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Carbohydrate polymers as wound management aids

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Abstract

Wound management aids have, in recent years, seen a transition from being simple natural coverings which give a wound protection from the external environment during the formation of the scab to specialized high technology materials which are produced from both synthetic and natural polymers. Much of the development has resulted from a greater understanding of the processes involved in wound healing coupled with advances in technology to produce biocompatible materials with the necessary physical and chemical characteristics for enhancement of the healing process. Polysaccharides, being naturally occurring biomolecules, were an obvious choice for investigation as potential wound management aids. In recent years it was recognised that not only can polysaccharides be produced with the required physical characteristics for a wound management product but that the actual polysaccharide or polysaccharide derivative may itself actively participate in the process of wound healing. This paper sets out to review the various types of polysaccharides which were used as wound management aids, the physical forms in which they are used and also the biological properties of polysaccharides which enable them to participate actively in the wound healing process.

Keywords: Wound management; Polysaccharides; Carbohydrate polymers; Branan ferulate

1. Function of a wound management aid

Historically wounds were treated by allowing them to dry and, hence, acquire a hard protective coating, the scab. This meant that the treatment involved applying very simple natural coverings such as gauze type materials produced from cotton or lint. This covering simply provided a protective layer which was capable of absorbing wound fluid and under which the scab could develop. About 30 years ago the treatment of wounds was revolutionized when it was discovered that a wound would heal faster when a 'moist' dressing was applied compared with the traditional 'dry' dressings. Natural skin is recognised as the ideal wound dressing and so the development of 'moist' dressings was based on the desire to replicate skin with its 85% water content and inherent permeability. The substantial interest in the development of dressings which can replicate the properties of skin has meant that dressings are now left in place longer with the accompanying enhancement of the healing process. However, the demands on a moist dressing which are left in contact with a wound without disturbance for long periods of time are much greater. In order that the wound should remain moist for periods of time measured in days and that the healing process should be enhanced the wound dressing must fulfil a number of requirements. The dressing material should: (1) be capable of maintaining high humidity at the wound-dressing interface whilst removing through adsorption excess wound exudate and associated toxic compounds; (2) permit the exchange of gases whilst maintaining an impermeable layer to microorganisms so preventing secondary infections; (3) provide thermal insulation; (4) all components of the dressing, including the adhesives, must be biocompatible and not provoke any allergic reaction through their prolonged contact with tissue; (5) there must be minimal adhesion to the surface of the wound so that the dressing can, when required, be removed without trauma; (6) the dressing must be physically strong even when wet; (7) be produced in a sterile form; and (8) easy to dispose of when removed at the end of use. If these criteria are met then the optimum healing environment for the wound would be maintained and the healing process enhanced.

2. Physical forms of wound management aids

Wound management aids are available in a range of

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physical forms including fibres and threads, films for use as a covering and gels and hydrocolloids. The various types of wound require different types of product, for example a simple skin lesion may require a coating while a cavity wound will require an infill material. Some of the more specific physical forms are discussed in more detail below.

2.1. Hydrogels/xerogels

A hydrogel is a three-dimensional network of hydrophilic polymer chains in which at least 20% by weight is retained water. If the water content is greater than 95% by weight then the hydrogel is termed a superabsorbent. The hydrogels swell and shrink in the presence/absence of water and if the water is completely removed they collapse to form a xerogel. The shrinking/swelling process is reversible so in the presence of water the xerogel will swell to give the hydrogel structure. In order for a hydrogel to maintain its three-dimensional structure the hydrophilic polymer chains are cross-linked either by covalent bonds or non-covalently by electrostatic, hydrophobic or van der Waals interactions. Hydrogels/xerogels are used as wound management aids where they are used as dressing materials. They can be manufactured so that they are flexible, durable, non-antigenic and permeable to water vapour and metabolites whilst also securely covering the wound so preventing infection by bacteria. There are a number of commercially available xerogel wound dressing preparations which are available in a number of physical forms including granules, sheets, fibres and flakes.

