

Wound Healing Dressings and Drug Delivery Systems: A Review

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ABSTRACT: The variety of wound types has resulted in a wide range of wound dressings with new products frequently introduced to target different aspects of the wound healing process. The ideal dressing should achieve rapid healing at reasonable cost with minimal inconvenience to the patient. This article offers a review of the common wound management dressings and emerging technologies for achieving improved wound healing. It also reviews many of the dressings and novel polymers used for the delivery of drugs to acute, chronic and other types of wound. These include hydrocolloids, alginates, hydrogels, polyurethane, collagen, chitosan, pectin and hyaluronic acid. There is also a brief section on the use of biological polymers as tissue engineered scaffolds and skin grafts. Pharmacological agents such as antibiotics, vitamins, minerals, growth factors and other wound healing accelerators that take active part in the healing process are discussed. Direct delivery of these agents to the wound site is desirable, particularly when systemic delivery could cause organ damage due to toxicological concerns associated with the preferred agents. This review concerns the requirement for formulations with improved properties for effective and accurate delivery of the required therapeutic agents. General formulation approaches towards achieving optimum physical properties and controlled delivery characteristics for an active wound healing dosage form are also considered briefly. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 97:2892–2923, 2008

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INTRODUCTION

Wound dressings and devices form an important segment of the medical and pharmaceutical

wound care market worldwide. In the past, traditional dressings 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. It has now been shown however, that having a warm moist wound environment achieves more rapid and successful wound healing. The last two decades have witnessed the introduction of many dressings, with new ones becoming available each year. For example, the number of newer dressings available

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on the Drug Tariff¹ in the UK increased from 4 in 1988 to 57 in May 1998 and by February 2007, the total number stood at 262. These 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.

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.² 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.

This review discusses the common wound healing dressings, their key advantages and shortcomings, and the need for dressings with improved properties. The definition and classification of wounds together with the different stages of wound healing are also briefly described, as they directly affect the choice of a particular dressing. In addition, recent advances in dressings are discussed within the context of the formulations for delivering therapeutic agents to moist wound surfaces. Finally, general physical characterisation of topical dressings, for application to wounds, in terms of their fluid handling, moisture vapour permeability, fluid affinity, water uptake, rheological properties (gel and tensile strength, elasticity), compressive and bio-adhesive properties are specifically discussed.

WOUNDS

A wound can be described as a defect or a break in the skin, resulting from physical or thermal damage or as a result of the presence of an underlying medical or physiological condition.

According to the Wound Healing Society, a wound is the result of 'disruption of normal anatomic structure and function'.³ Based on the nature of the repair process, wounds can be classified as acute or chronic wounds. Acute wounds are usually tissue injuries that heal completely, with minimal scarring, within the expected time frame, usually 8–12 weeks.⁴ The primary causes of acute wounds include mechanical injuries due to external factors such as abrasions and tears which are caused by frictional contact between the skin and hard surfaces. Mechanical injuries also include penetrating wounds caused by knives and gun shots and surgical wounds caused by surgical incisions to for example remove tumours. Another category of acute wounds include burns and chemical injuries, which arise from a variety of sources such as radiation, electricity, corrosive chemicals and thermal sources. The temperature of the source and the exposure time influence the degree of a thermal burn.⁵ Burns will normally require specialist care because of the associated trauma.

Chronic wounds on the other hand arise from tissue injuries that heal slowly, that is have not healed beyond 12 weeks⁶ and often reoccur. Such wounds fail to heal due to repeated tissue insults or underlying physiological conditions⁷ such as diabetes and malignancies, persistent infections, poor primary treatment and other patient related factors. These result in a disruption of the orderly sequence of events during the wound healing process (see later). Chronic wounds include decubitus ulcers (bedsores or pressure sores) and leg ulcers (venous, ischaemic or of traumatic origin).

Wounds are also classified based on the number of skin layers and area of skin affected.^{8,9} Injury that affects the epidermal skin surface alone is referred to as a superficial wound, whilst injury involving both the epidermis and the deeper dermal layers, including the blood vessels, sweat glands and hair follicles is referred to as partial thickness wound. Full thickness wounds occur when the underlying subcutaneous fat or deeper tissues are damaged in addition to the epidermis and dermal layers.

Ferreira et al.¹⁰ have described wounds both acute and chronic that are difficult to heal as 'complex wounds' with unique characteristics. The properties of complex wounds from their review can be summarised as: (a) extensive loss of the integument which comprises skin, hair, and associated glands, (b) infection (e.g. Fournier's gangrene) which may result in tissue loss,

(c) tissue death or signs of circulation impairment and (d) presence of pathology.

Wound Healing

Wound healing is a specific biological process related to the general phenomenon of growth and tissue regeneration. It is not the purpose of this paper to review in detail the physiology of wound healing, but to describe only that which is relevant to wound management and the choice of wound dressings. The reader is referred to the biological and physiological texts and literature for detailed scientific expositions.^{11–14} 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.^{15,16} The wound healing process has been reviewed and described by Schultz¹⁴ as

comprising five overlapping stages that involve complex biochemical and cellular processes. These are described as haemostasis, inflammation, migration, proliferation and maturation phases (Fig. 1). In fact, Cooper¹⁷ has argued for expanding the understanding of wounds beyond the cellular level to a molecular context as well. He emphasised the need to approach wound healing at multiple levels (cellular and molecular) to help improve wound treatment and management. Wound healing formulations (dressings) and novel technologies developed to date focus on one or more of these aspects of the natural healing process¹⁸ that are summarised briefly below.

Haemostasis and Inflammation

Bleeding usually occurs when the skin is injured and serves to flush out bacteria and/or antigens from the wound. In addition, bleeding activates

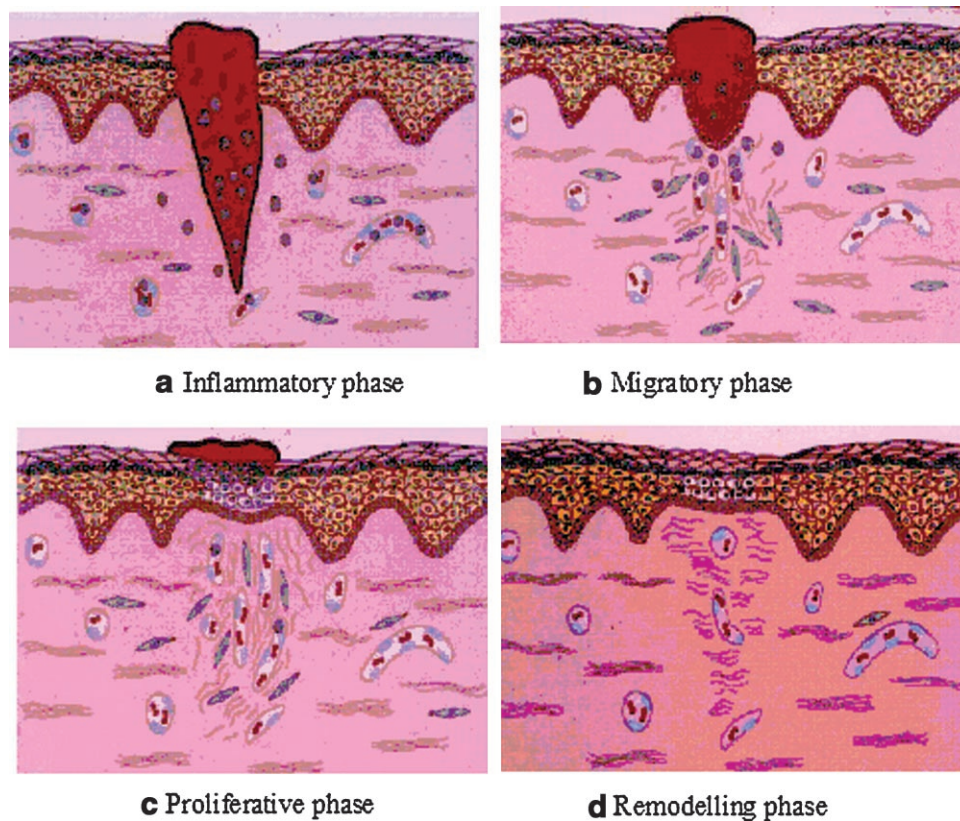


Figure 1. Schematic representation of the phases of wound healing (a) infiltration of neutrophils into the wound area (b) invasion of wound area by epithelial cells (c) epithelium completely covers the wound (d) many of the capillaries and fibroblasts, formed at early stages have all disappeared (adopted from Gandour—unpublished).

haemostasis which is initiated by exudate components such as clotting factors. Fibrinogen in the exudate elicits the clotting mechanism resulting in coagulation of the exudates (blood without cells and platelets) and, together with the formation of a fibrin network, produces a clot in the wound causing bleeding to stop. The clot dries to form a scab and provides strength and support to the injured tissue. Haemostasis therefore, plays a protective role as well as contributing to successful wound healing.¹⁹

The inflammatory phase occurs almost simultaneously with haemostasis, sometimes from within a few minutes of injury to 24 h and lasts for about 3 days. It involves both cellular and vascular responses. The release of protein-rich exudate into the wound causes vasodilation through release of histamine and serotonin, allows phagocytes to enter the wound and engulf dead cells (necrotic tissue). Necrotic tissue which is hard is liquefied by enzymatic action to produce a yellowish coloured mass described as sloughy (Tab. 1). Platelets liberated from damaged blood vessels become activated as they come into contact

with mature collagen and form aggregates as part of the clotting mechanism.

Migration

The migration phase involves the movement of epithelial cells and fibroblasts to the injured area to replace damaged and lost tissue. These cells regenerate from the margins, rapidly growing over the wound under the dried scab (clot) accompanied by epithelial thickening.

