Research Article

Polymer Biomaterials in Wound Dressing: A Review

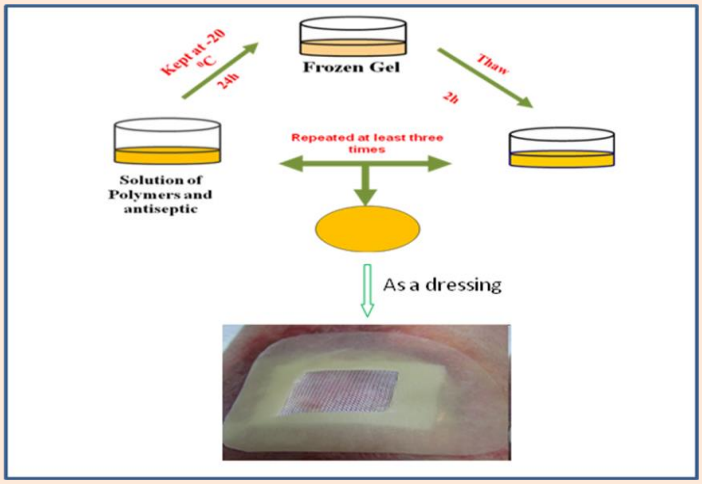
Jaya Bajpai[1], A.K.Bajpai[1], Amita Chhatri[2]*, Smarika Lawrance[2], and Anjali Dsouza[2]

[1]Department of Chemistry, Govt. Model Science College Jabalpur
[2]Department of Chemistry and Biochemistry, St. Aloysius College Jabalpur

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. Italso reviews many of the dressings and novel polymers used for the delivery of drugs toacute, 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

Keywords: wound dressing**,** wound healing, hydrogel



***Correspondence**
Author: Dr. Amita Chhatri
Email: amita_chhatri@yahoo.co.in

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' [1]. 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 [2]. 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. Wounds are also classified based on the number of skin layers and area of skin affected [3, 4]. Pictorial representation of wound has shown in **Figure 1**.

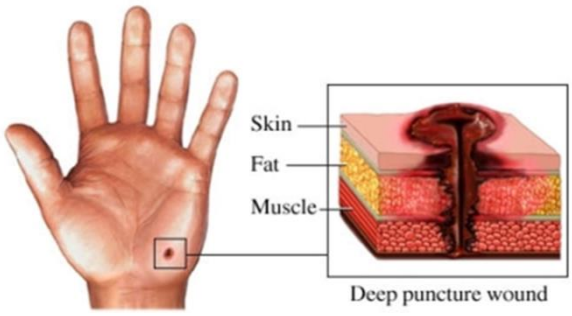


Figure 1 Pictorial presentation of anatomy of wound

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.

Types of wound

Wounds can be divided into four categories based on their appearance and stage of healing. Each wound type has slightly different characteristics and a wound healing by secondary infection will progress through these different stages over time. There is no 'one size fits all' dressing, hence wounds must be re-evaluated regularly in order to identify and respond to any changes.

Necrotic wounds

Necrotic wounds (**Figure 2a**) are usually black or dark green and contain devitalized tissue. Infected necrotic wounds require sharp surgical debridement back to viable tissue in order to prevent systemic sepsis. In the absence of infection, necrotic tissue will eventually separate from the wound bed by autolysis. Necrotic wounds are particularly susceptible to dehydration, and autolysis is inhibited if the wound is allowed to dry out; the main priority of a dressing is to maintain sufficient moisture in the local environment of the wound [5].

Sloughing wounds

Sloughing wounds (**Figure 2b**) contain a mixture of leukocytes, wound exudates, dead bacteria and fibrin, typically forming a glutinous yellow layer of tissue over the wound. The presence of slough predisposes to wound infection because it provides a nutrient-rich environment for bacterial proliferation. The formation of granulation tissue is delayed in a sloughing wound compared with a clean wound, and hence the optimal dressing will contribute towards wound debridement and maintenance of a clean wound bed [6].

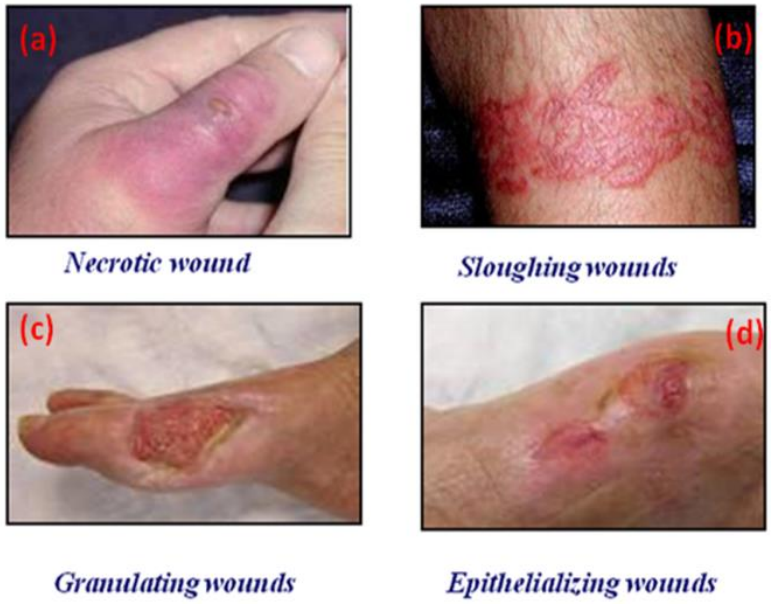


Figure 2 Different types of wounds.

Granulating wounds

Granulating wounds (**Figure 2c**) are highly vascularized and are a rich pink or red colour. The amount of exudate produced is often substantial, and a dressing with the capacity to absorb excess exudate is desirable. Significant heat loss may occur with wounds covering large areas, requiring a dressing with insulating properties. Overgranulating wounds have the following properties, they:

- contain excessive friable granulation tissue
- are prone to recurrent episodes of bleeding
- suffer from delayed epithelialization.

In this situation, caustic pencils containing silver nitrate or topical corticosteroid can be applied directly to the affected areas in order to control the excess tissue [7].

Epithelializing wounds

Epithelializing wounds (**Figure 2d**) contain new epithelial tissue (formed by migration of keratinocytes from the wound margins) or contain islands of tissue (formed from skin appendages in the wound bed). The main priorities for dressing are the maintenance of a warm, moist environment around the wound, and the use of low-adherence dressings (see below) to minimize the trauma of dressing changes. In addition to the type of wound, the location, size and depth of the wound may vary considerably. Along with the condition of the surrounding skin, these should also be considered when deciding the most suitable dressing [8].

Wound-Healing

Wound healing is a complex physiological process that is dependent on a number of inter-related factors. Wound assessment and treatment should be based on an understanding of normal tissue repair and factors affecting the process [9].

All tissues in the body are capable of healing by one of two mechanisms: regeneration or repair. Regeneration is the replacement of damaged tissues by identical cells and is more limited than repair. In humans, complete regeneration occurs in a limited number of cells for example, epithelial, liver and nerve cells. The main healing mechanism is repair where damaged tissue is replaced by connective tissue which then forms a scar. Wound healing can be defined as the physiology by which the body replaces and restores function to damaged tissues [10-11].

Inflammation Phase - Acute

Following injury, damaged blood vessels bleed causing hypoxia, the injured tissue contains dead cells and extravasated blood. This triggers a natural but essential inflammatory reaction, involving a vascular and cellular response with fluid exudate, resulting in oedema and phagocytic activity. Acute inflammation results from vasodilatation and vasopermeability of the blood vessels, initiated and controlled by a wide array of chemical mediators released by the damaged tissues. Clinically, acute inflammation manifests as swelling, erythema, increased temperature, pain, leading to loss of function. The physical characteristics of acute inflammation were first formulated by Celsus in (30 BC – 38 AD) using Latin; rubor, calor, tumor and dolor. Typically, the inflammatory phase (Lag phase) lasts between 4-6 days, and prepares the wound for the proliferation phase [12].

Proliferation Phase - Subacute

The proliferative phase is essentially the generation of repair material which involves the production of scar tissue (type III collagen), which commences after 2-3 days, reaching a peak at 2-3 weeks post-injury. There are two fundamental processes involved; fibroplasia (formation of collagen) and angiogenesis (formation of new local blood vessels) [13].

Although a short period of immobilization following injury is necessary, early controlled mobilization is essential for decreased healing time, increased vascular ingrowth, quicker regeneration of scar tissue and stronger mobile tissue. Prolonged immobilization leads to deleterious tissue effects such as; random deposition of collagen, excessive cross-link formation and atrophy. Consequently this leads to functional implications such as losses in range of movement and tensile strength. During early and intermediate subacute healing, new tissue is fragile and easily interrupted, consequently, mobilization too early or too intensively may re-rupture the injured tissue. Exercise loading and intensity should remain within the tensile capability of the healing tissue (Figure 2). Careful tensioning of the healing tissue during the proliferation phase increases collagen synthesis, thus, potentially speeds up the healing process [14-15].