2.2. Hydrocollolids

The term hydrocolloid is given to some commercial wound dressings which satisfy the criteria listed above. In order to maintain the moist healing environment they utilize a multilayer structure consisting of a protective outer layer, a backing material which may be a film, foam or fibre onto which is laminated a composite consisting of an adhesive through which are distributed hydrophilic particles. For the treatment of a cavity wound where extra absorbency is required an alternative construction is used where the layer in contact with the wound is a separately applied coating of a paste, powder or granules. Typical backing materials used in the manufacture of hydrocolloid dressings are non-woven polyester fibres and semipermeable polyurethane films and the hydrophilic component of the adhesive may contain several components, for example: synthetic polymers such as polyurethane gels, proteins such as gelatin and polysaccharides such as cellulose derivatives.

2.3. Bioactive dressings

The very early rationale for covering a wound was linked with the requirement to apply some form of medication to the injured site. The early remedies, such as bitumen and insect parts, had no scientific basis but in recent years as scientists have come to an understanding of the process of wound healing, beneficial agents such as steroids, antibiotics and growth factors were incorporated into the dressing. The use of 'moist' wound management aids creates an interface between the wound and the dressing surface which can be impregnated with an agent to stimulate healing or may contain as one of the components of the hydrophilic layer a polymer with known beneficial effects.

2.4. Tissue engineering

An extension of the bioactive dressings which incorporate a stimulus to the wound healing process is the development of tissue engineering supports. This technology uses a combination of biomaterials and biologically active molecules or cells to manipulate various types of tissue so effecting a repair or regeneration. The treatment involves incorporating into a suitable biocompatible and biodegradable support matrix some of the patients own cells which should then proliferate and produce new tissue that gradually replaces the matrix scaffold. The technology has so far been evaluated for its suitability in the regeneration of cartilage, repair of nerves and major skin defects such as those that occur in burn damage. For the treatment of full-thickness burn damage keratinocyte cultures are incorporated into the biodegradable matrix to effectively regenerate the skin following the format of the support material.

3. Polysaccharides

Polysaccharides are high molecular weight condensation polymers with tens and often hundreds of monosaccharides residues per polysaccharide chain. The monosaccharide units of which they are composed can be neutral, basic, acidic or combinations thereof and, hence, the polysaccharide may itself be a neutral basic or acidic polymer or indeed have the potential to have mixed/variable charge according to the monosaccharide residues of which it is composed and the environment. They maybe homopolymers composed of a single type monosaccharide residue or heteropolymers containing two or more types of monosaccharide and the structure can be linear or branched and in some instances cyclic. Polysaccharides are naturally occurring biomolecules which perform a number of different functions in living organisms. Some polysaccharides act as structural components, for example, in the cell walls of plants, some are food reserves, some act as protecting agents to seal off wound sites in plants and some also work as lubricating agents in joints. It is clear that with so many variations in composition, structure and function some polysaccharides may possess properties which would be beneficial in a wound management aid or indeed may themselves participate in the wound healing process.

Polysaccharides also have functional groups, primary and

secondary hydroxyls, amino and carboxylic acid funtionalities, which can be used as sites for chemical derivatisation or attachment of specific ligands. The naturally occurring polysaccharide molecule can therefore be modified to change its physical characteristics and, hence, improve its applicability for a specific application. Typical modifications used include altering the degree of polymerization (chain length), etherification, esterification, oxidation, cross-linking and graft copolymerization.