Proliferation

The proliferative phase occurs almost simultaneously or just after the migration phase (Day 3 onwards) and basal cell proliferation, which lasts for between 2 and 3 days. Granulation tissue is formed by the in-growth of capillaries and lymphatic vessels into the wound and collagen is synthesised by fibroblasts giving the skin strength and form. By the fifth day, maximum formation of blood vessels and granulation tissue

Table 1. Classification of Wounds Based on the Appearance

Wound Type	Appearance	Stage of Wound Healing Affected
Necrotic	Often black or olive green due to dead devitalised tissue, that is dry, thick and leathery to touch. Common with pressure sores	Under favourable conditions, dead tissue in a wound such as a pressure sore will usually separate spontaneously from the healthy tissue beneath. This occurs as a result of autolysis and presumably involves macrophage activity and the action of proteolytic enzymes which act at the interface of the necrotic and healthy tissue A dry environment prevents the autolytic and proteolytic actions of macrophages and enzymes
Sloughy	Fluid, moist, loose and stringy rehydrated necrotic tissue that is typically yellow in colour	Associated with excess exudates during inflammatory phase. Slough leads to wounds getting stuck in the late inflammatory stage leading resulting in delayed wound healing
Granulating	Significant quantities of granulation tissue, generally red or deep pink in colour. May produce excess exudate	Proliferative phase
Epithelialising	Pink in colour with formation of new epidermis	Involves both migratory and proliferative phases. Final stages of wound healing
Infected and malodorous	Red, hot inflamed tissue, pus present. Infection with anaerobic bacteria causes unpleasant odour	Inflammatory response, collagen synthesis, epithelisation. Infection prolongs the inflammatory process which delays wound healing

Each wound type represents the phases that a single wound may go through as it heals.²¹

has occurred. Further epithelial thickening takes place until collagen bridges the wound. The fibroblast proliferation and collagen synthesis continues for up to 2 weeks by which time blood vessels decrease and oedema recedes.

Maturation

This phase (also called the 'remodelling phase') involves the formation of cellular connective tissue and strengthening of the new epithelium which determines the nature of the final scar. Cellular granular tissue is changed to an acellular mass from several months up to about 2 years.

Table 1 describes the appearance of wounds in relation to the stages of wound healing. These descriptions relate not only to different types of wounds but also to the various stages through which a single wound may pass as it heals.^{20,21}

Wound Exudate

Thomas²² has described wound exudate as: 'a generic term given to liquid produced from chronic wounds, fistulae or other more acute injuries once haemostasis has been achieved'. It is essentially blood from which most of the red cells and platelets have been removed. Exudate is a key component in all the stages of wound healing, irrigating the wound continuously and keeping it moist.²³ The maintenance of a moist wound bed is widely accepted as the most ideal environment for effective wound healing.²⁴ Exudate also supplies the wound with nutrients and provides favourable conditions for migration and mitosis of epithelial cells.²⁵ In addition, exudate supplies the wound with leucocytes which helps to control bacteria and reduce the incidence of infection at the wound surface.

In certain conditions such as chronic wounds, there is excessive amounts of exudates present which can lead to complications. Excess exudate results from oedema caused by inflammation, reduced mobility and venous or lymphatic insufficiency.²⁶ Increased exudate levels may also be the result of liquefying hard and eschar-like necrotic tissue to produce a wet and sloughy mass by a process known as autolytic debridement. A key characteristic of modern wound dressings is the removal of excess exudate while maintaining moisture at the wound bed.²⁷

Factors Which Impair Wound Healing: Chronic Wounds

Although most wounds will heal uneventfully, problems can sometimes occur, that lead to failure of the wound to heal or a prolonged healing time. Failure of a wound to heal within the expected time frame usually results in a chronic wound. A chronic wound fails to heal because the orderly sequence of events is disrupted at one more of the stages of wound healing. Excessive production of exudates can cause maceration of healthy skin tissue around the wound²⁸ and inhibit wound healing. In addition, exudate from chronic wound differs from acute wound fluid with relatively higher levels of tissue destructive proteinase enzymes²⁹ and therefore more corrosive. The smell and staining caused by exudate can also have a negative impact on a patient's general health and quality of life.³⁰

Foreign bodies introduced deep into the wound at time of injury can cause chronic inflammatory responses delaying healing and sometimes leading to granuloma or abscess formation. Other problems associated with wound healing include the formation of keloid (raised) scars resulting from excess collagen production in the latter part of the wound healing process.¹⁹ Pathogenic bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyrogenes* and some *Proteus*, *Clostridium* and *Coliform* species can be detrimental to the healing process. Inadequate control measures to manage infected wounds can lead to cellulitis (cell inflammation) and ultimately bacteraemia and septicaemia, both of which can be fatal. It has been shown that the presence of *P. aeruginosa* and *S. aureus* significantly reduced skin graft healing and also that 94% of ulcers that were slow to heal, or recurred after discharge, contained *S. aureus*.³¹ In a review on improving the healing of chronic wounds, Krasner³² outlined a number of factors that needed to be controlled and managed effectively including preventing infection, optimising exudate control and removing foreign bodies which could lead to complications.

Poor nutritional status and old age³³ also reduce the ability to fight infection. Protein, vitamin (e.g. vitamin C) and mineral deficiencies impair the inflammatory phase and collagen synthesis, leading to prolonged healing times.³⁴⁻³⁶ Underlying diseases such as diabetes³⁷ and anaemia delay wound healing because compromised circulation results in the delivery of inadequate

nutrients, blood cells and oxygen to the wound. Treatment with drugs such as steroids suppress the body's inflammatory responses and thereby impede the inflammatory stage of wound healing, which eventually leads to a compromised immune system. Glucocorticoids for example have been shown to impair wound healing in both rats and humans^{38,39} and Chedid et al.⁴⁰ investigated the effect of glucocorticoids on keratinocyte growth factor (KGF) and its implications for wound healing inflammation. They suggested that observed inhibition of KGF *in vitro* could have similar effects during wound healing.

Effective Wound Management

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 2 describes factors to be considered in the choice of wound dressings based on their performance characteristics (functions).^{1,15,56}

Debridement

It is important to remove necrotic tissue or foreign material from areas around the wound to increase the chances of wound healing and this process is known as wound debridement. Debridement of the wound area is important because the open wound bed cannot be observed and assessed effectively with necrotic tissue. The presence of necrotic tissue or foreign material in a wound also increases the risk of infection and sepsis and also prolongs the inflammatory phase, which inhibits

Table 2. Functions (Desirable Characteristics) of Wound Dressings after Eccleston²¹

Desirable Characteristics	Clinical Significance to 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 cells and break down extracellular matrix materials and growth factors, thus delaying wound healing. Excess exudate can also macerate surrounding skin
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

wound healing. Several methods are employed for wound debridement including: surgical removal using scalpel and scissors, hydrotherapy or wound irrigation and autolytic removal by rehydration of necrotic tissue, for example using hydrogel dressings (see later), enzymatic removal using bacterial derived collagenases or preparations such as streptokinase.

Falabella⁴¹ has reviewed the various types of debridement in terms of their advantages and disadvantages as well as the basis for their clinical efficacy and safety. Leaper⁴² has noted in his review of the above debridement methods that, the surgical approach involving continuous tissue debridement using a scalpel should be considered the gold standard. However, this approach can only be undertaken by highly skilled and trained practitioners. A systemic approach for assessing and managing chronic wounds, referred to as wound bed preparation has been developed.⁴³ This approach comprises four individual steps described with the acronym 'TIME': tissue assessment and the management of tissue deficits, inflammation and infection control, moisture balance and enhancing epithelial advancement of wound edges. Other authors have subsequently reviewed the scientific and clinical principles underlying wound bed preparation and the reader is referred to these.⁴⁴⁻⁴⁷

There has been a resurrection of the ancient use of maggots for the debridement of wound surfaces and these insect larvae are now bred under aseptic conditions in the laboratory for such use.^{48,49} Maggots debride necrotic and sloughy wounds (see Tab. 1) by dissolving only dead and infected tissue. This is achieved by the secretion of proteolytic enzymes that liquefy necrotic tissue⁵⁰ and allows them to absorb the dead tissue in a semi-liquid form over the course of several days. In addition to removing necrotic tissue, maggots disinfect wounds by killing bacteria and also stimulate faster wound healing especially for chronic wounds.⁵¹⁻⁵³ It has been suggested that maggots also stimulate the production of granulation tissue.^{54,55}

Thomas⁵⁶ has noted in a review that, a key objective in the choice of a dressing is to 'provide an environment at the surface of the wound in which healing could take place at the maximum rate consistent with a completely healed wound, having an acceptable cosmetic appearance'. In most cases, a combination of dressings is needed in order to achieve complete wound healing in a reasonable time. Some dressings such as gauze

and saline are useful for the initial 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 and a detailed discussion is found in the ensuing sections.

WOUND DRESSINGS

Wound dressings have developed over the years from the crude applications of plant herbs, animal fat and honey to tissue engineered scaffolds. Many traditional medicinal plants used in Africa to treat wounds exhibit antibacterial activity.⁵⁷ The leaves of *Guiera senegalensis* used in Senegal and Nigeria for treating wounds and inflammatory swelling, show antibacterial and anti radical effects.⁵⁸ Ghanaian researchers have reported that extracts of *Commelina diffusa* herb and *Spathodea campanulata* bark used traditionally in wound treatment, show antimicrobial and antioxidant activity against *Trichophyton species*.⁵⁹ However, most plants, when applied directly, or as the crude extract, would contain microorganisms, making them potential sources of infection. Crude plant extracts also contain other chemicals which might be potentially harmful to exposed tissue and detrimental to the wound healing process. Recognition of the importance of cleanliness and good aseptic practice in medicine and surgery has led to improvements in the quality of wound management materials.