Remodeling Phase

Approximately 2-3 weeks post-injury, collagen maturation and remodeling initiate. With maturity, the collagen remodels becoming more obviously oriented in line with local stresses. A portion of the type III collagen is reabsorbed and is replaced by type I collagen with greater tensile strength Remodeling continues for months, even years. The tensile strength of the tissue improves due to formation of intra and extra molecular cross linkages between the collagen fibers [16-17].

Wound Dressing

The perfect dressing provides and maintains a moist environment and an adequate gaseous exchange at the wound surface that favors the proliferative phase of repair, particularly epithelialization. The dressing should also protect the wound from infection by acting as a bacterial shield and should provide thermal insulation. An ideal dressing occludes dead space, permits a traumatic removal of excessive exudate from the wound surface, and is easy to manipulate and nonantigenic [18].

Properties of the 'ideal' wound dressing

A dressing is an adjunct used by a person for application to a wound to promote healing and/or prevent further harm. A dressing is designed to be in direct contact with the wound, which makes it different from a bandage, which is primarily used to hold a dressing in place. The ideal dressing can be summarized as follows [19].

- Removes excess exudate, but prevents saturation of the dressing to its outer surface ('strike through')
- Permits diffusion of gases
- Protects wound from micro-organisms
- Provides mechanical protection
- Controls local temperature and pH
- Is easy and comfortable to remove/change
- Minimizes pain from the wound
- Controls wound odour
- Is cosmetically acceptable
- Is non-allergenic
- Does not contaminate the wound with foreign particles
- Is cost effective

Requirement for wound dressing

The successful wound dressing (**Figure 3**) must perform the following function

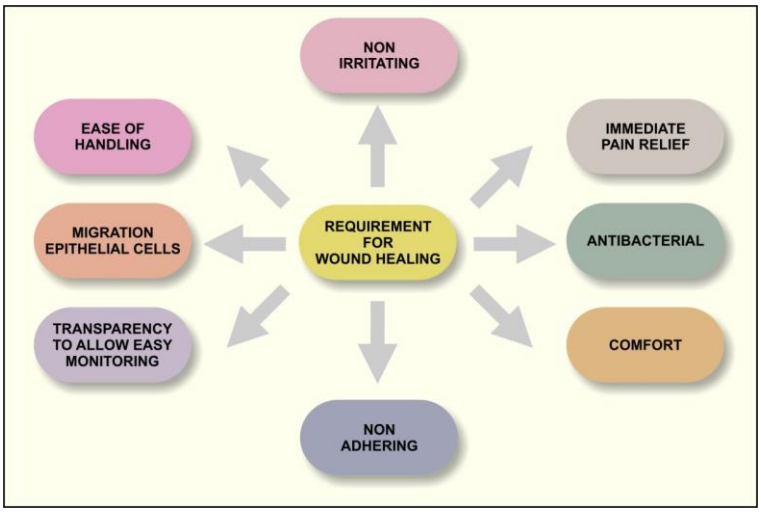


Figure 3 Diagrammatic presentation of requirements of wound Dressing.

- Seal the wound and prevent introduction of external stress and loss of energy
- Remove excess exudates and toxic components
- Maintain a high humidity at the wound dressing interface
- Provide thermal insulation
- Act as a barrier to micro organism
- Be free from particulates and toxic wound contamination
- Be removable without causing trauma at dressing change.

Types of Dressing

On the basis of nature: On the basis of their nature dressings can be classified as synthetic, semisynthetic, or biologic

1. *Synthetic Dressings*: Synthetic dressings (**Figure 4a**) are composed of man-made fabric or plastic materials in the form of gauze, films, sprays, foams, and gels [20].
2. *Semisynthetic Dressings*: Semisynthetic dressings (**Figure 4b**) are a combination of synthetic and biologic products. Biologic dressings are obtained from natural sources and include amnion, allografts, and xenografts as well as bioengineered tissues composed of various proteins (particularly collagen) or cultured wound-healing cells (primarily fibroblasts and keratinocytes) [21].
3. *Biologic Dressing*: Biologic dressings (**Figure 4c**) often exert a beneficial effect on the wound in addition to providing protective covering [22].

Figure 4 Picture of various types of dressing on the basis of nature.

According to their ability to adhere to a wound: According to their ability to adhere to a wound, dressings are also classified as adherent or non-adherent.

1. *Adherent Dressings:* Adherent dressings (**Figure 5a**) should be restricted to the initial inflammatory and debridement phases because they facilitate removal of debris and excess exudates but may damage fragile tissues formed in subsequent phases [23].
2. *Low-adherent Dressings:* Low-adherent (**Figure 5b**) products with a wound-contact surface that is designed to specifically to reduce adherence, for example some absorbent wound dressings [24].
3. *Non-Adherent Dressings:*A dressing (**Figure 5c**) that maintains a moist gel layer over the wound that is not expected to adhere, provided that it is not allowed to dry out. In other words those dressings that maintain a moist gel layer over the wound, for example hydrocolloids, hydrogels and alginates. These would not be expected to adhere provided that they are not allowed to dry out. The performance of some of these materials will be largely determined by the choice of a secondary dressing where this is required **[25]**.

According to their ability to permit passage of exudates and vapor: According to their ability to permit passage of exudates and vapors, dressings are further classified as occlusive, semi occlusive, or nonocclusive (permeable).

1. *Occlusive Dressings:* Occlusive dressings (**Figure 6a**) are impermeable to water vapors, fluid, and oxygen, thus providing an environment that favours proliferation of anaerobic bacteria. Because occlusive dressings encourage the formation of exuberant granulation tissue in equine wounds [26], it is recommended to restrict their use to the first 6 to 48 hours after dressings.
2. *Non-occlusive Dressings:* Non-occlusive dressings (**Figure 6b**) were developed to manage the moisture level at the wound surface. These dressings are designed to absorb excess exudates, and to allow evaporation of water vapors from the outside surface. They are, therefore, designed to handle a lot of fluid without feeling at all wet on their outside surface. The combined benefits of absorption and water vapor transmission allow large

quantities of exudates to be "managed" without maceration, while maintaining the moist wound healing environment that is conducive to repair [27].

Figure 5 various types of dressings on the basis of ability to adhere. (a) Adherent dressing, (b) Low-adherent dressing, (c) Non-Adherent dressing

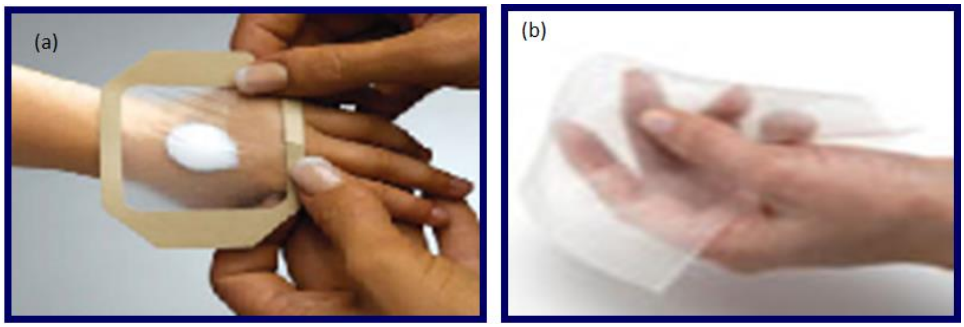


Figure 6 Pictures of various types of dressings on the basis of ability to permit passage of exudates and vapour. (a) Occlusive Dressing, (b) Non-occlusive Dressing

Modern 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.

1. *Tulle dressings:* Tulle Dressing are cotton or viscose gauze dressings impregnated with paraffin (antiseptic or antibiotic may also be incorporated). Paraffin lowers the dressing adherence, but this property is lost if the dressing dries out. The hydrophobic nature of paraffin prevents absorption of moisture from the wound, and frequent dressing changes are usually needed. Skin sensitization is also common in medicated types. Tulle dressings **(Table 1a)** are mainly indicated for superficial clean wounds, and a secondary dressing is usually needed [28].
2. *Hydrocolloids Dressings:* Hydrocolloids contain a hydrocolloid matrix of gelatin, pectin and cellulose mixed together to form a waterproof adhesive dressing that interacts with the wound bed. Exudates produced by the wound absorb into the dressing, which dissolves and forms a gel. The moisture from this gel enhances autolytic debridement of necrotic and sloughing tissues and promotes the formation of granulation tissue. Hydrocolloid dressings **(Table 1b)** absorb light-to-moderate levels of exudate, do not require a secondary dressing, and are shower-proof [29].
3. *Hydrofibres Dressings:* Hydrofibers **(Table 1c)** are produced from similar materials to hydrocolloids and also form a gel on contact with the wound, but are softer and more fibrous in appearance, with a greater capacity to absorb exudate. Moisture from the gel assists in debridement and facilitates non-traumatic removal [30].
4. *Films Dressings:* Films are made from a thin polyurethane film coated with adhesive. Film dressings are highly comfortable, shower-proof and their transparency allows for wound monitoring without dressing removal. Vapour-permeable films allow diffusion of gases and water vapour, but are minimally absorbed. Problems can arise if these dressings are applied to heavily exudating wounds because fluid tends to accumulate underneath the film, leading to maceration of the wound and the surrounding skin. Films **(Table 1d)** are thus suited to superficial, lightly exudating or epithelializing wounds [31].