3.1. Neutral polysaccharides (D-glucans)

The D-glucan classification of neutral polysaccharides are composed of D-glucopyranose residues joined by glucosidic linkages between the hemiacetal oxygen at C-1 on one monosaccharide residue and one of the four hydroxyls, C-2, C-3, C-4 or C-6, on the adjacent residue. Therefore theoretically there are eight different D-glucans which are homogeneous in respect to their linkage type and form i.e. four possible linkage positions and two possible configurations, α or β, of the anomeric hydroxyl group. All except the (1–2)-α-D-glucan occur naturally. In addition to the homogeneous polysaccharides there are many heterogeneous polymers which exist, mixed α and β forms have only occasionally been reported but polysaccharides with more than one linkage position are very common, e.g. the amylopectin component of starch which is a (1–4)(1–6)-α-glucan. As would be expected for a class of polysaccharides with so many structural variations the glucans are widely distributed amongst higher plants, lower plants, animals (mainly α-D-glucans) and microorganisms, and occur as structural components, e.g. cellulose, storage components e.g. starch and may also be at very specfic sites where their function is not clear. The heterogeneous glucans may have a linear or branched structure with the linkage arrangements being sequential or random. It would be expected that because of the diversity of structures of the glucan class of polysaccharides there would be a wide range of solubilities, some being totally insoluble and some being totally soluble. Also there would be a wide range in the shape of the glucan molecules as this would be governed by configuration and position of the glucosidic linkages. A number of glucans or glucan derivatives are utilized in the area of wound management as they either have inherent biological activity which is beneficial in a wound management regime or can be derivatized to provide materials with the necessary physical form.

3.1.1. Cellulose

Cellulose is a structural polysaccharide which is rigid and highly crystalline and is as a consequence very difficult to solubilize. It therefore in the native form is unsuitable for biomedical applications since flexibility and solubility are the normal prerequisites. In order to overcome these problems methods of chemical modification to produce soluble and flexible derivatives were developed. The primary derivatives produced for medical applications are biocompatible nontoxic and noncarcinogenic polymers, cellulose esters and cellulose ethers, which are classified as being generally recognised as safe (GRAS) in the USA.

3.1.2. Dextran

The name dextran is used to describe a wide range of related microbial glucans consisting of linear chains of (1–6)-linked α-D-glucopyranose residues with (1–3), (1–4) and less frequently (1–2) branch points off the main polysaccharide backbone. The degree of branching of the dextran produced by *Leuconostoc mesenteroides* B512F, which is used for clinical purposes, is reported to be approximately 5%. The characteristics of the branching, length and frequency of the chains, were shown to be dependent upon the temperature at which the dextran is synthesized (Sabatie et al., 1988) and the molecular weight of the polysaccharide (Kuge et al., 1987). Most of the physical properties of dextran fractions and their associated pharmacological properties are dependent upon their molecular weight distribution. Even at high molecular weight dextrans are readily soluble in water and electrolyte solutions.

Dextran was shown to be degraded in vivo, dextran degrading enzymes are present in mammalian tissue and the degradation products are gradually eliminated from the body. The role of dextran in fibrinolysis was shown to be complex but the evidence does suggest that dextran accelerates the polymerization of fibrin and will also influence the structure of the fibrin clot with the diameter of the fibrin fibres being broader when dextran is present (Carlin et al., 1976). Dextran would appear to have some possible beneficial activity in the treatment of wounds but its solubility is a limiting factor. In order to reduce solubility for use in the treatment of wounds an emulsion polymerization of dextran using epichlorohydrin as the cross-linking agent has produced insoluble beads which will swell in water. These beads were used in the treatment of skin lesions where they are reported to absorb approximately 4 ml g^{-1} of wound exudate from infected secreting wounds with an associated reduction in the time required for healing (Howcroft, 1979). These cross-linked dextran beads have also been reported to be able to assist in the wound management process by stimulating macrophages and inducing peritoneal exudate (Blanckmeister and Sussdorf, 1985).

3.1.3. (1–3)-β-D-glucans

It was reported by Leibovich and Danon (1980) that a topical application of a glucan from yeast induces a rapid repair of experimental wounds. Experimental data has shown that the rate of repair is faster for the glucan than for the polysaccharides carrageenan, levan, inulin, dextran and starch and inorganic talcum powder. It was proposed that this effect may be attributed to the induced reticuloendothelial system (RES) stimulation i.e. the stimulation of the lympho-reticular cells of the mammalian defense system including macrophages, endothelial and reticulum cells.