Classification of Dressings

Dressings are classified in a number of ways depending on their function in the wound (debridement, antibacterial, occlusive, absorbent, adherence),⁶⁰ type of material employed to produce the dressing (e.g. hydrocolloid, alginate, collagen)⁶¹ and the physical form of the dressing (ointment, film, foam, gel)⁶² and these have been reviewed recently.²¹ Dressings are further classified into primary, secondary and island dressings.⁶³ Dressings which make physical contact with the wound surface are referred to as primary dressings while secondary dressings cover the primary dressing. Island dressings possess a central absorbent region that is surrounded by an adhesive portion. Other classification criteria

include traditional dressings, modern and advanced dressings, skin replacement products and wound healing devices. There have been many studies conducted relating to specific dressings.^{2,15,56}

Classification criteria can be useful in the selection of a given dressing but many dressings fit all the criteria.⁶³ For example an occlusive dressing may also be a hydrocolloid. In this review dressings are classified according to traditional or modern (moist wound environment) dressings. Modern dressings are discussed under the type of material (hydrocolloid, alginate, hydrogel) employed to produce the dressing and the physical form (film, foam) of the dressing.

Traditional Wound Healing Agents

These were used commonly in the past and though now less widely used, they are still of some benefit in certain clinical settings for wound treatment. Traditional wound healing agents include topical liquid and semi-solid formulations as well as dry traditional dressings.

Topical Pharmaceutical Formulations

These formulations are prepared as liquid (solutions, suspensions and emulsions) and semi-solid (ointments and creams) preparations and their use is widespread. Solutions such as povidone-iodine are most effective in the initial stages of wound healing for reducing bacterial load and as debriding and desloughing agents to prevent maceration of healthy tissue by the removal of necrotic tissue from the fresh wound. Antimicrobial agents such as silver, povidone-iodine⁶⁴ and polyhexamethylene biguanide⁶⁵ are sometimes incorporated into dressings to control or prevent infection. Physiological saline solution is used for wound cleansing to remove dead tissue and also washing away dissolved polymer dressings remaining in a wound.⁶⁶⁻⁶⁸ Saline solution is also used to irrigate dry wounds during dressing change to aid removal with little or no pain. The major problem with liquid dosage forms, however, is short residence times on the wound site, especially where there is a measurable degree of suppuration (exuding) of wound fluid.

Semi-solid preparations such as silver sulphadiazine cream⁶⁹ and silver nitrate ointment⁷⁰ used to treat bacterial infection remain on the surface of the wound for a longer period of time compared with solutions. For highly exuding

wounds, semi-solid preparations are not very effective at remaining on the wound area as they rapidly absorb fluid, lose their rheological characteristics and become mobile.

Traditional Dressings

Traditional dressings include cotton wool, natural or synthetic bandages and gauzes. Unlike the topical pharmaceutical formulations, these dressings are dry and do not provide a moist wound environment. They may be used as primary or secondary dressings, or form part of a composite of several dressings with each performing a specific function. For example Gamgee tissue, comprising a tubular cotton gauze wrap surrounding a layer of absorbent cotton wool is used to absorb exudate and applied over a primary wound dressing to avoid contaminating the wound with cellulose fibres. Bandages are made from natural (cotton wool and cellulose) and synthetic (e.g. polyamide) materials which perform different functions. For example, Cotton Conforming Bandage 1988⁷¹ is used for the retention of light dressings, High Compression Bandages, are used for the application of sustained compression in the treatment of venous insufficiency. Short Stretch Compression Bandage is used for venous leg ulcers and lymphoedema. Polyamide and Cellulose Contour Bandage, Knitted BP 1988⁷² is used for dressing retention.

Gauze dressings are made from woven and nonwoven fibres of cotton, rayon polyester or a combination of both. The history of traditional gauze dressings and problems associated with their use has been reviewed by Jones.⁷³ In this review, issues are also addressed with reference to the continued use of traditional gauze dressings even with the introduction of more modern ones. The use of soaked gauze for packing open surgical and cavity wounds has also been reviewed in the light of their known shortcomings in comparison to the more recent dressings currently available for chronic wounds.⁷⁴ Sterile gauze pads are used for packing open wounds to absorb fluid and exudates with the fibres in the dressing acting as a filter to draw fluid away from the wound. Gauze dressings need to be changed regularly to prevent maceration of the healthy underlying tissue and have been reported to be less cost effective compared with the more modern dressings.⁷⁵

Though gauze dressings can provide some bacterial protection, this is lost when the outer surface of the dressing becomes moistened either

by wound exudate or external fluids. In addition gauze dressings tend to become more adherent to wounds as fluid production diminishes and are painful to remove, thus causing patient discomfort.⁷⁶ Gauze dressings also provide little occlusion and allow evaporation of moisture resulting in a dehydrated wound bed although gauze impregnated with soft paraffin is occlusive and easier to remove from the skin. It has been suggested that traditional dressings should be employed only for wounds that are clean and dry or used as secondary dressing to absorb exudates and protect the wound.²

Traditional wound healing agents have been largely replaced for chronic wounds and burns by the more recent and advanced dressings because topical liquid and semi-solid formulations do not remain on the wound surface long enough whilst dry traditional dressings do not provide a moist environment for wound healing.

Modern Wound Dressings

Modern dressings have been developed as an improvement upon the traditional wound healing agents described above. Their essential characteristic is to retain and create a moist environment around the wound to facilitate wound healing. The modern dressings are mainly classified according to the materials from which they are produced including hydrocolloids, alginates and hydrogels, and generally occur in the form of gels, thin films and foam sheets.

Hydrocolloid Dressings

Hydrocolloid dressings are among the most widely used dressings. The role of hydrocolloid dressings, their properties, mechanism of action and the range of wounds for which they are useful have been reviewed.^{68,77} The term 'hydrocolloid' describes the family of wound management products obtained from colloidal (gel forming agents) materials combined with other materials such as elastomers and adhesives. Typical gel forming agents include carboxymethylcellulose (CMC), gelatin and pectin. Examples of hydrocolloid dressings include GranuflexTM and AquacelTM (Conva Tec, Hounslow, UK), ComfeelTM (Coloplast, Peterborough, UK) and TegaserbTM (3M Healthcare, Loughborough, UK). They occur in the form of thin films and sheets (Fig. 2) or as composite dressings in combination with other



Figure 2. A typical hydrocolloid dressing, (TegaserbTM Thin Hydrocolloid Dressing, 3M Healthcare, Loughborough, UK). The dressing combines moisture vapour permeability with absorbency and conformability, and its transparency allows for wound observation.

materials such as alginates. Hydrocolloid dressings are useful clinically because unlike other dressings, they adhere to both moist and dry sites.⁷⁸ Hydrocolloid dressings are used for light to moderately exuding wounds (Tab. 1) such as pressure sores, minor burns and traumatic injuries. They are also used to manage leg ulcers where they appear to have advantages in the treatment of wounds that fail to respond to compression therapy alone.⁷⁹ In their intact state, hydrocolloid dressings are impermeable to water vapour but on absorption of wound exudate, a change in physical state occurs with the formation of a gel covering the wound. They become progressively more permeable to water and air as the gel forms.⁸⁰ As they do not cause pain on removal, they are particularly useful in paediatric wound care for management of both acute and chronic wounds.⁸¹ A comparative study conducted to evaluate a hydrocolloid dressing (Comfeel Ulcer DressingTM) combined with compression stocking and a rigid bandage (Unna boot) for treating venous ulcers⁷⁹ found the hydrocolloid dressing-compression stocking combination to be superior

to the rigid bandage. In that study the two groups of dressings were compared by monitoring time to complete healing, reduction of wound surface, pain during application and the total duration of dressing change. A randomised trial comparing paraffin gauze and a hydrocolloid dressing applied to skin graft donor sites showed that the hydrocolloid achieves faster healing and is a less painful dressing.⁸² Another study, involving patients with lacerations, abrasions and minor operation incisions, compared a hydrocolloid dressing with a nonadherent dressing. While time to heal was similar for both groups, patients using the hydrocolloid experienced less pain, required less analgesia and were able to carry out their normal daily activities including bathing or showering without affecting the dressing or the wound.⁸³ Some possible mechanisms involved in hydrocolloids' ability to reduce pain have been discussed.⁸⁴

Hoekstra et al.⁸⁵ found that Aquacel™ hydrocolloid dressing performed more efficiently compared with tulle gauze dressing, in terms of the acute inflammatory responses observed at the initial stages of wound healing, in partial thickness wounds in rats. Hydrocolloid dressings generally have an occlusive outer cover that prevents water vapour exchange between the wound and its surroundings. This can be disadvantageous for infected wounds that require a certain amount of oxygen to heal rapidly. Another disadvantage applies to dressings containing fibres that are deposited in the wound and often have to be removed during dressing change.

Microscopic studies comparing CMC hydrocolloid and alginate dressings for their ability to adsorb harmful bacteria showed the CMC dressings to be superior.⁸⁶ In that study, it was demonstrated that the CMC containing wound dressing produced a gel upon hydration that was effective in encapsulating large numbers of *P. aeruginosa* and *S. aureus*. The authors also demonstrated the ability of CMC to immobilise these bacteria within the swollen fibres unlike the alginate gel, which immobilised fewer numbers of these bacteria.

Alginate Dressings

Alginate dressings are produced from the calcium and sodium salts of alginic acid, a polysaccharide comprising mannuronic and guluronic acid units. Alginate dressings occur either in the form of freeze-dried porous sheets (foams) or as flexible fibres, the latter indicated for packing cavity

wounds. The use of alginates as dressings stems primarily from their ability to form gels upon contact with wound exudates (high absorbency). The high absorption occurs via strong hydrophilic gel formation, which limits wound secretions and minimises bacterial contamination.⁸⁷ Alginates rich in mannuronate, such as Sorbsan™ (Maersk, Suffolk, UK) form soft flexible gels upon hydration whereas those rich in guluronic acid, like Kaltostat™ (Conva Tec), form firmer gels upon absorbing wound exudate. Some contain calcium alginate fibre such as Sorbsan™ and Tegagen™ (3M Healthcare). Comfeel Plus™ is a hydrocolloid/alginate combination dressing.