5. *Foam dressings:* A foam dressing is constructed from polyurethane and absorbs exudate without interacting with the wound bed. They absorb low-to-moderate amounts of fluid and usually have a semi-permeable backing to allow the escape of moisture. Foams **(Table 1e)** do not require a secondary dressing and are often used as an outer dressing with other products [32].
6. *Alginates Dressing:* Alginates are derived from a calcium salt of alginic acid, producing highly absorbent dressings suitable for heavily exudating wounds; some alginates also possess haemostatic properties. As they absorb exudate, alginates change from a soft fibrous texture into a gel, facilitating easy removal and preventing dressing fibres from contaminating the wound. Alginates **(Table 1f)** are manufactured as flat sheets or as rope, and are suitable for packing cavities [33].
7. *Hydrogel Dressing:* Hydrogels are excellent materials and have all the properties required for wound dressings. These are capable of absorbing contaminated exudates and safely retaining them within the gel structure, which provides microclimate that stimulates and regulates all cellular activities and nutritional processes during the individual phases of wound healing. Hydrogels gel removed from the wound without pain thus avoiding and risk of wound irritation [34-37]. The hydrogel dressing **(Table 1g)** removal is almost painless because hydrogel does not adhere to the wound surface. Hydrogel stays permanently moist and can be easily removed after prolonged application without pain and risk of wound irritation. Due to above reasons the hydrogel wound dressing are highly accepted by the patient [38]. Hydrogels are prepared from synthetic and natural polymers. But blends of both represent a new class of materials with better mechanical properties, biocompatibility and flexibility than those of the single components [39]. Recently, blends of the synthetic polymers with natural polymers such as starch [40], cellulose [41], chitin [42], chitosan [43, 44], cotton [45], gelatin [46, 47], alginate [48], dextran [49] have been reported for the development of wounds dressings.

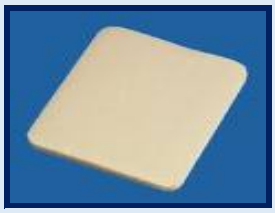
Table 1 Types of modern dressings


(a) Tulle dressings


(b) Hydrocolloids


(c) Hydrofibres


(d) Films


(e) Foams


(f) Alginates


(g) Hydrogels

Natural polymers are used in wound Dressings

Natural dressing provides a water-proof covering and prevents: (1) invasion of exogenous bacteria; (2) loss of water by evaporation; (3) protein loss by exudation; (4) pain from exposed nerve endings; (5) loss of heat, thereby reducing metabolic requirements; and (6) immobility that would be produced by heavy protective dressing. natural polymers (such as alginate, chitosan, gelatin and collagen, as well as some of their derivatives), are the most commonly used materials to prepare wound dressing [50].

Chitosan

Chitosan (**Figure 7)** [poly-(b-1/4)-2-amino-2-deoxy-D-glucopyranose] is a collective name for a group of partially and fully deacetylated chitin compounds [51]. Due to its unique biological characteristics, including biodegradability and nontoxicity, many applications have been found either alone or blended with other natural polymers (starch,

gelatin, alginates) in the food, pharmaceutical, textile, agriculture, water treatment and cosmetics industries [52-57]. Antimicrobial activity of chitosan has been demonstrated against many bacteria, filamentous fungi and yeasts [58-61]). Chitosan has wide spectrum of activity and high killing rate against Gram-positive and Gram-negative bacteria, but lower toxicity toward mammalian cells [62, 63]). Ever since the broad-spectrum antibacterial activity of chitosan was first proposed by Allen [64], along with great commercial potential, the antimicrobial property of chitosan and its derivatives have been attracting great attention from researchers.

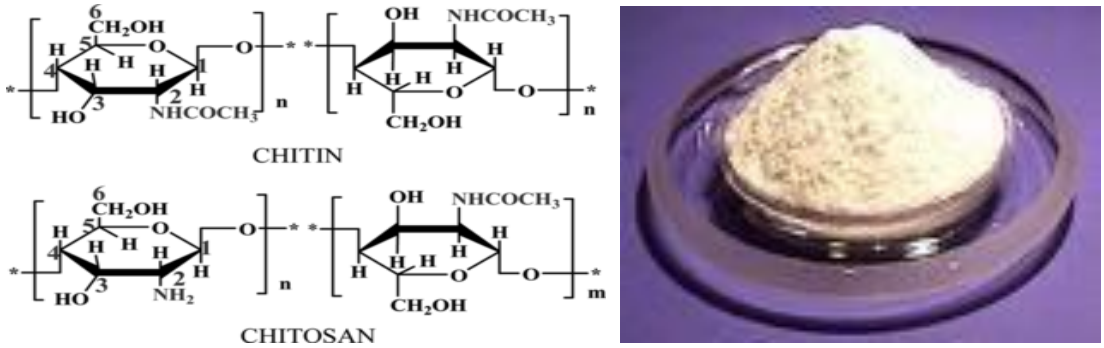


Figure 7 chemical structure of chitin and chitosan.

Alginates

Alginates (**Figure 8)** are produced from the naturally occurring calcium and sodium salts of alginic acid found in a family of brown seaweed (Phaeophyceae). They generally fall into one of two kinds: those containing 100% calcium alginate or those that contain a combination of calcium with sodium alginate, usually in a ratio of 80:20. Alginates are rich in either mannuronic acid or guluronic acid, the relative amount of each influencing the amount of exudate absorbed and the shape the dressing will retain. Alginates partly dissolve on contact with wound fluid to form a hydrophilic gel as a result of the exchange of sodium ions in wound fluid for calcium ions in the dressing. Those high in mannuronic acid (such as Kaltostat) can be washed off the wound easily with saline, but those high in guluronic acid (such as Sorbsan) tend to retain their basic structure and should be removed from the wound bed in one piece. Alginates can absorb 15 to 20 times their weight of fluid, making them suitable for highly exuding wounds. They shouldnot be used, however, on wounds with little or no exudate as they will adhere to the healing wound surface, causing pain and damaging healthy tissue on removal [65].

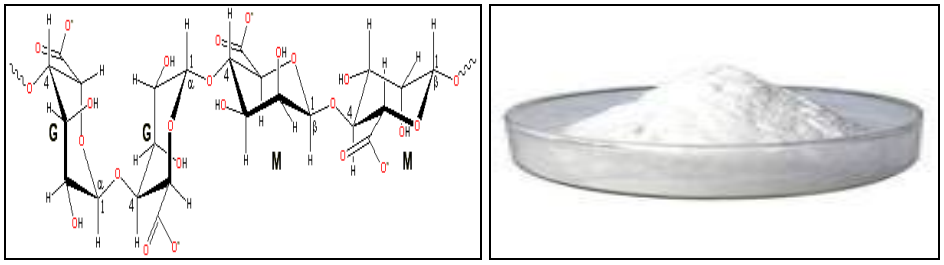


Figure 9 Structure of Alginate

Gelatin

Gelatin **(Figure 10)** is a natural polymer that is derived from collagen, and is commonly used for pharmaceutical and medical applications because of its biodegradability and biocompatibility in physiological environments as reviewed by Tabata and Mikos [66, 67]. These characteristics have contributed to gelatin's safety as a component in drug formulations or as a sealant for vascular prostheses [68]. Moreover, gelatin has relatively low antigenicity because of being denatured in contrast to collagen which is known to have antigenicity due to its animal origin. Gelatin contains a large number of glycine, proline and 4-hydroxyproline residues.

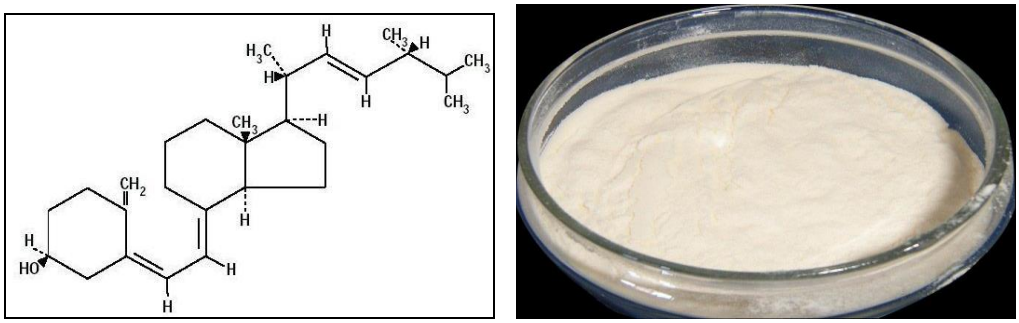


Figure 10 Structure of Geletin.

Caboxymethylcellulose

Caboxymethylcellulose **(Figure 11)** is a major commercial derivative of cellulose. Carboxymethylcellulose is a highly water soluble anionic polysaccharide which is widely used in pharmaceutical, cosmetics and food applications [69]. In biomedical fields it used to prevent the postoperative adhesion [70] and epidermal scarring. Moreover, its nontoxic, biocompatible, hydrophilic, chiral and semirigid nature makes it a functional material of first choice [71].