Although there are many different reports on the effects of β-D-glucans and the mechanisms involved, the most widely accepted dominant effect of yeast glucan when it is administered to mammals is the proliferation of macrophages. This is considered to be part of a generalized stimulation of the RES. By stimulating the macrophages several effects would be observed including an increased resistance to infection, an inhibition of tumour growth and an improvement in the wound repair process. The other (1–3)-β-D-glucan which was examined in detail is lentinan. It is a (1–3)-β-D-glucan with (1–6)-β-D-glucopyranoside branches and has antitumour activity in allogenic, syngenic and autochthonous primary hosts, suppressing chemical and viral oncogenesis and reportedly preventing cancer recurrence or metastasis after surgical intervention. There is also some evidence that the macromolecules are also able to increase the host resistance to a number of bacterial, viral and parasitic infections. The reported immunomodulating effect is possibly at the T-cell level. The literature is not clear as to how the initial interaction between the soluble or insoluble glucan and the surface of the macrophage or other cells take place. There are two distinct possibilities which could initiate a cellular response the first is a non-specific interaction which would have the effect of modifying the surface or it may be a specific glucan-receptor interaction. The chemical characteristics of the glucan which are able to elicit the response were investigated for a few systems with the aim of characterizing and understanding the response promoting mechanism. It was established that the active molecules must contain a (1–3)-β-D-glucan chain although activity was shown by carbohydrate molecules containing additional linkage types and with some alternative monosaccharide residues. It is apparent that it is the ability of the polysaccharide molecule to associate with other macromolecules, including those at the surface of cells, which is the dominant factor in determining biological activity and the enhanced wound healing observed with β-D-glucan treatments. A typical structure of a (1–3)-β-D-glucan with a (1–6)-β-D-glucopyranoside branch point is shown in Fig. 1.

3.2. Basic polysaccharides

3.2.1. Chitin and chitosan

Chitin is a naturally occurring polysaccharide found in the outer shell of crustaceans. It is a (1–4)-β-linked glycan composed of 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine). Chitosan is the name given to the total, partially (majorly) deacetylated form of chitin and is therefore composed primarily of 2-acetamido-2-deoxy-D-glucose and glucosamine residues. Chitosan is biocompatible with its degradation products being known natural metabolites and can be produced in powder, film, bead, fibre and fabric formats. Chitosan was evaluated in a number of medical applications including as a potential wound dressing where it was shown that it can enhance wound healing and/or blood clot formation. Many of chitosans properties depend upon its cationic nature. At acidic pH's it is a linear polyelectrolyte with a high charge density, one positive charge per glucosamine residue and so will interact with negatively charged molecules including proteins, anionic polysaccharides and nucleic acids, many of which are located in skin. It was shown that in the area of wound healing chitosan can reduce scar tissue (fibroplasia) by inhibiting the formation of fibrin in wounds, it is hemostatic and can form a protective film/coating. One reason postulated for the ability of chitosan to enhance wound healing is its biodegradability. It is a substrate for lysozyme with the degradation products being absorbed and possibly even having some nutrient value. Also chitin, chitosan and chitosan derivatives affect macrophage activity which will influence the wound healing process.

Chitosan is a high molecular weight polysaccharide which can be chemically modified to alter its physical and biological properties. Chemical modifications of the amino group and both the primary and secondary hydroxyl groups are possible. Possible derivatizations include cross-linking, etherification, esterification and graft copolymerization. The structure of chitin and chitosan with derivatization options is shown in Fig. 2.