When applied to wounds, ions present in the alginate fibre are exchanged with those present in exudate and blood to form a protective film of gel.⁸⁸ This helps to maintain the lesion at an optimum moisture content and healing temperature. The gelling property of the alginates is attributed to the presence of calcium ions which help to form a crosslinked polymeric gel that degrades slowly. The ability of calcium ions to form crosslinks with the alginic acid polymer makes calcium alginate dressings ideal materials as scaffolds for tissue engineering.^{89,90} A comparative study of hydrocolloid dressings and alginates showed that alginates gels remain on the wound for a longer period than hydrocolloids.⁹¹

Alginate dressings, as well as forming gels, have a pharmacological function due to the action of the calcium ions present in the dressing. The role of calcium alginate in the wound healing process was investigated by Schmidt and Turner⁹² who suggested that it may help in the production of mouse fibroblast. This process was further modelled *in vitro* by Doyle et al.⁹³ who showed that calcium alginate increased proliferation of fibroblasts but not their motility. This suggests that the effects of the dressing may have been mediated by calcium ions released from the alginate and therefore calcium alginate may improve some cellular aspects of wound healing but not others. Thomas et al.,⁹⁴ have reported that some alginate dressings activate human macrophages to produce tumour necrosis factor- α (TNF α) which initiates inflammatory signals, as part of the wound healing process. Lansdown⁹⁵ has reviewed the potential role of calcium released from alginates in the wound healing process. Alginate dressings are useful for all stages of wound healing described above. Calcium ions present in alginate dressings, when released into the wound, also play a physiological role aiding in

the clotting mechanism (haemostat) during the first stage of wound healing.^{96–99} The early use of alginates as haemostats and wound dressings and their apparent lack of toxicity are discussed by Blaine¹⁰⁰ and later, clinical studies proved their successful use in neurosurgery.¹⁰¹

Alginate dressings are useful for moderate to heavily exuding wounds. Alginate dressings in the form of fibres when trapped in a wound are readily biodegradable¹⁰² and can be rinsed away with saline irrigation. Subsequent removal therefore, does not destroy granulation tissue, making dressing change virtually painless. The ease of biodegradation is exploited in making alginate sutures used in surgical wound closures. A study of different brands of alginate dressings showed significant differences in characteristics such as fluid retention, adherence and dressing residues.¹⁰³ Since alginate dressings require moisture to function effectively, they cannot be used for dry wounds and those covered with hard necrotic tissue. This is because it could dehydrate the wound, delaying healing and this is their major disadvantage.

Hydrogel Dressings

Hydrogels are insoluble, swellable hydrophilic materials made from synthetic polymers such as poly(methacrylates) and polyvinylpyrrolidone. Some dressings such as Nu-gelTM (Johnson & Johnson, Ascot, UK) and PurilonTM (Coloplast) are hydrogel/alginate combinations. Hydrogels can be applied either as an amorphous gel or as elastic, solid sheet or film (Fig. 3). To prepare the sheets, the polymeric components are crosslinked



Figure 3. An example of a polymeric hydrogel sheet wound dressing. Hydrogel sheets do not need a secondary dressing and due to their flexible nature, can be cut to fit around the wound.

so that they physically entrap water. The sheets can absorb and retain significant volumes of water upon contact with suppurating wounds. Lay-Flurrie¹⁰⁴ has reviewed the properties of hydrogels by investigating the results from studies into their efficiency and discussed the wound types that are suited for hydrogel treatment. When applied to the wound as a gel, hydrogel dressings usually require a secondary covering such as gauze and need to be changed frequently.¹⁸ The sheets however, do not need a secondary dressing as a semi-permeable polymer film backing, with or without adhesive borders, controls the transmission of water vapour through the dressing. In addition the sheets can be cut to fit around the wound due to their flexible nature. The gels are used as primary dressings whereas the hydrogel films may be used as primary or secondary dressings (Fig. 3). Hydrogel dressings contain significant amounts of water (70–90%) and as a result they cannot absorb much exudate, thus they are used for light to moderately exuding wounds. Fluid accumulation can lead to skin maceration and bacterial proliferation which produces a foul smell in infected wounds. In addition, hydrogels have low mechanical strength and therefore difficult to handle¹⁰⁵ and this has been noted to affect patient compliance.¹⁰⁶

Hydrogels possess most of the desirable characteristics of an ‘ideal dressing’¹⁰⁶ (Tab. 2). They are suitable for cleansing of dry, sloughy or necrotic wounds by rehydrating dead tissues and enhancing autolytic debridement (Tab. 1). Hydrogel dressings are nonreactive with biological tissue, permeable to metabolites and are nonirritant.¹⁰⁷ Hydrogels also promote moist healing, are nonadherent and cool the surface of the wound, which may lead to a marked reduction in pain and therefore have high patient acceptability. In a clinical case study, Moody¹⁰⁸ reports the use of a hydrogel gel dressing to treat a chronic leg ulcer for a patient who could not tolerate even reduced compression therapy due to pain, and the hydrogel helped reduce the pain considerably. Hydrogels also leave no residue, are malleable and improve reepithelisation of wounds.¹⁸ Morgan² has stated that hydrogels ‘are suitable for use at all four stages of wound healing with the exception of infected or heavily exuding wounds’.

Semi-Permeable Adhesive Film Dressings

These dressings have been used for a long time and their effects on moist wound healing were first

investigated by Winter¹⁰⁹ and Hinman and Maibach.¹¹⁰ Film dressings were originally made from nylon derivatives supported in an adhesive polyethylene frame which made them occlusive. The original nylon derived film dressings, however, have limited ability to absorb sufficient quantities of wound exudates which results in the accumulation of excess exudates beneath the dressing.¹⁸ This leads to skin maceration and bacterial proliferation and the risk of infection and therefore require regular changing as well as irrigation of the wound with saline, making them unsuitable as wound dressings. The original nylon dressings are also difficult to apply and tend to wrinkle on removal from their packs. OpsiteTM (Smith and Nephew, Hull, UK) is a thin semi-permeable film made from polyurethane covered with hypoallergenic acrylic derivatives and is more porous and permeable to water vapour and gases but no liquid from exudates.¹¹¹ The films can be transparent, conform to contours (due to their elastic and flexible nature) such as elbows, knees and sacral areas and do not require additional taping. However, they are too thin to be packed into deep or cavity wounds and only suitable for relatively shallow wounds. Other available products include CutifilmTM (B.D.F. Medical, Milton Keynes, UK), BioocclusiveTM (Johnson & Johnson) and Tegaderm (3M Healthcare). Most of the existing brands differ in terms of vapour permeability, adhesiveness, conformability and extensibility.¹¹²

Foam Dressings

These dressings consist of porous polyurethane foam or polyurethane foam film, sometimes with adhesive borders.² Some foam dressings such as TielleTM have additional wound contact layers to avoid adherence when the wound is dry and an occlusive polymeric backing layer to prevent excess fluid loss and bacterial contamination.¹¹³ Foam dressings maintain a moist environment around the wound, provide thermal insulation and are convenient to wear.¹¹⁴ They are highly absorbent, absorbency being controlled by foam properties such as texture, thickness and pore size. The open pore structure also gives a high moisture vapour transmission rate (MVTR).^{115,116} The porous structure of the dressings, make them suitable for partial- or full-thickness wounds with minimal or moderate drainage, to highly absorbent structures for heavily exuding wounds.⁵⁶ In a systematic review of clinical trials conducted to

investigate the efficacy of various dressings including foam and gauze on postoperative wounds without closure, it was found that foam was preferred to gauze in terms of pain reduction, patient satisfaction and nursing time.¹¹⁷

Foam dressings are also indicated for granulating wounds where they are reported to help treat over granulation.¹¹⁸ They are used as primary wound dressings for absorption and insulation and a secondary dressing is usually not required due to their high absorbency and moisture vapour permeability. Foam dressings are not suitable for dry epithelialising wounds or dry scars as they rely on exudates unlike the polymer films, to achieve an optimum wound healing environment.¹¹⁶ The sheet dressings are not suitable as packs for cavity wounds,¹⁰⁶ though they may be used as secondary dressings for such wounds. Examples of foam dressing include: Lyfoam[®] (Conva Tec) and Allevyn[®] (Smith and Nephew).

Biological Dressings

These dressings are made from biomaterials that play an active part in the wound healing process and sometimes referred to as 'bioactive dressings'. Bioactive wound healing dressings also include tissue engineered products derived from natural tissues or artificial sources.¹¹⁹ These technologies usually combine polymers such as collagen,¹²⁰ hyaluronic acid,¹²¹ chitosan,¹²² alginates and elastin. Biomaterials have the advantage of forming part of the natural tissue matrix, are biodegradable and some play an active part in normal wound healing and new tissue formation.^{123,124} These characteristics make them attractive choices from a biocompatibility and toxicological point of view. In some cases they may be incorporated with active compounds such as antimicrobials and growth factors for delivery to the wound site.

