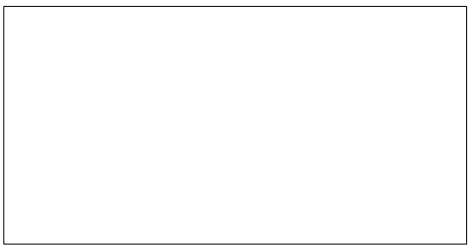

Gupta, Abhishek, Kowalczuk, Marek, Heaselgrave, Wayne, Britland, Stephen T., Martin, Claire and Radecka, Iza (2019) The production and application of hydrogels for wound management: A review. European Polymer Journal, 111. pp. 134-151.

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Title: Production and Application of hydrogels in Wound Management: A Review

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Highlights:

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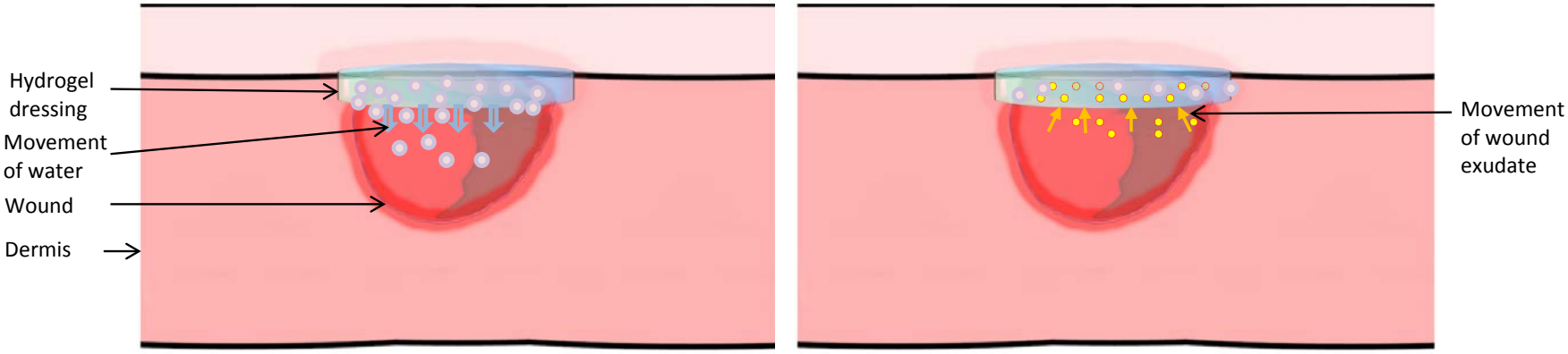
- Advanced wound dressings account for over 60% of sales in a market worth $11.4 billion annually
- Increased cases of diabetes worldwide and diabetic ulcers is key driving factor for the growth of this industry
- Hydrogels are an innovative type of dressing which uses moisture to aid the healing process
- Our focus is preparation methods, wound products and material aspect of hydrogel dressings.

Abstract

Wound treatment has gained huge impact in the wound care sector due to the pervasiveness of chronic wounds in the high risk population including, but not limited to, geriatric population, immunocompromised and obese patients. Rising prevalence of diabetes is another leading factor of the growth in chronic wound. According to the World Health Organization (WHO), the global diabetic prevalence has increased from 4.7% in 1980 to 8.5% in 2014. Moreover, according to the National Institute for Health and Care Excellence (NICE), in 2016, the prevalence of chronic venous leg ulcers alone was around 0.1% to 0.3% in the U.K. Wound dressings play an imperative role in wound healing process as they protect the wound site from external environment and are capable of interacting with the wound bed to facilitate and accelerate healing. Hence, the demand for advanced wound dressing products is rising. Advanced wound care that hydrogel wound dressings form part of, make up around $7.1 billion of the market and they are growing at an annual rate of 8.3% with the market projected to be worth $12.5 billion by 2022. Hydrogels, due to high water content, are ideal candidates for wound management as advanced moist dressings for wound healing. These wound dressing materials can be used for both: exudating or dry necrotic wounds. Additionally, hydrogels demonstrate other important features such as softness, malleability and biocompatibility. Presented review focuses on hydrogel wound dressings, their main characteristics and their wound management applications. It also describes recent technologies used for their production and the future potential developments.