3.3. Acidic polysaccharides

3.3.1. Alginic acid/ailginate

The algal polysaccharide, alginic acid, is obtained from the cell walls of brown algae (Phaeophyta) such as the seaweeds *Laminaria* sp. and *Ascophyllum* sp. It is a linear block copolymer composed of two hexuronic acid monosaccharide residues, D-mannuronic acid and L-guluronic acid (Fig. 3) and where the distribution of the two monosaccharides along the chain is non-random but involves

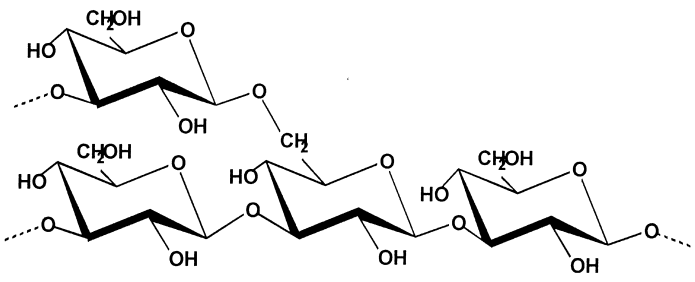

Fig. 1. A glucan structure showing (1–3)-β-D-glucan backbone with a (1–6)-β-D-glucopyranoside branch point.

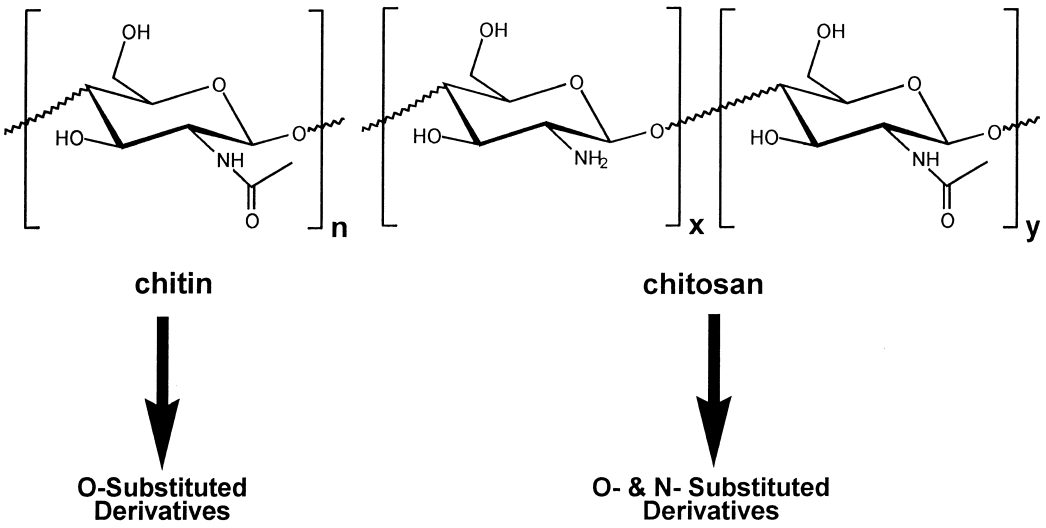

Fig. 2. The repeat units of the basic polysaccharides chitin and chitosan with the types of possible derivatization identified.

relatively long sequences containing only one hexuronic acid. In the presence of divalent cations, such as calcium, alginic acid/alginate is able to form gels because of association between the calcium ion and two guluronic acid residues. The cross-linking in alginate gels is therefore ionic, based on calcium bridges, with the degree of cross-linking depending upon the concentration of calcium ions and the number of guluronic acid sequences in the polysaccharide. Alginates have historically been known to have a haemostatic function and to be capable of absorbing specific solutes therefore it is logical that they should be evaluated as suitable components for modern wound management aids.