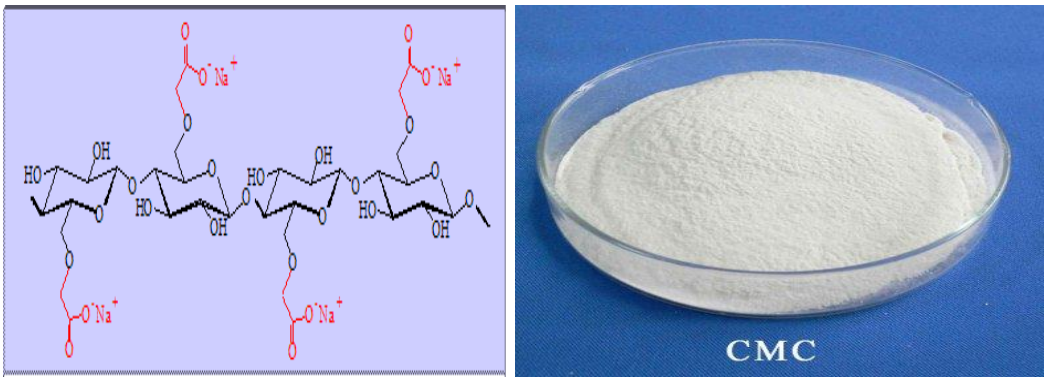


Figure 11 Structure of Corboxymethylcellulose.

sterculia gum

Sterculia gum **(Figure 12)**, a medicinally important naturally occurring polysaccharide, has unique features such as high swelling and water retention capacity, high viscosity and inherent nature of anti-microbial activity [72]. These features can be exploited for developing the wounds dressing. It has been used to prepare the controlled- release matrix and has shown superior muco-adhesion than guar gum [73]. Sterculia gum composed of galacturonic acid, b-D-galactose, glucuronic acid, L-rhamnose, and other residues [74]. It is obtained from the tree Sterculia urens and is commonly known as karaya gum or sterculia gum [75].

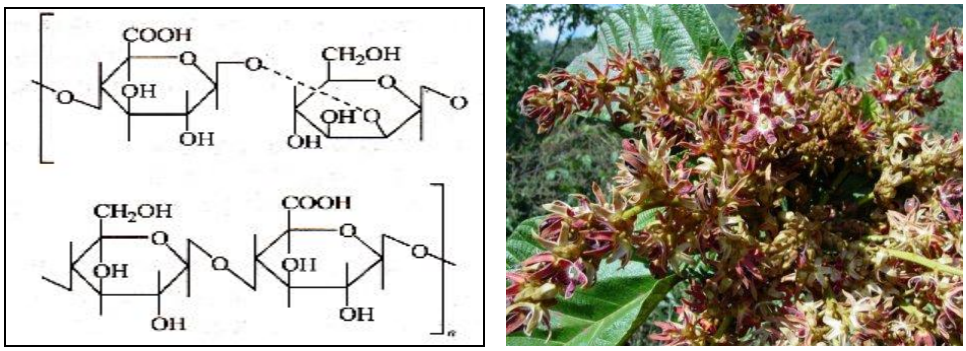


Figure 12 Structure of sterculia gum

Synthetic polymers are used as wound dressing

Synthetic polymer based dressings have a long shelf life, inducing minimal inflammatory reaction and carry almost no risk of pathogen transmission [76]. In recent years, researchers have focused on biologic synthetic dressings, which are bilayered and consist of high polymer and biologic materials [77-79]. These three categories of wound dressing are all used frequently in the clinical settings, but none is without disadvantages. Synthetic polymers like poly(urethanes), poly(ethylenes), poly(-caprolactone), poly(lactic acid), poly(glycolic acid), poly(glycolic-lactic acid), poly(acrylonitrile), poly(amino acids), silicone rubbers are used as dressing materials.

Polyurethane

Polyurethane (**Figure 13**) dressings are highly conformable, nonadherent, and semiocclusive. The foam can be used to absorb exudate from the wound, thereby decreasing tissue maceration; simultaneously, they maintain a moist environment while, with the sheet form (Opsite; Smith & Nephew, Indianapolis, IN), exudating pools beneath the dressing. These dressings can be used in the early inflammatory phase as well as in the proliferative phase of repair because they do not adhere to the regenerating tissue and leave it undisturbed at bandage changes. In heavily exuding wounds, these dressings should be replaced frequently to increase comfort, whereas the frequency of dressing change decreases as healing progresses and less fluid is produced by the wound [80].

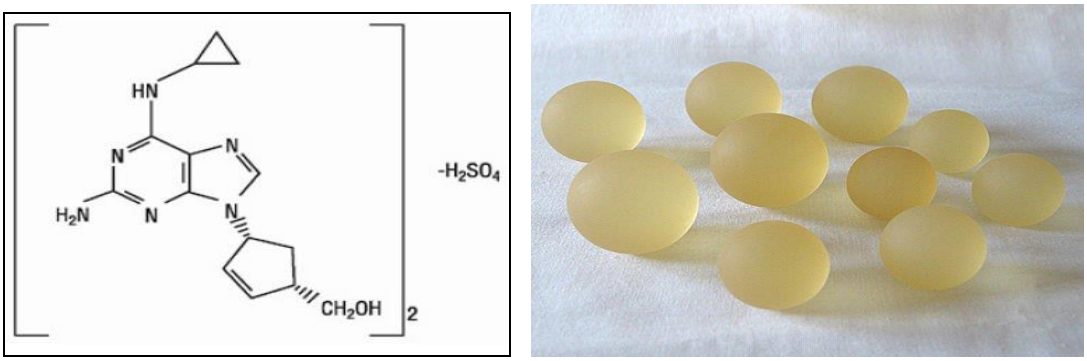


Figure 13 Structure of Polyurethane

Silicone

Silicone (**Figure 14)** dressings are used as an effective alternative to intra-lesional corticosteroids, surgical excision, laser surgery, and cryosurgery for the management of excessive scarring in man. It appears that this type of synthetic, non-adherent, and fully occlusive dressing surpasses other modalities in decreasing the amount of scar tissue while exerting no negative side effects. In a recent study performed in wounds of the distal limbs of horses, the silicone dressing surpassed a conventional permeable, non-adherent dressing in preventing the formation of exuberant granulation tissue and improving tissue quality [81].

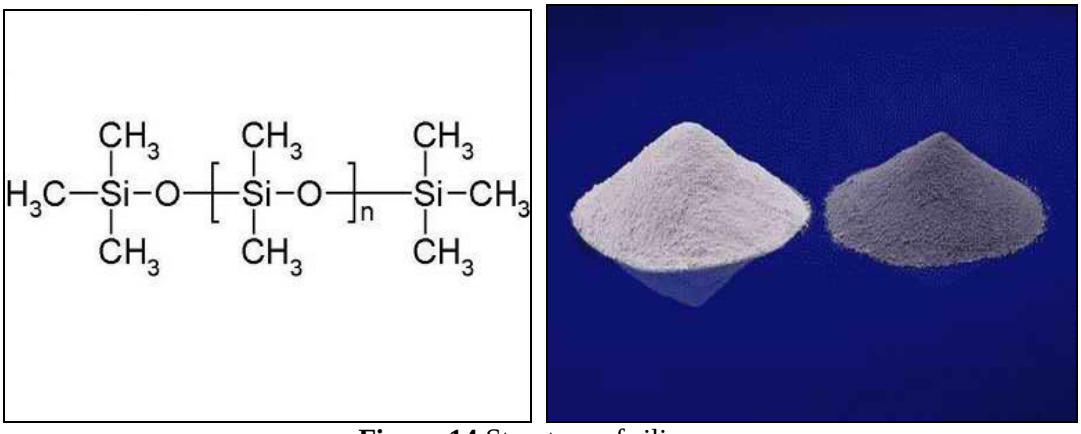


Figure 14 Structure of silicone

Polyvinyl pyrrolidone (PVP)

Polyvinyl pyrrolidone (PVP) **(Figure 15)** is a synthetic polymer that has been shown to be biocompatible; UV-cured films of N-vinyl pyrrolidone copolymers have been proposed as a potential bioadhesive wound dressing matrix (Kao *et al* 1997) [82]. Due to its lubricity and viscous properties, PVP has been used to coat tissue contacting surfaces (Howard 1988) [83] and as vitreous humor substitute (Hong *et al* 1998) [84].