Graphical abstract



Hydrogel dressing: Keeps the dry wound optimally moist by donating moisture

Water molecules

Hydrogel dressing: Keeps the wound optimally moist by absorbing excessive exudate

Wound exudate Water molecules

Keywords: Hydrogels; Chronic wounds; Wound healing; Wound management; Moist wound dressings

1. Introduction

A wound is an injury that disrupts the integrity of the epidermis as a physical barrier thereby interrupting its normal anatomical structure and physiology [1]. Dermal injury can be caused by acute trauma or surgical event. The resultant damage can affect local epidermal tissue, the vascular network and depending on the nature and depth of the wound, dermal intricate structure may also get damaged. In the case of surgical incisions, as the tissue loss is minimal and the healing process is rapid, wounds can be closed by variety of techniques including adhesive strips, sutures or skin adhesives (closure by primary intention) unless there is any underlying pathological condition hindering the healing process. In the case of acute trauma associated with substantial dermal matrix loss, closure by secondary intention, allowing the defect to be filled with granulation tissue is the primary approach followed for repair process. Reparative process is protracted when the defect area is large due to increased demand for production of dermal matrix forming cells for healing [2].

Wound healing is a complex biological process that varies in completeness and length of time to resolution depending on whether the wound is acute or chronic [3]. Acute wounds follow the normal healing path and are generally resolved within 8-12 weeks; however chronic wounds like diabetic foot ulcers, pressure ulcers, venous leg ulcers, are difficult to heal and generally exceed 12 weeks to full resolution [4,5].

1.1. The Wound Healing Process

Wound healing is a continuous process that follows a complex series of cellular and biochemical cascades occurring in orderly, sequential but overlapping phases to repair and regenerate the damaged tissue [6]. The healing process occurs in the

following four stages (Figure 1): exudative, inflammatory, proliferative and regenerative [7]. Various growth factors, cytokines, chemokines and other biomolecules are involved in this process [7,8,9] and their role in wound healing are summarised in Table 1. The exudative stage, also called coagulation and haemostasis, consists of stopping blood loss and preventing excessive bleeding. Although the act of bleeding is beneficial; washing the damaged tissue and reducing microbial invasion, it is controlled by haemostatic reflex vasoconstriction (local and systemic) and by the formation of insoluble fibrin plug, to prevent excessive blood loss. As blood interacts with exposed collagen and other components of the extracellular matrix, activated platelets release clotting factors and aggregate into a plug-like matrix, thus controlling blood loss [10]. Once haemostasis has been achieved, the inflammatory (or resorptive) stage begins with an increased infiltration of phagocytes (neutrophils and macrophages). The presence of neutrophils is time restricted to the early stages of healing, whereas macrophages persist through all phases from exudative to regenerative [11]. Within 24-36 hours post-injury, neutrophils migrate into the wound site and initiate phagocytic activity of macrophages by releasing proteolytic enzymes, chromatin, protease 'traps' and free-radical reactive oxygen species (ROS), with concurrent localised inflammation, heat and redness. The combined activity of neutrophils and macrophages helps to clear damaged and/or necrotic tissues, particulate contaminants and microorganisms from the wound site [12,13,14]. To enable the healing process to progress, neutrophils are removed from the wound site by apoptosis, phagocytosis (by macrophages), and disposal from the surface by sloughing or autolytic debridement. Modified monocyte macrophages arrive at the wound site 48-72 hours post-injury and phenotypically change into reparative tissue macrophages [11,15,16] that both promote and resolve

inflammation as well as removing apoptotic cells (by phagocytosis) [13,14]. Macrophages stimulate angiogenesis and granulation tissue formation in the later stages [17]. Infected wounds typically become halted in the inflammatory stage and hence fail to follow the normal healing process [18]. Wound debridement, which involves the removal of non-viable, hyperkeratotic tissue and microorganisms, is a vital stage of the healing process; chronic wounds can develop from a combination of poor debridement and microbial invasion, that both delay proliferation and tissue regeneration [19].

Once autolytic debridement is successfully achieved and the immune response has resolved, wound healing progresses into the proliferation stage which is the phase of tissue formation. During this stage tissue repair starts and wound closure is initiated. The wound site is filled with granulation tissue and epithelialisation from the wound edges takes place. The epithelial cells around the wound edges divide mitotically and migrate until a continuous sheet of cells is formed. Collagen (type III) formation by fibroblasts acts as a provisional matrix and provides strength to the newly formed granulation tissue which is responsible for scar formation [6,20]. To ensure the supply of oxygen and nutrients to newly formed tissue, angiogenesis also occurs at this stage with a microvascular network of new blood capillaries forming from the surrounding viable blood vessels [14,21]. The final stage of wound healing is regeneration where normal dermal architecture is restored and scar tissue tensile strength increased. Inflammatory cells clear from the regenerated area whilst collagen undergoes remodelling to increase the tensile strength of the tissue [6].