The calcium alginate gels have a large pore size and high water absorbency making them potentially useful as wound management aids, of the 'moist' dressing type. The hydrophilic sponges produced from calcium alginate were reported to have good absorptive properties for both blood and wound exudate with values of 22 g g^{-1} being reported (Schmidt, 1986). The alginate gels are thermally stable and have also been reported to deodorize wounds and absorb pain-stimulating compounds. However, when the calcium ions are exchanged for monovalent ions such as sodium the cross-linking is lost and the gel losses its rigidity and stability. Numerous types of wounds were successfully treated using alginate preparations but after a period of time the dressing becomes partially liquid as the sodium present in the wound exudate is gradually exchanged for the calcium. A reported disadvantage with alginate based wound dressings is that if they are not saturated with wound fluid they may be incorporated into the developing granulation tissue. Where there is sufficient wound exudate alginate dressings are beneficial to wound healing. This effect was attributed to an increase in the calcium ion concentration in the wound fluid, sodium exchange with the calcium alginate dressing, as the calcium effects many cellular activities including adhesion, differentiation and proliferation.

3.3.2. Hyaluronic acid/hyaluronate

Hyaluronic acid is a naturally occurring polysaccharide which is widely distributed in the connective tissue and vitreous and synovial fluids of mammals. It acts as a lubricant and shock-absorbing material in the fluid of joints. It is a linear polysaccharide consisting of a disaccharide repeat

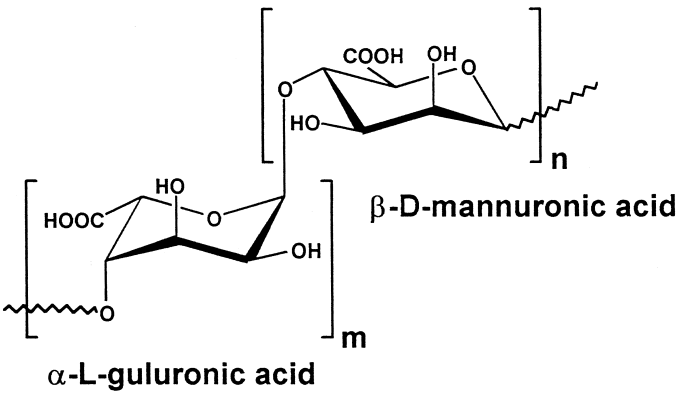

Fig. 3. The two monosaccharide residues and linkage identified in the acidic polysaccharide alginic acid.

unit of D-glucuronic acid and 2-acetamido-2-deoxy-D-glucose monosaccharides residues where the glycosidic bond is a (1–3) linkage between the β-D-glucopyranosyluronic acid and the 2-acetamido-2-deoxy-D-glucopyranosyl residues, Fig. 4. Between the 2-acetamido-2-deoxy-D-glucopyranosyl and the β-D-glucopyranosyluronic acid residues the linkage is (1–4) which gives the repeating disaccharide unit (…–4)-O-(β-D-glucopyranosyluronic acid)-(1–3)-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1–…). The large hyaluronic acid/hyaluronate polysaccharide molecules are water soluble giving solutions which are very viscous even at low concentrations. However its biological function is more than just being a high viscosity space filler it is capable of interacting with a wide range of biomolecules including tissue components, protein, proteoglycans and growth factors. It is the ability of hyaluronic acid/hyaluronate to interact and to recognize and be recognized by other biological molecules which makes it of potential use in the area of tissue repair. In a wound environment it is able to act as a scavenger for free radicals so modulating inflammation, it is recognised by receptors on a variety of cells which are associated with tissue repair and regeneration. It has also been reported that incorporating hyaluronic acid/hyaluronan into wounds where the normal healing process was compromised, for example at points of infection, can accelerate the wound repair/healing process as in addition to the properties mentioned previously it can also act as a bacteriostat. This enables some control over wound healing, vascular repair and regeneration and cell differentiation to be achieved. Commercial preparations are available which are used in many types of eye surgery and as a viscosupplementation to improve joint movement. There are however severe limitations on the use of hyaluronic acid/hyaluronan in wound management aids because of its solubility in water, rapid resorption and short residence time in tissue. To increase the usability of this polysaccharide where its biological properties offer significant benefit, attempts were made to modify the molecule chemically to reduce its solubility i.e. produce a 'solid' material which can be used in various treatments. Polysaccharides can be cross-linked using difunctional agents such as carbodiimides and epichlorohydrin to give insoluble three-dimensional networks. However, the cross-linking agents may themselves be toxic chemicals and the stabilized three dimensional matrix may not have the same degree of biological activity as the flexible water soluble molecule. An alternative to cross-linking was evaluated for tissue engineering applications where the solubility of hyaluronic acid/hyaluronan is modified by esterification of the free carboxyl groups of the glucuronic acid residues in the polysaccharide chain (Williams, 1997). It was possible through the use of different ester types and controlling the degree of esterification to produce polymers of varying solubility, water soluble to insoluble biodegradable derivatives. These esterified hyaluronic acid/hyaluronan derivatives can be manipulated by extrusion, lyophilization and spray drying to produce different physical forms including membranes, fibres, sponges and microspheres.