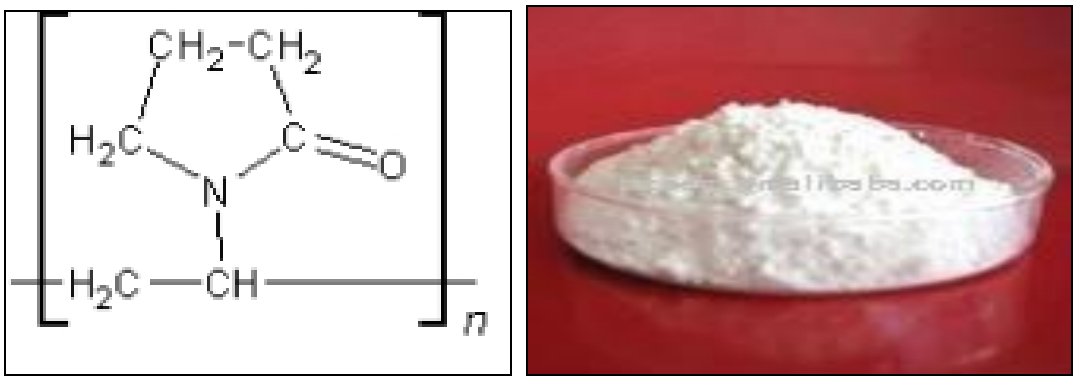


Figure 15 Structure of Polyvinyl pyrrolidone

Polyvinyl alcohol (PVA)

Polyvinyl alcohol (PVA) (**Figure 16)** has several useful properties including non-toxicity, biocompatibility, high hydrophilicity, fiber/film forming ability, and the chemical and mechanical resistance. It has been widely commercialized and studied in the chemical and medical industries for the productions of fibers, films, coatings, cosmetics, pharmaceuticals, and so on [85]. PVA hydrogels produced by using the freezing–thawing technique form a matrix of physically crosslinked polymeric chains containing uncrosslinked polymer and water. The use of freeze–thawed PVA hydrogels has been explored for biomedical and pharmaceutical applications. These gels are non-toxic, non-carcinogenic, have good biocompatibility, and have desirable physical properties such as rubbery nature and high degree of swelling in water [86]. PVA must be crosslinked if it is to be used in biodegradable materials. PVA hydrogel has excellent transparency and is smooth as membrane, and it is also biologically inactive and bio-compatible. It has attracted much attention to be widely used as a good material for temporary skin covers or burn dressings [87].

Figure 16 Structure of PVA

Antiseptics used in wound dressing

Antiseptics (from Greek ἀντί - *anti*, "'against"[1] + σηπτικός - *sēptikos*, "putrefactive"[2]) are antimicrobial substances that are applied to living tissue/skin to reduce the possibility of infection, sepsis, or putrefaction. Antiseptics are generally distinguished from *antibiotics* by the latter's ability to be transported through the lymphatic system to destroy bacteria within the body, and from *disinfectants*, which destroy microorganisms found on non-living objects. Some antiseptics are true *germicides*, capable of destroying microbes (bacteriocidal), whilst others are bacteriostatic and only prevent or inhibit their growth. Antibacterials are antiseptics that have the proven ability to act against bacteria. Microbicides which kill virus particles are called viricides or antivirals [88].

Use of antiseptics in wound management still remains a controversial issue, with varying advantages and disadvantages. However, antiseptics are agents that destroy or inhibit the growth and development of microorganisms within or on ing tissue. Unlike antibiotics that act selectively on a specific target, antiseptics have multiple targets and a broader spectrum of activity that includes bacteria, fungi, viruses, protozoa, and even prions [89, 90]). Antiseptics are expected to play an even more important role in controlling microbes in both veterinary and human medical clinical practice [91, 92]). Several antiseptic agents are mainly intended to clean intact skin and are used in the preoperative preparation of patients, prior to intramuscular injections or venous punctures, pre- and postoperative scrubbing in the operating room [93]. When used properly, antiseptics are effective in both the prevention and treatment of wound infections [94-97]. Antiseptics are usually the weakest and least toxic among the surface antimicrobials [98]. Regardless of the use, antiseptics should exert a sustained effect against microorganisms without causing tissue damage [99,100].

Chlorohexidine

Chlorohexidine **(Figure 17)** was discovered in 1946 and introduced into clinical practice in 1954 [101]. It is widely used as an antiseptic in handwashing, and as a surgical scrub, but in wounds its application has been limited largely to irrigation. The mode of action has been studied extensively. Chlorohexidine is available as diacetate, digluconate and dihydrochloride; the digluconate is most frequently used in wound management. It has rapid, bactericidal activity against a wide spectrum of non-sporing bacteria by damaging outer cell layers and the semi-permeable cytoplasmic membrane to allow leakage of cellular components. It also causes coagulation of intracellular constituents, depending on concentration [102]. Antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and a range of clinical isolates has been documented [103], however in MRSA, resistance has been observed [104].

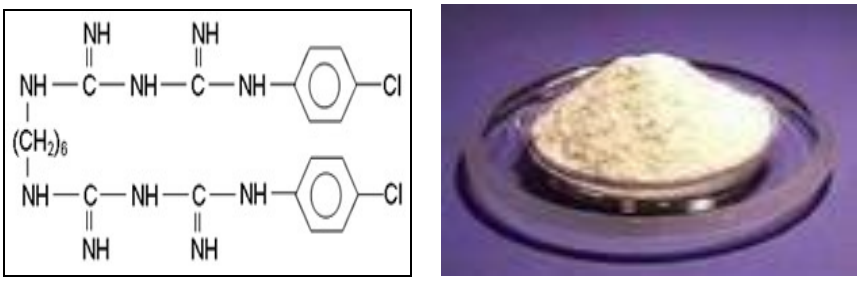


Figure 17 Structure of chlorohexadiene.

Honey

Honey **(Figure 18)** is an ancient remedy [105] which has been re-discovered for the treatment of wounds [106]. Many therapeutic properties have been attributed to honey including antibacterial activity and the ability to promote healing [107]. Evidence of antibacterial activity is extensive, with more than 70 microbial species reported to be susceptible [108]. Later *in vitro* studies have shown that active manuka honey is bactericidal against strains of antibiotic resistant bacteria isolated from infected wounds [109-111], so adding MRSA, vancomycin-resistant enterococci (VRE) and *Burkholderia cepacia* to the list of susceptible bacteria.

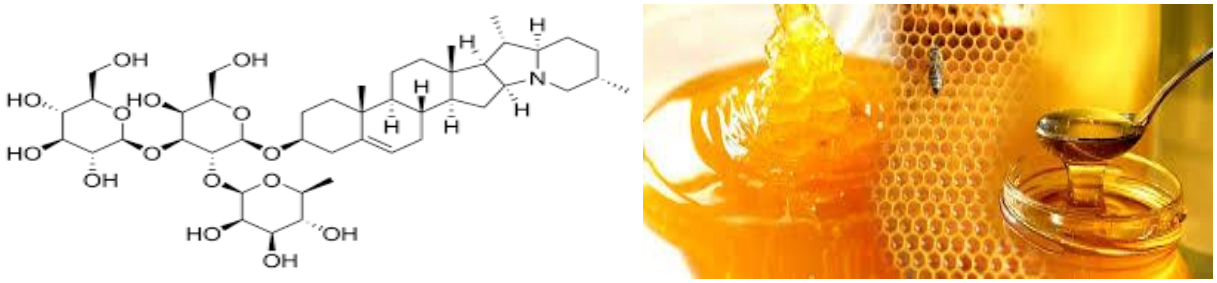


Figure 18 Structure of Honey.

Hydrogen peroxide

Hydrogen peroxide (**Figure 19)** has been widely used as an antiseptic and disinfectant. A 3% (10 volumes) solution has most often been used to clean wounds. It is a clear, colourless liquid that decomposes in contact with organic matter. It has a broad spectrum of activity against bacteria, with greater effect on Gram positive species than Gram negatives. Hydrogen peroxide functions as an oxidising agent by producing free radicals that react with lipids, proteins and nucleic acids to affect cellular constituents non-specifically. Its use in cleaning superficial trauma wounds has declined since the formation of air emboli was reported [112], yet analysis of studies in animals and humans [113] failed to find any negative effects on wound healing. At present there seems to be insufficient evidence to base definitive judgments about the merits of hydrogen peroxide on wound healing.

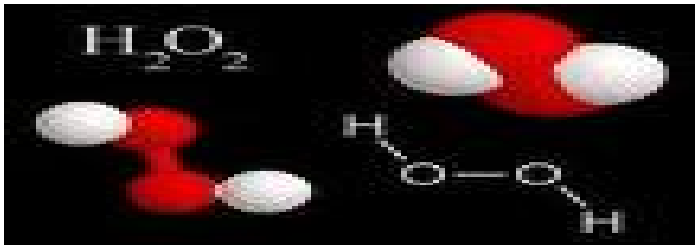
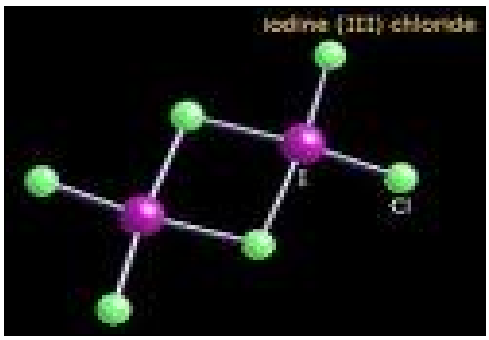


Figure 19 Structure of Hydrogen peroxide.

Iodine

Iodine **(Figure 20)** is an element that was discovered in 1811. It is a dark violet solid that dissolves in alcohol and potassium iodide. Its first reported use in treating wounds was by Davies in 1839, and later it was used in the American Civil War. Early products caused pain, irritation and skin discolouration, but the development of iodophores (povidone iodine and cadexomer iodine) since 1949 yielded safer, less painful formulations.

