytarabine from poly (2-hydroxyethyl methacrylate-co-N-vinyl-2-pyrrolidone. J Biomater Sci Polym Ed 1997;8:709-19.
32. Gottrup F, Jorgensen B, Karlsmark T, Sibbald RG, Rimdeika R, Harding K, *et al*. Less pain with Biatain-Ibu: Initial findings from a randomised, controlled, doubleblind clinical investigation on painful leg ulcers. Int Wound J 2007;4:24–34.
33. Jorgensen B, Friis GJ, Gottrup F. Pain and quality of life for patients with venous leg ulcers: Proof of concept of the efficacy of Biatain-Ibu, a new pain reducing wound dressing. Wound Repair Regen 2006;14:233–9.
34. Jorgensen B, Price P, Andersen KE, Gottrup F, Bech-Thomsen N, Scanlon E, et al. The silver-releasing form dressing, Contreet Foam, promotes faster healing of critically colonized venous leg ulcers: A randomised, controlled trial. Int Wound J 2005;2:64–73.
35. Rayman G, Rayman A, Baker NR, Jurgeviciene N, Dargis V, Sulcaite R, *et al*. Sustained silver-releasing dressing in the treatment of diabetic foot ulcers. Br J Nursing 2005;9:109–14.
36. Cho YS, Lee JW, Lee JS, Lee JH, Yoon TR, Kuroyanagi Y, *et al*. Hyaluronic acid and silver sulfadiazine-impregnated polyurethane foams for wound dressing application. J Mater Sci Mater Med 2002;13:861–5.
37. Cutting K, White RJ. Maceration of the skin and wound bed 1: Its nature and causes. J Wound Care 2002;11:275–8.
38. Chen WYJ, Rogers AA, Lydon MJ. Characterization of biological properties of wound fluid collected during early stages of wound healing. J Invest Dermatol 1992;99:559–64.
39. Hareendran A, Bradbury A, Budd J, Geroulakos G, Hobbs R, Kenkre J, *et al*. Measuring the impact of venous leg ulcers on quality of life. J Wound Care 2005;14:53–7.

40. Krasner D. Minimizing factors that impair wound healing: A nursing approach. Ostomy Wound Manag 1995;41:22–6.
41. Lee J, Singletary R, Anderson DJ, Bolognesi M, Kaye KS. Surgical site infection in the elderly following orthopaedic surgery: Risk factors and outcomes. J Bone Jt Surg Am Vol 2006;88:1705-12.
42. Hemila H, Douglas RM. Vitamin C and acute respiratory infections. Int J Tuberculosis Lung Dis 1999;3:756-61.
43. Rojas AI, Philips TJ. Patients with chronic leg ulcers show diminished levels of vitamins A and E, carotenes and zinc. Dermatol Surg 1999;25:601-4.
44. Patel GK. The role of nutrition in the management of lower extremity wounds. Int J Lower Extremity Wounds 2005;4:12–22.
45. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet 2005;366:1736-43.
46. Gu F, Amsden B, Neufeld R. Sustained delivery of vascular endothelial growth factor with alginate beads. J Control Release 2004;96:463-72.
47. Schaller M, Laude J, Bodewaldt H, Hamm G, Korting HC. Toxicity and antimicrobial activity of a hydrocolloid dressing containing silver particles in an ex vivo model of cutaneous infection. Skin Pharmacol Physiol 2004;17:31–6.
48. Lin SS, Ueng SW, Lee SS, Chan EC, Chen KT, Yang CY, *et al*. *In vitro* elution of antibiotic from antibiotic-impregnated biodegradable calcium alginate wound dressing. J Trauma 2000;47:136-41.
49. Meaume S, Vallet D, Morere MN, Teot L. Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection. J Wound Care 2005;14:411–9.
50. Luo Y, Kirke KR, Prestwich GD. Crosslinked hyaluronic acid hydrogel films: New biomaterials for drug delivery. J Control Release 2000;69:169–84.
51. Yerushalmi N, Arad A, Margalit R. Molecular and cellular studies of hyaluronic acid-modified liposomes as bioadhesive carriers for topical drug delivery in wound healing. Arch Biochem Biophys 1994;313:267–73.
52. Defail AJ, Edington HD, Matthews S, Lee WC, Marra KG. Controlled release of bioactive doxorubicin from microspheres embedded within gelatin scaffolds. J Biomed Mater Res 2006;79:954-62.
53. Maeda M, Kadota K, Kajihara M, Sano A, Fujioka K. Sustained release of human growth hormone (hGH) from collagen film and evaluation of effect on wound healing in mice. J Control Release 2001;77:261–72.
54. Aoyagi S, Onishi H, Machida Y. Novel chitosan wound dressing loaded with minocycline for the treatment of severe burn wounds. Int J Pharm 2007;330:138–45.
55. Mi FL, Wu YB, Shyu SS, Schoung JY, Huang YB, Tsai YH, *et al*. Control of wound infections using a bilayer chitosan wound dressing with sustainable antibiotic delivery. J Biomed Mater Res 2002;59:438–9.
56. Denkbas EB, Ozturk E, Ozdemir N, Kececi K, Agalar C. Norfloxacin-loader chitosan sponges as wound dressing material. J Biomater Appl 2004;18:291–303.
57. Ishihara M, Fujita M, Obara K, Hattori H, Nakamura S, Nambu M, *et al*. Controlled releases of FGF-2 and paclitaxel from chitosan hydrogels and their subsequent effects on wound repair, angiogenesis, and tumour growth. Curr Drug Delivery 2006;3:351–8.
58. Sawada Y, Ara M, Yotsuyanagi T, Sone K. Treatment of dermal depth burn wounds with an antimicrobial agent-releasing silicone gel sheet. Burns 1990;16:347–52.