The ester derivatives of hyaluronic acid/hyaluronan which were most widely investigated for use in wound management aids are the ethyl and benzyl derivatives with a high degree of esterification. The benzyl ester product where the degree of esterfication is 100% absorbs water to give a 40% increase in weight and the ethyl ester derivative with 100% esterification absorbs water to give a 200% weight increase. As the degree of esterification is decreased the water absorbancy increases until the point is reached at which the material dissolves. By controlling the degree of esterification materials can be produced which will dissolve rapidly or when placed in a wound site will remain as a semi-solid hydrogel for long periods of time. This has lead to the evaluation of these materials as tissue engineering supports where a biodegradable matrix is required for the incorporation into keratinocyte cultures which then enables effective regeneration of skin in full-thickness burn injuries.

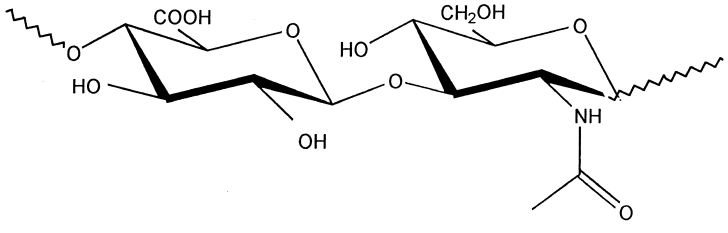

Fig. 4. The disaccharide repeat unit in the acidic polysaccharide hyaluronic acid.

3.4. Sulphated polysaccharides

The group of naturally occurring sulphated polysaccharides including heparin, heparin sulphate, dermatan sulphate, keratan sulphate and chondroitin sulphate exhibit extensive biological activity. Some or all have shown anticoagulant activity, lipemia clearing activity, an interaction with growth factors and fibronectin and in some cases an anti-human immunodeficiency virus effect. It was proposed that it is the negative charge on the polysaccharide which is essential for biological activity as it is this which is responsible for both the specific and non-specific interactions between the polysaccharide and protein molecules. There is however little work reported in the area of wound management.

3.5. Complex polysaccharides

In addition to the polysaccharides discussed in the previous sections research is now focusing on the suitability of more complex polysaccharides for use in wound management aids. One particular polysaccharide based product, Sterigel®, which has recently been commercialized is a cross-linked gel produced from a polysaccharide, branan ferulate, which is extracted from corn bran using alkali. This polysaccharide was characterized (Lloyd et al., 1997) and shown by gel permeation chromatography to have a pullulan polysaccharide equivalent peak molecular weight of 200 000 Daltons. Methylation analysis and enzymolysis showed the polysaccharide backbone to be a highly substituted (1–4)-β-D-xylan. The polysaccharide backbone is substituted with α-L-arabinofuranoside residues and α-D-glucopyranosyluronic acid residues. Some of the arabinose side chains are also substituted with cinnamic acid derivatives, in particular ferulic acid. Amino acid analysis revealed there to be 4.4% w/w amino acid content with hydroxyproline accounting for 0.22%. A schematic of the polysaccharide structure is shown in Fig. 5. The polysaccharide as extracted is a powder material but the ferulic acid constituents can be cross-linked using peroxidase which then forms a three-dimensional structure. In the presence of water the cross-linked bran ferulate polysaccharide forms a hydrogel which was shown to be suitable for use as a wound management aid. It is unique in the area of wound management aids as the cross-linking is achieved using an enzyme, peroxidase, to link two of the native polysaccharide subsituents, ferulic acid groups. The degree of cross-linking will therefore be determined by the peroxidase activity or in the presence of excess peroxidase the number and accessibility of the ferulic acid residues in the polysaccharide molecules.