Povidone iodine is a polyvinylpyrrolidone surfactant/iodine complex (PVP-I); cadexomer iodine is composed of beads of dextrin and epichlorhydrin that carry iodine. Both release sustained low concentrations of free iodine whose exact mode of action is not known, but involves multiple cellular effects by binding to proteins, nucleotides and fatty acids. Iodine is thought to affect protein structure by oxidizing S-H bonds of cysteine and methionine, reacting with the phenolic groups of tyrosine and reacting with N-H groups in amino acids (such as arginine, histidine and lysine) to block hydrogen bonding. It reacts with bases of nucleotides (such as adenine, cytosine and guanine) to prevent hydrogen bonding, and it alters membrane structure by reacting with C=C bonds in fatty acids. It has a broad spectrum of activity against bacteria, mycobacteria, fungi, protozoa and viruses [114].



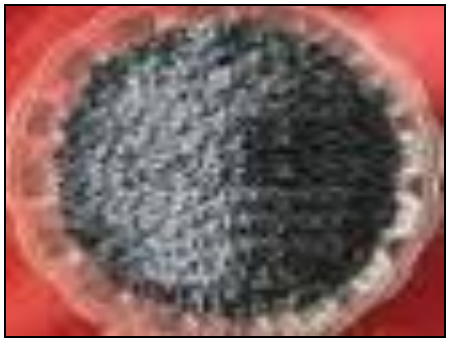


Figure 20 Structure of Iodine.

Proflavine

Proflavine **(Figure 21)** is a brightly coloured acridine derivative that was extensively used during the Second World War in the treatment of wounds [115]. Modern use is as a prophylactic agent in surgical wounds packed with gauze soaked in proflavine hemisulphate solution, even though calcium alginate has been reported to promote better results [116]. It is an intercalating agent that inhibits bacteria by binding to DNA and prevents unwinding prior to DNA synthesis. Although it is effective against sulphonamide-resistant bacteria, strains of MRSA that are resistant to proflavine by possessing efflux pumps (mechanisms associated with bacterial membranes that export materials from

cells) have been isolated [117]. Acridines are photosensitive; it has therefore been proposed that new derivatives should be sought for topical therapy promoted by light [118]. However, the ability to induce mutations in bacterial [119] and cell cultures [120] raises suspicion about the safety of proflavine.

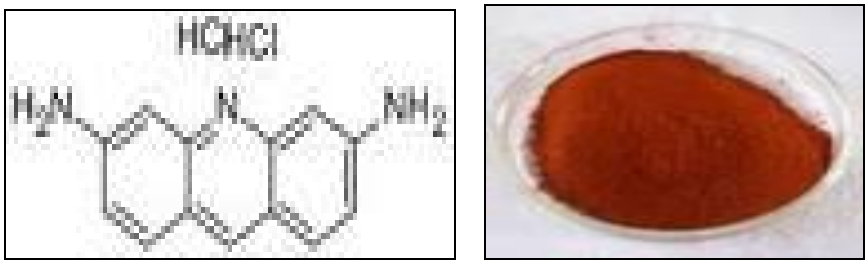


Figure 21 Structure of Proflavine.

Silver

Silver **(Figure 22)** has a long history as an antimicrobial agent [121, 122], especially in the treatment of burns. An awareness of its role in inhibiting micro-organisms has developed since the late 19th century [123]. Metallic silver is relatively unreactive, but in aqueous environments silver ions are released and antimicrobial activity depends on the intracellular accumulation of low concentrations of silver ions. These avidly bind to negatively charged components in proteins and nucleic acids, thereby effecting structural changes in bacterial cell walls, membranes and nucleic acids that affect viability. In particular silver ions are thought to interact with thiol groups, carboxylates, phosphates, hydroxyls, imidazoles, indoles and amines either singly or in combination, so that multiple deleterious events rather than specific lesions simultaneously interfere with microbial processes [124]. Hence silver ions that bind to DNA block transcription, and those that bind to cell surface components interrupt bacterial respiration and ATP (adenosine triphosphate) synthesis [125].

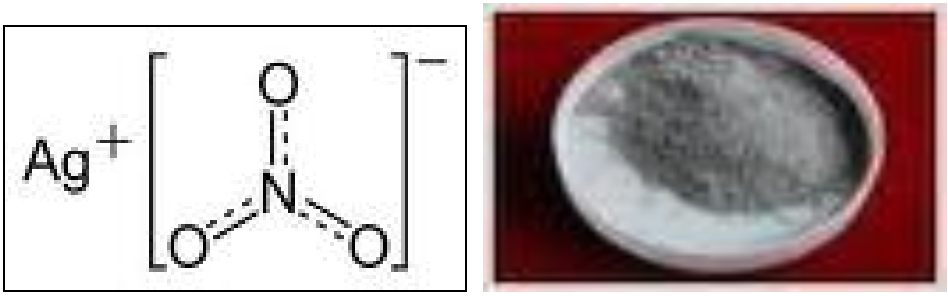


Figure 22 Structure of silver.

Polymer blends as wound dressing materials

Blending of polymers has emerged as an important route to design new, high-performance polymeric materials over the last 50 years. Blends are, in fact, attractive materials because their properties can be easily adjusted by varying the ratio and nature of constituent components [126]. This class of materials also has considerable potential owing in part to the large number of polymers that can be mixed.

Blending is a simple method to combine the advantages of different polymers, depending on the proportion of components and condition of mixing [127]. The resulting polymer blends show synergistic properties. Thus, technique of blending polymers offers means to obtain tailor made products with a good range of properties at low cost for specific applications. The blending of hydrophilic/hydrophobic polymer produces phase separated composite hydrogels. Polymer blend hydrogels are mostly composed of water- soluble polymer such as Alginate, starch-(EVOH), hydroxypropyl lignin, polyvinyl alcohol, alkyl cellulose, etc. Recently there has been an increasing interest in starch-based biodegradable blends [128, 129], offering a method to modify both the properties and degradation rates. A hypothetical scheme depicting the formation of binary blend from its constituent polymers is shown in **Figure 23**.

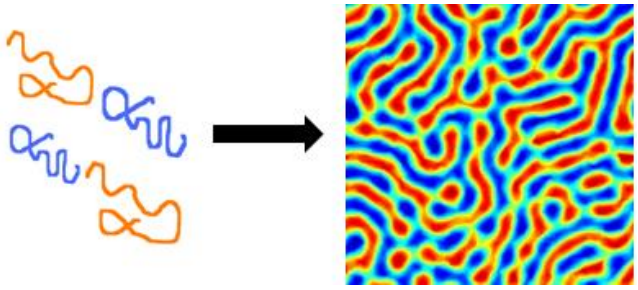


Figure 23 A hypothetical scheme depicting the formation of binary polymer blend.

Types of Polymer Blends

Blends of two polymers may be classified as compatible (miscible) or incompatible (immiscible), depending on the miscibility of components at the molecular level.

Miscible Polymer Blends

Miscible polymer blends behave similar to what is expected of a single phase system. Their properties are a combination of the properties of pure components. The characteristics of the components affecting the properties of miscible blends are their chemical structure, molecular weight, concentration and the intermolecular interaction, including crystallizability.

Immiscible Polymer Blends

In immiscible blends two or more multiple phases, both the polymers remain well separated into small domains. Most polymers are usually immiscible, and blending usually results in heterogeneous morphologies. The morphology of immiscible blend can be controlled by varying the conditions of mixing and use of compatibilizers. In the case of immiscible polymer blends, important characteristics are chemical nature of the components, blend composition, phase morphology, degree of crystallinity and interfacial interactions between the phases.

Techniques for Blend Preparation

The objective of mixing is to bring the components in close proximity. This is aided by solvents, heat and shearing force. Polymer blends have the advantage of being produced by simple techniques [130]. Most of the studies on polymer blending have been focused on element process such as drop (de) formation, thread break-up coalescence. The common methods used to blend polymers are:

Melt blending

In this method [131], the blending is done at high temperature (in melt or in near melt state) by using shearing force. The various devices used for this purpose are –roll-mill, banbury mixer, brabender mixer, Extruder and minimax mixer.

Melt- blending can be achieved by extrusion with blowing agents and compression moulding. In the extrusion process, the polymers were previously mixed with blowing agents in a rotating drum prior to processing in twin-screw extruder [132]. The compression moulding is based on blending together polymer and leachable particles (eg. starch and salt particles) to provide a continuous phase of a polymer and dispersed phase of leachable particle in the blend. The blend was then compression moulded into a desired shape, the resultant samples were then immersed in distilled water to remove unblended leachable particles [133].

Solution Cast Method

Solution blending [134] can be done by dissolving the two components in common solvent and then precipitating out the blend by addition of a suitable precipitant or by simple removal of solvent by evaporation, e.g. in cast films. The resulting materials have micro separated structure and offer improved miscibility via hydrogen bonding among polymers, resulting in a transparent material.

The choice of technique of blending depends on the pair of polymers. Melt blending has the risk of degradation of one or both components, while solution blending has the difficulty of finding a common solvent in many cases. Commercial large scale blending is preferably by melt blending, while in laboratory scale, solution blending is preferable due to the small amount of polymers to be mixed.