59. Sawada Y, Tadashi O, Masazumi K, Kazunobu S, Koichi O, Sasaki J. An evaluation of a new lactic acid polymer drug delivery system: A preliminary report. Br J Plast Surg 1994;47:158-61.
60. Burrell RE, Morris LR. Anti-microbial coating for medical devices. US Patent; 1998.
61. Keuch P, Murdock K, Czap CA, Lennon L. Non-Stingy adhesive hydrophilic gels. US Patent; 1992.
62. Smith DJ, Pulfer S, Shabani M. Polymeric Wound healing accelerators. US Patent; 1996.
63. Suwelack W, Tewes-Schwarzer P, Ecmayer Z. Freeze-dried polysaccharide bio-matrix useful as pharmaceutical or cosmetic carrier. German Patent DE4328329; 1994.
64. Holgaard A. Pharmaceutical preparation. World Patent WO9119480; 1991.
65. Qin Y, Keith D, Nephente W. Dehydrated hydrogels. World patent WO 9739781; 1997.
66. Sakchai W, Churrerat P, Srisagul S. Development and *in vitro* evaluation of chitosan-eudragit RS 30D composite wound dressings. AAPS Pharm Sci Tech 2006;7:E1–E6.
67. Mangala E, Kumar TS, Baskar S, Rao KP. Dev of chitosan/polyvinylalcohol blend membranes as burn dressings. Trends Biomater Artif Organs 2003;17:34-40.
68. Whitaker MJ, Quirk RA, Howdle RA, Shakesheff KM. Growth factor release from tissue engineering scaffolds. J Pharm Pharmacol 2001;53:1427-37.
69. Storie H, Mooney DJ. Sustained delivery of plasmid DNA from polymeric scaffolds for tissue engineering. Adv Drug Delivery Rev 2006;58:500–14.
70. Kumar TRS, Bai MV, Krishnan LK. A freeze-dried fibrin disc as a biodegradable drug release matrix. Biologicals 2004;32:49–55.
71. Matthews KH, Auffret AD, Humphrey MJ, Stevens HNE, Eccleston GM. Wafers for wound healing. Int J Pharm 2005;289:51–62.
72. Hubbell JA. Hydrogel systems for barriers and local drug delivery in the control of wound healing. J Control Release 1996;39:305-13.
73. Shang-Yang L, Shao-Ko C, Run-Chu L. Organic esters of plasticizers affecting the water absorption, adhesive property, glass transition temperature and plasticizer performance of Eudragit acrylic films. J Control Release 2000;68:343-50.
74. Burnett S, Edwardson PAD, Mandley DJ, Velada J. World Patent WO 0234304A1; 2002.
75. Knapp B, Disalvo R. Gel-based cosmetic and wound healing formulation and method. US Patent 2004101515; 2004.
76. Walacavage AJ, Holland JF. Biodegradable wound dressing. US Patent 2004131663; 2004.
77. Matthews KH, Auffret AD, Humphrey MJ, Stevens HNE, Eccleston GM. Gamma irradiation of lyophilised wound healing wafers. Int J Pharm 2006;313:78-86.
78. Dijke P, Iwata KK. Growth factors for wound healing. Biotechnol 1989;7:793–8.
79. Hansen SL, Voigt DW, Wiebelhaus P, Paul CN. Using skin replacement products to treat burns and wounds: Advances in Skin & amp. Wound Care 2001;14(1):37–45.
80. Pham C, Greenwood J, Cleland H, Woodruff P, Maddern G. Bioengineered skin substitutes for the management of burns: A systematic review. Burns 2007;33(8):946–57.
81. Hansbrough JF, Mozingo DW, Kealey GP, Davis M, Gidner A, Gentzkow GD. Clinical trials of a biosynthetic temporary skin replacement, dermagraft-transitional covering, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. " J Burn Care Rehabil 1997;18(1):I43–51.
82. Spielvogel RL. A histologic study of Dermagraft-TC in patients burn wounds. J Burn Care Rehabil 1997;18(1):S16–S18.
83. Jones I, Currie L, Martin R. A guide to biological skin substitutes. British J Plast Surg 2002;55(3):185–93.
84. Falanga V, Margolis D, Alvarez O. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Arch Dermatol 1998;134(3):293-300.
85. Gottlieb ME. Management of complex and pathological wounds with Integra: The Wound Management Manual, McGraw-Hill, New York, NY, USA; 2004. p. 226–89.
86. R Goldman. Growth factors and chronic wound healing: past, present, and future. Adv Skin Wound Care 2004;17:24.
87. Bennett SAL, Birnboim HC. Receptor-mediated and protein kinase-dependent growth enhancement of primary human fibroblasts by platelet activating factor. Mol Carcinog 1997;20(4):366-75.
88. Barnes CP, Sell SA, Boland ED, Simpson DG, Bowling GL. Nanofibers technology: Designing the next generation of tissue engineering scaffolds. Adv Drug Delivery Rev 2007;59:1413-33.
89. Gunn J, Zhang M. Polyblend nanofibers for biomedical applications: perspectives and challenges. Trends Biotechnol 2010;28:189-97.

90. Zahedi P, Rezaeian I, Ranaei-Siadat SO, Jafari SH, Supaphol P. A review on wound dressings with an emphasis on electro spunnanofibrous polymeric bandages. Polym Adv Technol 2010;21:77-95.
91. Singer AJ, Dagum AB. Current management of acute cutaneous wounds. N Engl J Med 2008;359:1037.
92. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010;33(5):998-1003.
93. Abidia A, Laden G, Kuhan G. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomized-controlled trial. Eur J Vascular Endovascular Surg 2003;25(6):513–8.