4. Conclusions

Whilst it has not been possible within the scope of this review to detail all the polysaccharides which were used as wound management aids or have some biologically activity which may be of importance in a wound environment, examples were selected which cover the range of polysaccharide sources and types. Examples of modifications to the chemical structure which can be carried out to improve the polysaccharide applicability have also been included. The field of wound management has in recent years been transformed from what was essentially a very simple requirement to cover a wound, to a high technology multi-million pound industry where the researchers are now developing products with specific properties for the management of different

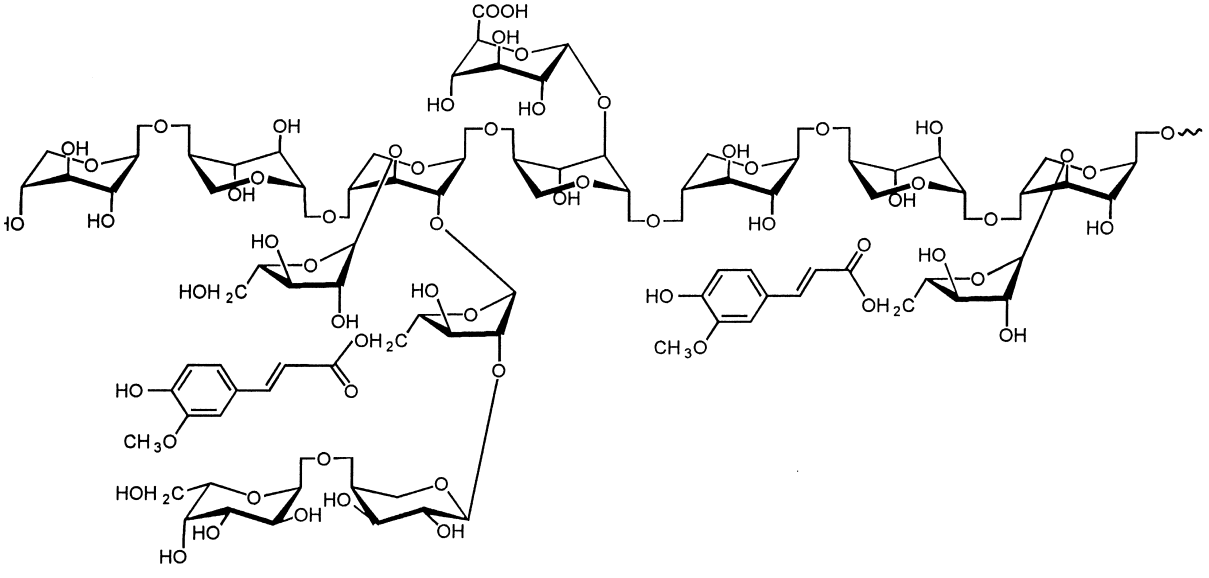

Fig. 5. A schematic of the complex heteropolysaccharide, branan ferulate, which is cross-linked using peroxidase to give the hydrogel wound management aid, Sterigel®.

types of wounds. We are almost entering the time of ‘designer’ products where a product is produced specifically for the treatment of one type of wound.

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