Collagen is a natural constituent of connective tissue and a major structural protein of any organ. Its structural, physical, chemical, biological and immunological properties have been discussed widely in the literature.^{120,125,126} Collagen is known to play a vital role in the natural wound healing process from the induction of clotting to the formation and appearance of the final scar.⁶⁰ It stimulates formation of fibroblasts and accelerates the migration of endothelial cells upon contact with damaged tissue.¹²⁷ Schwarzer¹²⁸ reported the production of freeze-dried collagen biomatrices with the ability to pick up fluid, debris

and inflammatory cells containing phagocytosed bacteria. The matrix can also be medicated, thus serving as a reservoir for drug delivery. The use of collagen matrices for delivery of different classes of antibiotic drugs have been discussed extensively.¹²⁹

Hyaluronic acid is a glycoaminoglycan component of extracellular matrix with unique physicochemical and biological functions such as lubrication of joints and inflammation processes. It is naturally biocompatible, biodegradable and lacks immunogenicity.¹³⁰ Crosslinked hyaluronic acid hydrogel films have also been produced for use as polymeric drug delivery biomaterials.¹³¹ Hyaluronic acid-modified liposomes as bioadhesive carriers for delivering growth factors to wound sites have been studied and reported.¹³² A recent open ended study of hyaluronic acid based dressing found them to be effective for managing acute wounds particularly in terms of its safety and efficacy.¹³³ In this study however, no standard wound dressing was selected for comparison and the dressing was applied to different wound types. Chitosan is known to accelerate granulation during the proliferative stage of wound healing,¹⁰¹ and its wound healing application has been reviewed.¹³⁴ Bioactive dressings are reported to be more superior to conventional and synthetic dressings such as gauze and hydrogel dressings respectively.¹³⁵

Tissue Engineered Skin Substitutes

Traditional and modern dressings though useful, cannot replace lost tissue, particularly missing dermis as occurs in severe burns. In more advanced applications, 'smart' polymers from modifications of synthetic and bioactive polymers have been developed.¹³⁶ Advances in the fabrication of biomaterials and the culturing of skin cells have led to the development of a new generation of engineered skin substitutes.¹³⁷ Such polymers act as scaffolds for tissue engineered substrates that replace lost tissue rather than just facilitate wound healing. The use of 'smart' polymers either in the natural biological form or semi-synthetic forms are reported to be able to mimic normal physiologic responses during wound healing.^{138,139} This can help natural cell and tissue regeneration, particularly for chronic wounds that are difficult to heal.

Two major matrices are employed in tissue engineered skin substitutes. These are referred

to as acellular and cell containing matrices. Acellular matrices are produced either from synthetic collagen and extracellular matrix combinations such as hyaluronic acid,¹⁴⁰ for example IntegraTM, or native dermis with the cellular components removed but preserving the dermal architecture,¹¹⁶ for example AllodermTM. Cell-containing tissue engineered dressings include biodegradable films formed from, for example, collagen and glycosaminoglycans (e.g. ApligrafTM) as scaffolds onto which skin cells (patient derived or from recombinant sources) can be seeded for the growth of new tissues. These scaffold dressings possess mechanical properties and anatomic characteristics ideally approaching that of the tissue (normal dermis) they are to replace.¹⁴¹ When introduced into the body they gradually degrade, leaving behind a matrix of connective tissue with the appropriate structural and mechanical properties. Some of the developed tissue engineered products and skin substitutes available are summarised in Table 3.

Engineered scaffolds either from natural or synthetic sources are potentially useful for the delivery of additional bioactive materials such as growth factors and genetic materials to a wound. Storie and Mooney¹⁴² have reviewed the utility of DNA delivery from polymeric systems in the regeneration of skin tissue in cases such as diabetes foot ulcers. Hoffman¹⁴³ has described the ideal properties of hydrogels designed to serve different functions as tissue engineered scaffolds such as possessing spores capable of accommodating living cells. Alternatively, they may be designed to dissolve or degrade and release growth factors in the process as well as creating pores into which living cells can penetrate and subsequently proliferate, to replace lost or damaged tissue. Ruszczak¹⁴⁴ has reviewed the effect of collagen on dermal wound healing and noted the advantage of combining collagen with patient derived dermal cells, recombinant growth factors, cytokines, living cells and antimicrobial agents. This could help speed up formation of granulation tissue and reepithelisation during wound healing.

Though these advanced dressings have great potential for treating chronic wounds and third degree burns, they are still limited by the high costs involved, the risk of infection carry over and antigenicity as well as having to create a second wound in the case of harvesting patient's own cells to aid wound healing. These shortcomings in addition to the legal and ethical issues surrounding stem cell research have probably contributed

Table 3. Tissue Engineered Skin Substitutes Available Commercially

Dressing	Type	Major Components	Manufacturers
Integra™	Artificial skin	Collagen/chondroitin-6 sulphate matrix overlaid with a thin silicone sheet	Integra LifeScience (Plainsborough, NJ)
Biobrane™	Biosynthetic skin substitute	Silicone, nylon mesh, collagen	Dow Hickham/Bertek Pharmaceuticals (Sugar Land, TX)
Alloderm™	Acellular dermal graft	Normal human dermis with all the cellular material removed	Lifecell Corporation (Branchberg, NJ)
Dermagraft™	Dermal skin substitute	Cultured human fibroblasts on a biodegradable polyglycolic acid or polyglactin mesh	Advanced Tissue Sciences (LaJolla, CA)
Epicel™	Epidermal skin substitute	Cultured autologous human keratinocytes	Genzyme Biosurgery (Cambridge, MA)
Myskin™	Epidermal skin substitute	Cultured autologous human keratinocytes on medical grade silicone polymer substrate	Celltran Limited (University of Sheffield, Sheffield, UK)
TranCyte™	Human fibroblast derived skin substitute (synthetic epidermis)	Polyglycolic acid/polylactic acid, extracellular matrix proteins derived from allogenic human fibroblasts and collagen	Advanced Tissue Sciences
Apligraf™	Epidermal and dermal skin substitutes	Bovine type I collagen mixed with a suspension of dermal fibroblasts	Organogenesis (Canton, MA)
Hyalograft 3-D™	Epidermal skin substitute	Human fibroblasts on a laser-microperforated membrane of benzyl hyaluronate	Fidia Advanced Biopolymers (Padua, Italy)
Laserskin™	Epidermal skin substitute	Human keratinocytes on a laser-microperforated membrane of benzyl hyaluronate	Fidia Advanced Biopolymers
Bioseed™	Epidermal skin substitute	Fibrin sealant and cultured autologous human keratinocytes	BioTissue Technologies (Freiburg, Germany)

to the slow adoption of these dressings in routine clinical practice.¹⁴⁵

MEDICATED DRESSINGS FOR DRUG DELIVERY

The active ingredients used in wound management have evolved alongside the pharmaceutical agents and dressings used to deliver them. The use of topical pharmaceutical agents in the form of solutions, creams and ointments to wound sites have already been described. For example solutions such as thymol and hydrogen peroxide¹⁰⁶ used commonly for cleansing and debridement, also possess antiseptic and antibacterial actions.

A new generation of medicated dressings incorporate new chemicals which have therapeutic value, and overcome some of the disadvantages associated with topical pharmaceutical agents as

described in previous sections. Traditional dressings commonly used to deliver drugs include plain gauze and paraffin impregnated gauze (tulle gras). The modern dressings used to deliver active agents to wounds include hydrocolloids, hydrogels, alginates, polyurethane foam/films and silicone gels.¹⁴⁶ The incorporated drugs play an active role in the wound healing process either directly or indirectly as cleansing or debriding agents for removing necrotic tissue, antimicrobials which prevent or treat infection or growth agents (factors) to aid tissue regeneration. Some of the commonly used active compounds and the dressings (and novel polymer systems) used to deliver them to wound sites are described below.

Antimicrobials

The purpose of applying antibiotics and other antibacterials is mainly to prevent or combat

infections especially for diabetic foot ulcers,^{147,148} surgical and accident¹⁴⁹ wounds where the incidence of infections can be high due to reduced resistance resulting from extreme trauma. In some cases, the delivery of certain antibiotics from paraffin based ointments such as bismuth subgallate are known to take active part in the wound healing process.¹⁵⁰ Common antibiotics incorporated into available dressings for delivery to wounds include dialkylcarbamoylchloride which is incorporated into Cutisorb[®] a highly absorbent cotton wool dressing, povidone-iodine used with fabric dressing and silver used with most of the modern dressings.¹ Silver impregnated modern dressings available on the UK Drug Tariff include Fibrous Hydrocolloid, Polyurethane Foam Film and Silicone gels.¹ Other antibiotics delivered to wounds include gentamycin from collagen sponges,¹⁵¹ ofloxacin from silicone gel sheets^{152,153} and minocycline from chitosan film dressings.¹⁵⁴

Some of the reported novel antimicrobial wound healing dressings reported include, freeze-dried fibrin discs for the delivery of tetracycline¹⁵⁵ and lactic acid based system for the delivery of ofloxacin and the inhibition of *Staphylococcus aureus* and *P. aeruginosa* in split-thickness wounds in rats.¹⁵³ Treatment of dermal depth burn wounds using antimicrobial releasing silicone gel sheets which promotes epithelisation of superficial burns has been described by Sawada et al.¹⁵² A chitosan-polyurethane film dressing incorporating minocycline has also been developed for treating severe burn wounds.¹⁵⁶

The delivery of antibiotics to local wound sites may be a preferred option to systemic administration for several reasons. Antibiotic doses needed to achieve sufficient systemic efficiency often results in toxic reactions such as the cumulative cell and organ toxicity of the aminoglycosides in the ears and kidneys.^{157,158} The use of dressings to deliver antibiotics to wound sites can provide tissue compatibility, low occurrence of bacterial resistance and reduced interference with wound healing.¹²¹ The use of lower antibiotic doses within the dressings also reduces the risk of systemic toxicity considerably. In addition, local delivery from dressings can overcome the problem of ineffective systemic antibiotic therapy resulting from poor blood circulation at the extremities in diabetic foot ulcers.