Freeze-Thaw method

PVA hydrogels are physically cross-linked using freeze–thaw cycles, allowing tailoring of the hydrogel network. During exposure to cold temperatures, water freezes, expelling PVA and forming regions of high PVA concentration. As the PVA chains come into close contact with each other, crystallite formation and hydrogen bonding occur. These interactions remain intact following thawing and create a nondegradable three-dimensional hydrogel network [135].

Poly (vinyl alcohol) is a water–soluble polymer. When aqueous solutions of PVA are stored at room temperature, they gradually form a gel, however, of low mechanical strength. Interestingly, once aqueous solutions of this polymer undergo a freeze–thawing process, a strong and highly elastic gel is formed [136]. The properties of gel depend on the molecular weight and concentration of PVA in water, the temperature and time of freezing and the number of freezing cycles. Gel formation is ascribed to the formation of PVA crystallites which act as physical crosslinking sites in the network [137]. Gel formation is most likely caused by crystallization due to association of chains through hydrogen bonding. **Figure 24** shows a schematic representation of gel formation by freezing–thawing method [138].

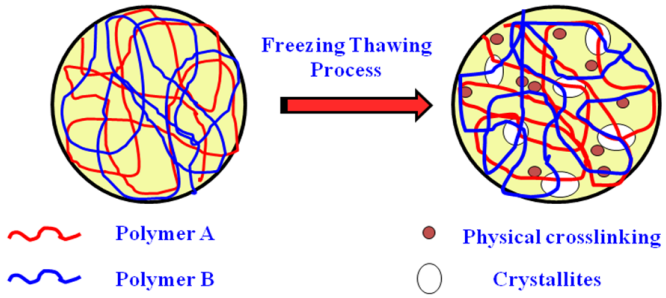


Figure 24 A schematic representation of gel formation by freezing–thawing process

Superiority of physical blends prepared by freeze-thaw method

Hydrogels prepared by repeated freezing–thawing process have following special properties which make them more effective in biomedical applications. The hydrogels which are prepared by repeated freezing–thawing process are porous, spongy, rubbery and elastic and displayed good mechanical strength [139].

For the entrapment and encapsulation of labile bioactive substances and living cells, physically crosslinked gels are of great interest especially when the gel formation occurs under mild conditions in the absence of organic solvents.

Poly (vinyl alcohol) (PVA) gels that are prepared by freezing and thawing techniques have shown many improved properties over hydrogels prepared by traditional chemical crosslinking techniques. It has been shown that repeated cycles of freezing at –20ºC and thawing at 25ºC result in the formation of crystalline regions that remain intact upon being placed in contact with water or biological fluids at 37ºC. These PVA hydrogels show increased mechanical strength over most hydrogels because the crystalline regions are capable of better distributing a given mechanical load or stress. Additionally, the gel show high elasticity and are capable of being extended to five or six times their initial length. Because of these characteristics, the potential for such materials for a variety of biomedical and pharmaceutical application is quite obvious [140, 141].

Mechanism of blend formation by Freeze- Thaw method

Although formation of elastic gel either upon standing an aqueous solution of PVA at room temperature or successively freezing thawing a moderately concentrated PVA solution is not a new concept [142]. However, a molecular explanation for this phenomenon has yet to come. Three basic models, including hydrogen bonding, polymeric crystalline formation and liquid-liquid phase separation, have been suggested to explain the mechanism of gel formation. A mechanism of blend preparation involves “physical” crosslinking due to crystallite formation. This

method addresses toxicity issue because it does not require the presence of a chemical crosslinking agent [143, 144]. The process of cryogels produced by freezing-thawing method may be explain due to the fact that whereas the freezing of a PVA results in the formation of ice crystal domains within the polymer mixture matrix, the thawing process results in melting of the ice crystals, thus leaving wide pores in the gel. A repeated performance of the two processes widens the pore sizes and thus enhances the porous nature of hydrogel. The formation of porous network due to freezing-thawing method is modelled in **Figure 25**.

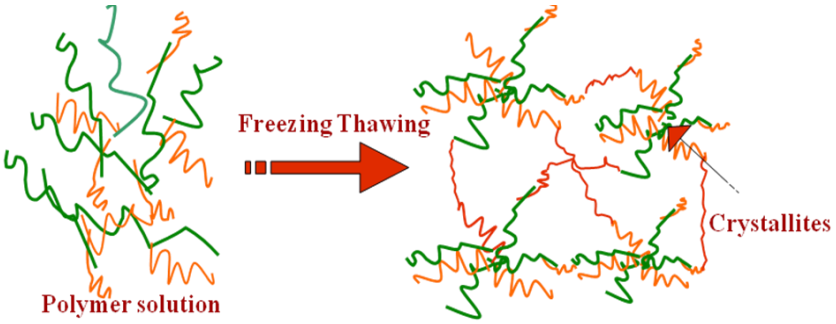


Figure 25 Mechanism of cryogel formation

Properties of polymer blends

There is a growing interest in developing engineered actuation systems that have properties more in common with soft biological materials, such as muscles and tendons, then with traditional engineering materials. In an aqueous environment, blend hydrogels may undergo a reversible phase transformation that results in dramatic volumetric swelling and shrinking upon exposure and removal of a stimulus. Thus, these materials, normally composed of ionic polymers, can be used as muscle like actuators, fluid pumps and valves. Interest in blend hydrogels has gained momentum recently because these materials can be actuated by a variety of stimuli such as pH, salinity, electrical current, temperature and antigens [145].

Swelling properties

The swelling kinetics of hydrogels can be classified as diffusion–controlled (Fickian) and relaxation–controlled (non–Fickian) swelling. When water diffuses into the hydrogel much faster than the relaxation of the polymer chains, the swelling kinetics is relaxation–controlled. A nice mathematical analysis of the dynamics of swelling has been presented by Peppas and Colombo [146].

Besides the nature, the crosslinking ratio is one of the most important factors that affect the swelling of blends. It is defined as the ratio of moles of crosslinking agents to the moles of polymer repeating units. The higher the crosslinking ratio, the more crosslinking agent is incorporated in the hydrogel structure. Highly crosslinked blends have a tighter structure, and will swell less compared to the same blends with lower crosslinking ratio. Crosslinking hinders the mobility of the constituent polymer chains, thus, lowering the swelling ratio.

The chemical structure of the polymer may also affect the swelling ratio of the blend hydrogels. Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. Hydrophobic groups collapse in the presence of water, thus, minimizing their exposure to the water molecule. As a result, the hydrogels will swell much less compared to hydrogels containing hydrophilic groups. Superabsorbent polymers which may be termed as materials capable of absorbing and holding large amount of water, have gained considerable attention and may be very useful in the biomedical fields. These materials have extensive commercial applications such as 'infant diapers', 'feminine hygiene products' and 'incontinency products'. These materials can be fruitfully prepared by radiation grafting technique [147].

pH–sensitive blends

Blend hydrogels exhibiting pH–dependent swelling behaviour can be swollen due to ionic networks (**Figure 26**). These ionic networks contain either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize, developing fixed charges on the constituent polymer chains [148-149**]**. As a result of the electrostatic repulsions, the uptake of solvent (water) in the network is increased.

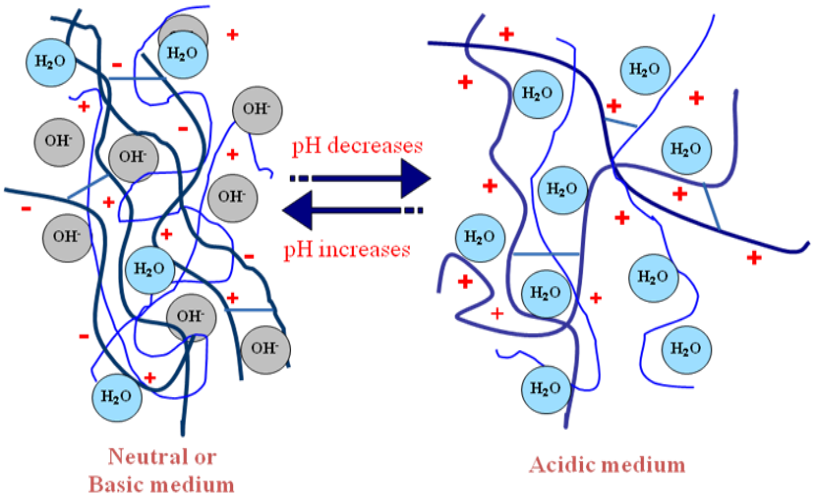


Figure 26 The swelling phenomena of a hydrogel in a buffered pH solution.

Ionic hydrogels are swollen polymer networks containing pendant groups, such as carboxylic or sulfonic acid, which show sudden or gradual changes in their dynamic and equilibrium swelling behaviour as a result of changing the external pH. In these gels, ionization occurs when the pH of the environment is above the pKa of the ionizable groups. As the degree of ionization increases (increased system pH), the number of fixed charges increases, resulting in an increased electrostatic repulsions between the chains. This, in turn, results in an increased hydrophilicity of the network, and greater swelling ratios.

There are many advantages in using ionic over neutral networks in drug delivery. Their characteristics can be exploited for in a wide variety of biomedical applications, such as dental adhesives and restorations, controlled release device, prodrugs and adjuvants, and biocompatible materials [150].