Growth Factors

Whilst antibacterial agents prevent or treat infections and can aid in wound healing, they

do not necessarily take an active physiological part in the wound healing process. Growth factors are involved with cell division, migration, differentiation, protein expression and enzyme production. The wound healing properties of growth factors are mediated through the stimulation of angiogenesis and cellular proliferation, which affects both the production and the degradation of the extracellular matrix and also plays a role in cell inflammation and fibroblast activity.¹⁵⁹ Growth factors therefore affect the inflammatory, proliferation and migratory phases of wound healing.¹⁶⁰ A variety of growth factors have been reported which participate in the process of wound healing including, epidermal growth factor (EGF), platelet derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF- β 1), insulin-like growth factor (IGF-1), human growth hormone and granulocyte-macrophage colony-stimulating factor (GM-CSF).^{161,162} In a study of the influence of GM-CSF in full thickness wounds in transgenic mice, Mann et al.¹⁶³ suggested that GM-CSF is of fundamental importance in the wound healing repair and a deficiency of this growth factor resulted in delayed wound healing and poor quality of newly formed scar tissue. Lee et al.¹⁶⁴ have reported that silver sulphadiazine alone can impair wound healing and that EGF helps reverse this impairment when both are applied together.

Different dressings have been used to topically administer some of the above growth factors to wound sites. These include hydrogel dressings for delivering transforming growth factor- β 1 (TGF- β 1),^{165,166} collagen film for delivering PDGF¹⁶⁷ and human growth hormone,¹⁶⁸ alginate dressings in the form of beads used to deliver endothelial growth factor,¹⁶⁹ polyurethane and collagen film dressings for delivery of EGF.¹⁷⁰ Park et al.¹⁷¹ showed that a novel porous collagen-hyaluronic acid matrix, containing tobramycin, basic FGF and platelet-derived growth factor significantly enhanced wound healing compared with matrix containing only the antibiotic. It has been reported that EGF when applied to partial thickness incisions as a cream, stimulated epidermal regeneration.¹⁷² Most of these growth factors are recombinant proteins and the choice of appropriate dressing is critical for effective release and action at the wound site. A review of the potential role of growth factors for treating chronic leg ulcers by Khan and Davies¹⁷³ reported encouraging clinical results, though factors such as small sample size and inconsistent endpoints in

clinical studies have prevented definite conclusions being reached.

Supplements

Another group of active compounds important to the wound healing process are vitamins and mineral supplements¹⁷⁴ including vitamins A, C, E as well as zinc and copper. The dressings employed for the delivery of vitamins and minerals include oil based liquid emulsions, creams, ointments, gauze and silicone gel sheets.

Vitamin A is involved with epithelial cell differentiation,¹⁷⁵ collagen synthesis and bone tissue development.¹⁷⁶ It has also been shown to facilitate normal physiological wound healing as well as reversing the corticosteroid induced inhibition of cutaneous wound healing and post operative immune depression.^{177,178} Vitamin C is an essential compound for the synthesis of collagen and other organic components of the intracellular matrix of tissues such as bones, skin and other connective tissues.¹⁷⁵ It is also involved with normal responses to physiological stressors such as in accident and surgical trauma and the need for ascorbic acid increases during times of injury.¹⁷⁹ In addition, vitamin C aids in improving immune function particularly during infection.^{24,180} The use of vitamins E and C acid has been reported to help accelerate wound healing.¹⁸¹ Vitamin E is also capable of preserving important morphological and functional features of biological membranes¹⁵⁹ though its use in topical applications has however, been discouraged due to the problem of contact dermatitis.¹⁸² In addition, vitamin E is reported to have antioxidant and anti-inflammatory activity¹⁸³ as well as promoting angiogenesis and reduces scarring.¹⁸⁴

The delivery of vitamins to wounds from dressings is sparsely reported in the literature; they are mostly administered orally to supplement body stores but this is outside the scope of this review. Vitamin E has been used in combination with silicone gel sheets for the treatment of hypertrophic and keloid scars.¹⁸⁵ Lazovic et al.¹⁸⁶ have reported the application of collagen sheet dressings wetted with vitamins A and C solutions over burn wounds and showed significant improvements in healing of the wound. Topical zinc can stimulate the healing of leg ulcers through enhancement of reepithelialisation and also corrects a local zinc deficiency of the metal.¹⁸⁷

Keitzman and Braun¹⁸⁸ has noted that the low molecular weight protein group, metallothioneins are upregulated around wound margins following topical application of zinc and copper. He suggested that the action of these proteins resulted from the many zinc and copper dependent enzymes required for cell proliferation and reepithelisation.

Topical pharmaceutical formulations in the form of liquid emulsions and ointments incorporating zinc have been applied frequently in the past and at present. Lansdown¹⁸⁹ found that a combined formulation of zinc oxide and cod liver oil emulsion was more effective than vehicle only controls as well as those containing a single active ingredient. He also found the zinc oxide emulsion to be most efficient in rapid healing of wounds retarded by corticosteroid treatment. In another study to investigate the effect of topical agents on the healing rate of deep second-degree burn wounds, application of zinc containing topical formulation reduced healing times significantly.¹⁹⁰ This reduction in healing time was further improved when basic FGF and EGF were used in combination with the zinc preparation. In a randomised double-blind placebo controlled trial, the effects of topical zinc oxide and mesh on secondary healing pilonidal wounds were compared. Topical zinc was shown to aid faster wound healing times, decrease *Staphylococcus* load in the wound and also no associated cellular abnormalities.¹⁹¹ However, in another study by Cangul et al.¹⁹² to evaluate the clinical and histopathological effects of topically applied zinc and copper based dressings on open-wound healing in rabbits, it was found that copper based topical agents caused wound contraction and coverage of the wound bed with granulation tissue at a faster rate than zinc based dressings.

CONTROLLED DRUG DELIVERY TO THE WOUND

Controlled release of drugs to a given target generally involves prolonging the action of the active drug over time by allowing continual release from a polymeric dosage form.¹⁹³ There is however, little literature on the controlled delivery of drugs from polymeric wound dressings. The use of hydrophilic polymers as controlled release dressings has great promise because of the potential advantages they offer.

Advantages of Controlled Drug Delivery

Controlled delivery dressings can provide an excellent means of delivering drugs to wound sites in a consistent and sustained fashion over long periods of time without the need for frequent dressing change.¹⁹⁴ Bioadhesive, synthetic, semi-synthetic and naturally derived polymeric dressings are potentially useful in the treatment of local infections where it may be beneficial to have increased local concentrations of antibiotics while avoiding high systemic doses¹⁹⁵ thus reducing patient exposure to an excess of drug beyond that required at the wound site.¹⁹⁶ In addition, they are readily biodegradable and therefore can be easily washed off the wound surface, once they have exerted their desired effect.¹⁹⁷ Improvement of patient compliance is another advantage especially in chronic wound management where patients usually undergo long treatments and frequent changing of dressings that can lead to noncompliance. A dressing that will deliver an active substance to a wound site in a controlled fashion for a sustained period of about a week could help solve or minimise this problem.

Polymeric Drug Delivery Dressings

Most modern dressings are made from polymers which can serve as vehicles for the release and delivery of drugs to wound sites. The release of drugs from modern polymeric dressings to wounds has been sparsely reported in the literature with few clinical studies carried out to date. The polymeric dressings employed for controlled drug delivery to wounds include hydrogels such as poly(lactide-co-glycolide)¹⁹⁸ poly(vinyl pyrrolidone),¹⁴³ poly(vinyl alcohol)¹⁸⁸ and poly(hydroxy-alkylmethacrylates)^{199–202} polyurethane-foam,^{203–207} hydrocolloid⁵⁶ and alginate dressings.^{169,208–210} Other polymeric dressings reported for drug delivery to wounds comprise novel formulations prepared from polymeric biomaterials such as hyaluronic acid,^{131,132} collagen^{166,168} and chitosan.^{156,211–213} Synthetic polymers employed as swellable dressings for controlled drug delivery include silicone gel sheets,¹⁵² lactic acid.¹⁵³ Some of these novel polymeric dressings for drug delivery exist as patents.^{214–219} Composite dressings comprising both synthetic and naturally occurring polymers have also been reported for controlled drug delivery to wound sites.^{220,221}

Sustained release tissue engineered polymeric scaffolds for controlled delivery of growth factors

and genetic material to wound sites have also been reported.^{138,142} 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^{155,222–228} or as tissue engineered polymeric scaffolds.^{155,160}

Mechanism of Controlled Delivery to Wounds

Drug release from polymeric formulations is controlled by one or more physical processes including (a) hydration of the polymer by fluids and (b) swelling to form a gel, (c) diffusion of drug through the swollen gel and (d) eventual erosion of the polymer gel.^{229–236} Although there is little literature in this area for polymeric wound dressings such as hydrocolloids, alginate, hydrogels and polyurethane, it seems feasible that swelling, erosion and subsequent drug diffusion kinetics will play a part in controlled drug release from these dressings when they come into contact with wound exudate. Upon contact of a dry polymeric dressing with a moist wound surface, wound exudate penetrates into the polymer matrix. This causes hydration and subsequent swelling of the dressing to form a gel over the wound surface.²³⁷ Gombotz and Wee²³⁸ have reviewed the controlled release of proteins from alginate matrices including dressings to mucosal tissues such as wounds. They described the swelling behaviour of the polymer to form a gel which acts as a barrier to drug diffusion. As with all polymers, the swelling observed is due to solvation of the polymer chains, which leads to an increase in the end-to-end distance of the individual polymer molecules. In certain wound dressings, the mechanism for drug release has been explained by the hydrolytic activity of enzymes present in the wound exudates²³⁹ or from bacteria in the case of infected wounds.²⁴⁰ Different techniques have been employed in studies to characterise the swelling behaviour of hydrophilic polymers upon contact with water.^{241,242} It has been shown that in an aqueous medium, the polymer also undergoes a relaxation process resulting in slow, direct erosion (dissolution) of the hydrated polymer.^{243,244} It is possible for both swelling and dissolution to operate simultaneously in wound dressings with each contributing to the overall release mechanism. Generally, however, the rate of release of drug is determined

by the rate of diffusion of dissolution medium (exudates) into the polymer matrix. Narasimhan and Peppas²⁴⁵ have suggested that erosion is the dominant mechanism controlling the latter part of most release profiles. Factors such as erosion of the polymer matrix following water diffusion and swelling in other dosage forms are known to be the main reason for deviations from square root of time kinetics.²³¹ Different models have been proposed for investigating controlled drug release mechanisms that combine diffusion, swelling and erosion.²³² These models are based on the penetration of water into the dry matrix and polymer dissolution based on the reptation theory of polymers in solution.^{245,246} A detailed discussion is however, beyond the scope of this review.

PHYSICAL CHARACTERISATION OF WOUND DRESSINGS

The physical properties of all pharmaceutical formulations including wound dressings influence their ultimate performance and contribute to satisfying the desirable properties of dressings (see Tab. 2). The specific property to be characterised will depend on both the type of wound dressing, the nature of the surface to which the dressing will be applied and any secondary dressings that may be involved.⁵⁶ As for controlled drug delivery from polymeric dressings, there is very little literature on the physical characterisation of the modern dressings.

Standard Tests

The standard tests are generally based on specifications of the Official Compendia (e.g. British and US Pharmacopoeia), National Test Standards (e.g. British Standards and American Standards for Testing and Materials), and accredited laboratories such as the Surgical Materials Testing Laboratory (SMTL). The standard tests for characterising wound dressings are usually to determine the absorbent properties of dressings such as hydrocolloids, alginates, polyurethane foam and hydrogel sheets. These tests include fluid handling properties, moisture vapour permeability, fluid affinity, water uptake and gelling properties.^{81,247} Evaluation of absorbent properties, have been reported to aid in exudate management around the wound area.²⁴⁸

Fluid Handling Properties (Fluid Handling Capacity)

This test is employed for hydrocolloid, alginate and polyurethane foam dressings in the SMTL test method TM-65,²⁴⁹ which is based upon specifications in the British Standards²⁵⁰ and also described in the BP monographs for hydrocolloids²⁵¹ and alginate²⁵² dressings. The fluid handling capacity (FHC) of the dressing is defined as the sum of the weight of test solution retained by the dressing and the weight of fluid lost by transmission through the dressing as moisture vapour. The FHC provides information on (a) a dressing's ability to absorb and retain wound fluid (absorbency) and (b) evaporation of a proportion of the aqueous component of wound fluid through the outer surface of the dressing to the external environment (moisture vapour loss). These two processes form important mechanisms of exudate management.²⁵³ The fluid handling property is also related to the gel forming characteristics of hydrocolloid and alginate dressings.^{91,247} A comparative study of the physical properties of six different hydrocolloid dressings, from different manufacturers, demonstrated that they differed widely in their fluid handling and other absorbent related characteristics such as swelling force.²⁵⁴ Waring and Parsons²⁵⁵ have investigated the effect of chemical and crystalline structures of carboxymethylated cellulose and alginate fibre dressings on their hydration properties when in contact with wound exudates. They observed that the dressings immobilised fluid by gel blocking and suggested their beneficial effects in the treatment of chronic wounds by reducing the incidence of skin maceration caused by excessive wound exudates. Thomas²⁵⁶ has reported on the use of this test for characterising alginate dressings.

The FHC test is carried out by adding a combined salt solution of sodium and calcium chloride (representing salt concentrations of serum and wound fluid) to samples of known weight cut from each dressing in the upper flange of Paddington cups.^{251,252} The cups are then sealed, weighed and placed in an inverted position in an incubator at 37°C together with a tray containing freshly regenerated self indicating silica gel for 24 h. The cups are removed from the incubator at the end of 24 h, allowed to equilibrate to room temperature and reweighed. To determine the amount of fluid retained by the dressing, the base of each cup is removed and any free fluid remaining in the cup that has not been absorbed by the dressing is allowed to drain away.

The cup is then reweighed once again and the weight of fluid retained by the dressing calculated by difference.

Water Vapour Permeability (Moisture Penetration)

The dressings commonly indicated for this method are the hydrocolloid dressings, usually in the form of sheets or film dressings.²⁴⁹ The water vapour permeability is officially referred to as MVTR in the British Pharmacopoeia²⁵⁰ and measures the amount of water vapour lost through a dressing to the atmosphere from the wound bed over defined time periods. The test is described in SMTL test method TM-8²⁴⁸ for hydrocolloid dressings and is based on the methods described in British Standards.²⁵⁷ Unlike the FHC test, it gives an indication of time-related changes that may take place in the permeability of some dressings, which can increase dramatically as the product absorbs liquid to form a gel, reaching a steady state after a number of hours. In some dressings, the moisture vapour transmission mechanism involves the absorption and moving of fluid away from the wound-skin interface by an absorbent lower layer towards a nonocclusive upper layer where some fluid is lost to the atmosphere by evaporation.²⁴⁸ This mechanism is intended to increase the fluid-handling capacity of the dressing^{258,259} though there are no clinical data to confirm its efficacy in practice.²⁶⁰

During testing, a sample of each dressing is applied to a Paddington cup containing 20 mL of test solution. The cup is then placed in an inverted position upon the pan of a top pan balance in an incubator at 37°C. A tray containing 1 kg of freshly dried silica gel is placed at the bottom of the incubator to maintain a low relative humidity within the chamber. The balance is connected to an electronic data capture device to continually record changes in the weight of the cup resulting from the loss of moisture vapour through the dressing for 48 h. The weight of water transmitted through the dressing over a given time period is used to calculate the MVTR.

Though officially specified for hydrocolloid dressings, the MVTR test has been applied to other type of dressings such as hydrogel and polyurethane films. A hydrogel film dressing comprising chitosan and Eudragit was designed and evaluated using a modified approach based on MVTR.²⁶¹ Bottles were filled with silica instead of test of solution, and the bottles were covered with the film dressing and then sealed. The percentage

increase in weight of the bottles containing the silica gel was measured over a 48 h period and showed an increase in water vapour penetration over time. Khan and Peh²⁶² compared the rate of water vapour permeability of chitosan films with Omiderm[®] polyurethane film dressing using the USP XXII test method for the evaluation of moisture permeability of containers and packaging materials. The USP test differs from the BP method because it uses calcium chloride instead of dried silica gel and has a control sample set with glass beads in place of the calcium chloride. The humidity of the experimental chamber is also kept constant with a saturated sodium chloride solution and weight measurements are recorded after 14 days.

Fluid Affinity

The fluid affinity is determined in the SMTL test method TM-238,²⁴⁹ and based upon British Standard specification.²⁶³ This test is investigates a dressing's ability to donate moisture to, or absorb liquid from standard substrates. It is largely applicable to amorphous hydrogel dressings which have the ability both to donate and absorb wound exudates. The ability of hydrogel dressings to donate fluid helps to facilitate the rehydration of dry necrotic tissue to promote autolytic debridement.²⁶⁴ In addition a high fluid affinity will help absorb excess wound exudate and liquefied tissue debris once autolytic debridement has taken place. Thomas and Hay^{265,266} have reported on the fluid handling properties and the hydro-affinity of hydrogel dressings.

In the fluid affinity test method, 10 g samples of the test material are placed onto the surface of a series of 10 g plugs of gelatine (35%) or agar (2%) contained within the barrel of 50/60 mL syringes from which the closed (nozzle) ends have been removed to form smooth-sided cylinders. Once the test materials are in place, the open ends of the cylinders are sealed with an impermeable cover. Following incubation of the sealed syringes for 48 h at 25°C the test material is gently removed from the plugs, which are then reweighed. From these results the percentage change in weight of each hydrogel sample is calculated.

Water Uptake (Fluid Retention)

This is a gravimetric test and determines the maximum amount absorbed and retained by the dressing as a percentage. The fluid retention test is designed to determine how a dressing performs

under more extreme conditions than they are likely to encounter *in vivo*. Essentially, the increase in weight of the dressing after absorbing fluid and swelling over a given time period is measured and used as an indication of the water uptake and retention. Thomas et al.²⁶⁴ have observed that in some cases, some samples appeared to lose weight after 48 or 72 h after progressively increasing in weight with time as they absorb test solution. This was attributed to the dressings forming soluble or mobile gels which could escape through bags in which the dressings were retained. Ferrari et al.²⁵⁴ have employed this test for evaluating the water absorption and swelling properties of hydrocolloid dressings from different manufacturers. A more advanced approach using this method was developed with computer linked video camera used to determine changes in the thickness of hydrocolloid dressings in contact with liquid.²⁶⁷ A dressing combining hydrocolloid, hydrofibre and foam film layers has been evaluated to determine clinical performance by assessing dressing integrity and absorption.²⁶⁸ This composite dressing was observed to have very high exudate absorption ability beyond its expected performance.

Though the above tests represent a meaningful means of characterising the different dressings, they are mainly based on the structure (hydrocolloid, alginate or hydrogel) rather than the performance of the dressings. As a result, they are limited in predicting a dressing's performance *in vivo*. The standard test results are also specific to individual dressing groups and the fluid handling properties of hydrocolloid dressings for example could not be compared with those of alginate dressings. Thomas and Fram²⁶⁹ have proposed a novel approach for predicting the exudates handling properties of dressings based on criteria such as suitability for characterising a wide range of dressings and therefore allow direct comparison of results. Other important physical properties of dressings include tensile strength (films), bioadhesivity, rheological properties (gels and films) and resistance to compressive forces (sheets).

Tensile Tests

Tensile mechanical tests are employed for characterising pharmaceutical film formulations including film dressings as well as materials such as packaging for control and specification pur-

poses.²⁷⁰ Characterisation of the mechanical properties is important because film dressings are required to be durable, stress resistant, soft, flexible, pliable and elastic to be able to cope with the stresses exerted by different parts of the body having varying contours, especially around the joints such as knees and elbows.^{261,271} In addition, they should be easy to apply and remove without incurring any trauma or damage to new sensitive epithelial cells during change of dressing.¹⁰⁶ These desirable characteristics can be achieved by investigating their tensile properties to ensure a balance between flexibility and rigidity.