The swelling force is reduced due to increased gel counter ion interaction and a decrease in the osmotic swelling forces. As the ionic strength of the swelling agent increases, the concentration of ions within the gel must increase in order to satisfy the Donnan equilibrium. Khare and Peppas [151] examined the swelling kinetics of Poly (MAA) or poly (acrylic acid) with poly (hydroxy ethermethacrylate). They observed pH and ionic strength–dependent swelling kinetics in these gels.

Mechanical properties

Mechanical properties of blend hydrogels are very important for pharmaceutical applications. For example, the integrity of the drug delivery device during lifetime of the application is very important to obtain FDA approval, unless the device is designed to protect a sensitive therapeutic agent, such as protein must maintain its integrity to be able to protect the protein until it is released out of the system.

Changing the degree of crosslinking has been utilized to achieve the desired mechanical property of the blend hydrogel. Increasing the degree of crosslinking of the system will result in a stronger gel. However, a higher degree of crosslinking creates a more brittle structure. Hence, there is an optimum degree of crosslinking to achieve a relatively strong and yet elastic hydrogel. Copolymerization has also been utilized to achieve the desired mechanical properties of hydrogel. Incorporating a counter polymer that will contribute to H–bonding can increase the strength of the blend hydrogel [152].

Temperature sensitive hydrogels

Temperature–sensitive hydrogels have gained considerable attention in the pharmaceutical field due to the ability of the hydrogels to swell or deswell as a result of changing the temperature of the surrounding fluids. Numerous researchers studied various applications of these hydrogels, such as on–off drug release regulations, biosensors and intelligent cell culture dishes [153].

Thermosensitive hydrogels can be classified as positive or negative temperature–sensitive systems. A positive temperature–sensitive hydrogel has an upper critical solution temperature (UCST). Such hydrogels contract upon cooling below the UCST. Negative temperature–sensitive hydrogels have a lower critical solution temperature

(LCST). These hydrogels contract upon heating above the LCST. Some ionic and non–ionic hydrogels undergo volume–phase transition with temperature. This volume change depends on both the degree of ionization and the stiffness of the components of the polymer chains and is reversible. Potential applications of this phenomenon include extractive separations, controlled drug release, development of biosensors and membrane separation [154].

Tanaka [155] reported the temperature–sensitive swelling behaviour of poly(N–isopropyl acrylamide) hydrogels and used thermodynamics approaches to theoretically explain this behaviour.

Cytotoxicity and in–vivo toxicity

Cell culture methods, also known as cytotoxicity tests, can be used to evaluate the toxicity of blend hydrogels. Three common ways to evaluate the toxicity of materials include exact dilution, direct contact and agar diffusion. Most of the toxic problems with toxicity associated with blend hydrogels are due to the unreacted monomers, oligomers and initiators that leach out during application. Therefore, an understanding of the toxicity of the various monomers used as the building blocks of the blend hydrogels is very important.

The relationship between chemical structures and the cytotoxicity of acrylate and methacrylate monomers has been studied extensively [156]. Several measures have been taken to solve this problem, including modifying the kinetics of polymerization in order to achieve a higher conversion and extensive washing of the resulting hydrogel. The formation of hydrogels without any initiators has been explored to eliminate the problem of the residual initiator, the most commonly used technique has been gamma irradiation [157-161] Hydrogels of PVA have also been made without the presence of crosslinker by using thermal cycle to induce crystallization [162] in which the crystals formed act as physical crosslinks. These crystals will be able to absorb the load applied to the blends.

Survey of Recent Literature

Zeng and coworkers [163] prepared microporous chitosan membrane by selective dissolution of its blend. Two synthetic polymers, e.g. polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG), were chosen to be the counterpart polymers. Results of Fourier transform infrared (FTIR) characterization, differential scanning calorimeter (DSC) analysis, wide angle X-ray diffraction (WAXD) measurements showed that there are special interactions between chitosan and the counterpart polymers. Singh et.al [164] studied modification of sterculia gum by PVA–PVP through radiation crosslinking,to develop the hydrogels meant for the delivery of antimicrobial agent to the wounds. The hydrogels were characterized by SEM, FTIR, TGA and swelling studies. Witthayaprapakorn and coworkers [165] designed the synthetic hydrogels for biomedical use as wound dressings. Crosslinked polymers of 2-acrylamido-2-methylpropane sulfonic acid (AMPS) and its sodium salt (Na-AMPS) were prepared via free radical polymerization in aqueous solution using photo initiation.

Ezequiel and coworkers [166] studied the development and characterization of novel polymer blends based on chitosan and poly (vinyl alcohol) and chemically crosslinked by glutaraldehyde for possible use in a variety of biomedical applications. Mansur and coworkers [167] reported the preparation, characterization and cytocompatibility of novel polymeric systems based on blends of chitosan and poly (vinyl alcohol) (PVA) and chemically crosslinked by glutaraldehyde. The structure of the hydrogels was characterized through Fourier Transform Infrared spectroscopy (FTIR) and their swelling behavior was investigated. Sikareepaisana and coworkers [168] successfully prepared the wound dressing materials from alginate, a natural polymer capable of forming hydrogels, and asiaticoside (PAC), a substance from the plant Centella asiatica which is commonly been used in traditional medicine to heal wounds. Liua and coworkers [169] prepared the poly (vinyl alcohol)/gelatin hydrogels as potential vascular cell culture biomaterials, tissue models and vascular implants. The PVA/Gelatin hydrogels were physically crosslinked by the freeze-thaw technique, which is followed by a coagulation bath treatment. In this study, the thermal behavior of the gels was examined by differential scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA). Fathia and coworkers [170] designed the physically crosslinked hydrogels composed of different amounts of dextran in PVA matrix by applying freeze–thaw cycles to their aqueous solutions. Morphology, thermal properties and FTIR spectra of the resulting blend xerogels were examined by SEM, DSC, TGA and FTIR spectroscopy.

Wu and coworkers [171] prepared the porous gelatin scaffolds with microtubule orientation structure by unidirectional freeze-drying technology, and their porous structure was characterized by scanning electron microscopy. Sung and coworkers [172] developed a minocycline-loaded wound dressing with an enhanced healing effect. The cross-linked hydrogel films were prepared with polyvinyl alcohol (PVA) and chitosan using the freeze-

thawing method. Their gel properties, *in vitro* protein adsorption, release, *in vivo* wound healing effect and histopathology were then evaluated. Saha et.al [173] focused on the significant properties of hydrogels prepared with polymeric biomaterials: solely biopolymers (gelatin (G) and sodium alginate (SA) as base polymer) or in combination with synthetic and bio polymers polyvinylpyrrolidone (PVP) and carboxymethylcellulose (CMC)) for biomedical application. Singh et.al [174] studied the modification of sterculia gum to develop novel wounds dressings for the delivery of antimicrobial agent (tetracycline hydrochloride). The sterculia crosslinked PVA (sterculia-cl-PVA) hydrogels were characterized by FTIR and swelling studies. Yang and coworkers [175] prepared the poly (vinyl alcohol) (PVA)/water soluble chitosan (ws-chitosan)/glycerol hydrogels by g-irradiation followed by freeze-thawing. The effects of irradiation dose and the contents of PVA and agar on the swelling, rheological, and thermal properties of these hydrogels were investigated. Mc Gann and coworkers [176] prepared the physically cross-linked hydrogels composed of 75% poly(vinyl alcohol) PVA and 25% poly(acrylic acid) by a freeze/thaw treatment of aqueous solutions. Between 0.5 and 1 wt% of aspirin was incorporated into the systems. The purpose of the research was the development of a novel pH-sensitive hydrogel composite for the delivery of aspirin to wounds. Jayakumar and coworkers [177] studied the wound dressing of chitin and chitosan. The adhesive nature of chitin and chitosan, together with their antifungal and bactericidal character, and their permeability to oxygen, is a very important property associated with the treatment of wounds and burns. Kofuji and coworkers [178] obtained a transparent wound dressing sheet by forming a complex between b-glucan and chitosan (CS). These materials were chosen for their biocompatible, bioabsorbable, and biodegradable properties, expected to promote the therapeutic efficacy of the dressing by increasing the wound healing response.

Tsao and coworkers [179] present a novel design for an easily stripped polyelectrolyte complex (PEC), which consists of chitosan as a cationic polyelectrolyte and poly (glutamic acid) (PGA) as an anionic polyelectrolyte, as a wound dressing material. Sirousazara and coworkers [180] prepared the hydrogel wound dressings based on polyvinyl alcohol by cyclic freezing-thawing method and their dehydration process was investigated by experimental and mathematical methods. Mishra and coworkers [181] prepared the hydrogels of caboxymethyl cellulose (CMC)/ poly (vinyl alcohol) (PVA)/gelatin and crosslinked polyacrylamide (PAM). The prepared hydrogels were loaded with Povidone-iodine for using as wound dressing. Release and swelling characteristics were also studied for loaded hydrogels and found to be dependent on chemical architecture. Blood compatibility was also studied by clot formation and haemolysis assay.

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Publication History
Received 06th Oct 2015
Revised 20th Nov 2015
Accepted 05th Dec 2015
Online 30th Dec 2015