The commonly measured tensile properties include: 'percent strain at break', tensile strength, and the elastic modulus. Standard methods exist for determining these properties, the most common being the American Society for Testing and Materials (ASTM) test methods of tensile properties of thin plastic sheeting.²⁷² The SMTL has a tensile test for film dressings based on the specification for the elastic properties of fabric dressings in the British Standards BS 7505.²⁷³ A bilayered wound dressing matrix combining elastomeric hydrogel poly(ethylene glycol) or poly-L-lactide polymers and cell seeded skin substitute was produced and the elastic moduli evaluated.²⁷⁴ The results showed that the elastic moduli matched those reported for human skin. Jurgens et al.²⁷⁵ have compared the elastic properties (elongation and elastic moduli) of novel biodegradable lactic acid and caproic acid copolymer film dressing for treating burn wounds. These dressings exhibited high elongation and low elastic modulus which were ideal for covering burns as they degrade readily thus avoiding painful removal. The effectiveness of UV and chemical crosslinking of collagen membranes as dermal dressings has been evaluated by measuring their mechanical properties and resistance to collagenase as good indicators of the fabrication process.²⁷⁰

During tensile testing, a sample (usually dumbbell shaped) undergoes elongation till it reaches a maximum at break point (Fig. 4).²⁷⁶ Elongation is defined as the increase in length produced in the gauge length of the test specimen by a tensile force.

Percent Strain at Break

This is a measure of the ductility and brittleness of the film and related to the elongation of the films at breaking point and corresponds to the point 'B'

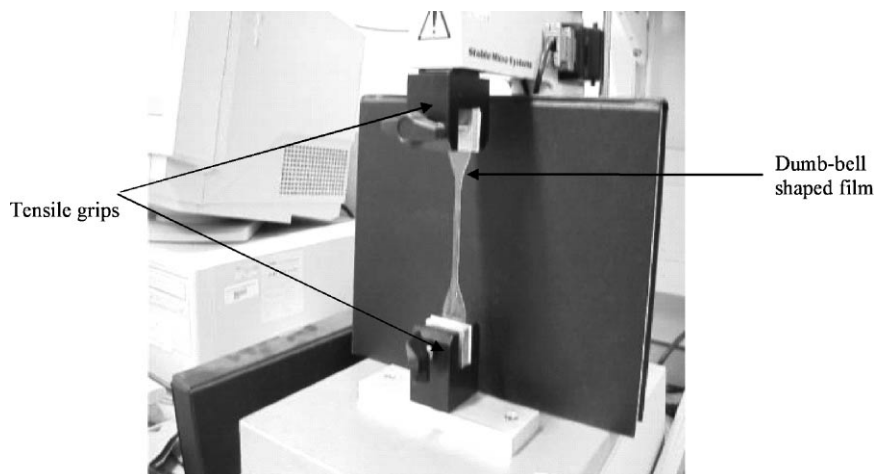


Figure 4. A dumb-bell shaped film undergoing stretching between two grips in tensile mode (Texture Analyser™, Stable Micro Systems, Surrey, UK).

in Figure 5. Turhan and Sahbaz²⁷⁷ determined the effect of polyethylene glycol (PEG) plasticiser on percent elongation of methylcellulose films and showed them to go from brittle through pseudo ductile and ductile to elastic with increasing PEG content. Debeaufort and Voilley²⁷⁸ also explained that increases in percent elongation mainly occur when films become rubbery, that is films changed from ductile to elastic.

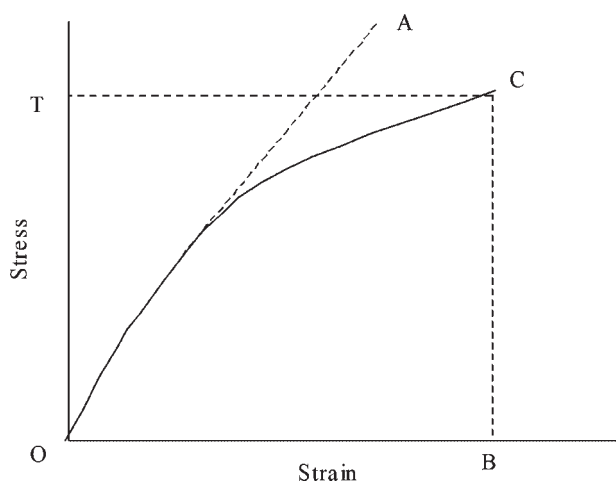


Figure 5. Typical tensile profiles obtained by stretching films to break point showing the different tensile properties described in the text (OA = initial linear portion of stress strain curve, slope of this line gives the elastic modulus; B = percent strain at break; C = the point at which a film breaks and related to the elastic limit; T = tensile strength).

Tensile Strength

The tensile strength is the maximum stress (force per unit area) applied to a point at which the film breaks (represented by the stress “T” in Fig. 5) and describes how hard and brittle the film is. It has been reported that the tensile strength is affected by the type and amount of polymer(s)^{279,280} and its molecular weight.^{281,282} Remunan-Lopez and Bodmeir²⁸³ have also shown that the tensile strength of alginate films increased with the concentration of calcium chloride which acts a crosslinking agent.

Elastic Modulus

This is the most fundamental and structurally important mechanical property of films and is a measure of film stiffness and rigidity. The elastic modulus is calculated from the slope of the initial linear portion of the stress-strain curve (OA in Fig. 5). A high elastic modulus indicates a hard, rigid film that is difficult to break. The elastic modulus, like the tensile strength is very sensitive to the presence of plasticisers such as water and glycerol.^{281,284,285} It has been used together with thermal techniques to determine the efficiency of different plasticisers in ethylcellulose films.²⁸⁶ The elastic modulus is the major property employed during dynamic mechanical (or thermal) analysis (DMA/DMTA) for measuring the glass transition temperature for characterising amorphous polymers and other polymeric dressings.^{287,288}

Compressive Tests

For formulations of greater thickness than films, for example foam and hydrogel sheets, other tests such as 'hardness' can be employed for characterising their mechanical properties. Hardness is defined as the resistance of the formulation to compressive forces of deformation and measured in units of force per unit area. Hardness provides an idea of brittleness, gel strength (upon hydration) and elasticity. The mechanical and drug release properties of drug loaded alginate and chitosan wound healing sponges have been described by Lai et al.²⁸⁹ Their study showed that the chitosan sponges had greater mechanical strength ('hardness') than the alginate sponges, with intermediate strength obtained when both polymers were mixed together. This allowed the drug release characteristics to be manipulated to achieve desired dissolution profiles. In some cases the measurement of mechanical 'hardness' allows the choice of particular polymeric grade with optimum properties for a given application and to determine the effects of different variables on the formulation.²⁹⁰

Rheological Tests

Dressings such as amorphous hydrogels can be characterised by measuring rheological properties such as viscosity and viscoelastic strength though the literature is very scanty. The rheological properties of rehydrated polymer dressings (gels) following gamma-irradiation in the glassy state have been investigated by Matthews et al.²²⁸ with a view to the suitability of gamma-radiation as a method of sterilising such medicated dressings designed to remain on the surface of suppurating wounds for long periods of time. Razzak et al.²⁹¹ have investigated the quality of a hydrogel dressing comprising polyvinyl alcohol and polyvinyl pyrrolidone by measuring viscosity, gel fraction, glass transition temperature and water content. The authors noted that such properties when optimised could help meet ideal requirements of wound dressings such as absorbing fluid effectively, painless on removal, high elasticity and good transparency.

Bioadhesive Strength

Another important physical property of dressings meant for application to moist wound surfaces, is

adhesive strength both *in vivo* (bioadhesivity, mucoadhesion) and *in vitro* (adhesivity). Adhesivity has been defined as the force required to detach a sample from the surface of excised porcine skin²⁹² (using a Texture Analyser, a common type of mechanical testing equipment). The test is adopted from characterisation of bioadhesive polymeric formulations meant for application to other moist surfaces such as vagina, buccal and nasal cavities.^{271,293-296} Sakchai et al.²²⁰ have determined the bioadhesive properties of Eudragit-chitosan film dressings by measuring the force required to detach the film from pig large intestine washed in physiological solution. Peppas and Buri²⁹⁷ have discussed the surface and interfacial phenomena that occur during bio-adhesion of polymeric molecules to soft tissue including wound surfaces. Adhesivity can also be determined by evaluating various tensile responses of different gels.²⁹⁶ Adhesivity is important in wound healing where dressings should be self adhesive with the wound, easily removed and painless (i.e. it must have reduced adhesiveness with time).²⁹⁶ The force of adhesion depends on factors such as hydrophobicity which is reported to improve bioadhesion,¹⁰⁵ level of hydration and rate of polymer erosion in contact with the hydrating surface.²⁹⁸ A novel drug-loaded wound dressing with optimised adhesive drug releasing properties was developed by binding self-adhesive Eudragit E (cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters) film with antibacterial loaded poly(*N*-isopropyl-acrylamide) microgel beads to achieve adhesive, absorptive and easy to peel functions.²⁹⁹

CONCLUDING REMARKS

This review 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 therapeutic agents highlighted were antibiotics, growth factors, vitamins and mineral supplements, nitrogen oxides, genetic material, specific plant materials used as medicinal herbs in some African countries as well as debriding action of maggots. 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.

Several challenges remain that need to be taken into consideration in developing novel wound healing drug delivery formulations. For example, large variations in the rate of production of wound exudate, suggests the difficulty in finding a single ideal dressing capable of application to all wound types. 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 individualised 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. However, large, randomised and controlled clinical trials to examine safety and efficacy will need to be carried out for many of these advanced dressings to speed up their use in routine clinical practice. 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 review article can provide a key to this knowledge.

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