Healthy wound healing follows these sequential stages but delayed healing can result from several factors, including, but not limited to, underlying long term disease states such as diabetes, an impaired (HIV) or altered immune response (patients

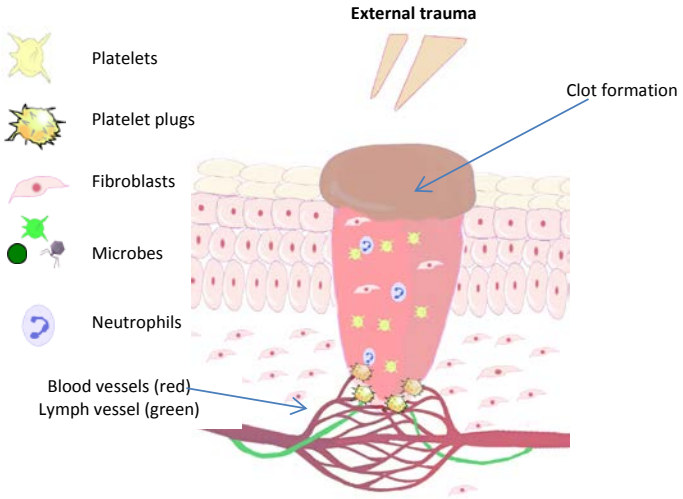
undergoing immunosuppression therapy) and/or a high level of microbial burden on and around the wound [22,23].

A retrospective cohort analysis revealed that during 2012/2013, the total annual health economic burden spent by the National Health Service (NHS) in the UK on wound management was nearly £5.3billion which equated to approximately 4% of the annual public health expenditure in the UK in 2013 (£125.5 billion), spent on wound management alone. During this year, wound care was provided to estimated 2.2million patients and the outcome of the treatment revealed that only 61% wounds healed whereas 39% of wounds didn't heal during the duration of the study. Since many chronic non-healing wounds do not respond to the standard care, the cost of management for these wounds was substantially greater (£3.2 billion) than acute wounds (2.1 billion) [24]. While chronic non-healing wounds occur in all age groups but these are prevalent in elderly population. Moreover, obese community and diabetic patients are more at risk. Globally, the population is aging rapidly; obesity and diabetic cases are also increasing, which is leading to the staggering increase of number of chronic wound. Studies suggested an estimated annual increase of 6-7% in the number of venous and pressure ulcers and around 9% increase in cases of diabetic ulcers, which would put extra financial strain on health services [25].

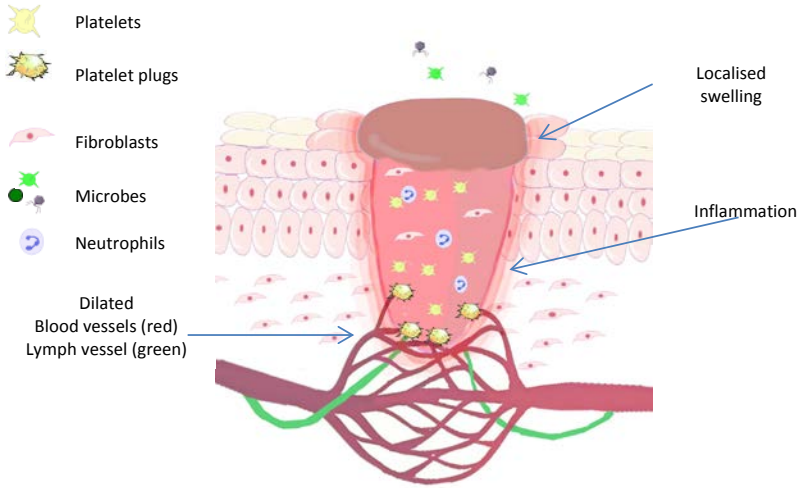
Despite the emergence of new therapies and vast variety of dressings, there is still an urgent need for effective approach to tackle this growing challenge and hydrogels are a vital candidate as an advanced wound dressing to encounter this problem.

Figure 1. Illustration of the stages of wound healing, (a) Exudative stage with the formation of blood clot (b) Inflammatory stage, marked with oedema, pain and inflammation (c) Proliferation stage with granulation tissue formation and (d) Regenerative stage, characterised by scar tissue formation.

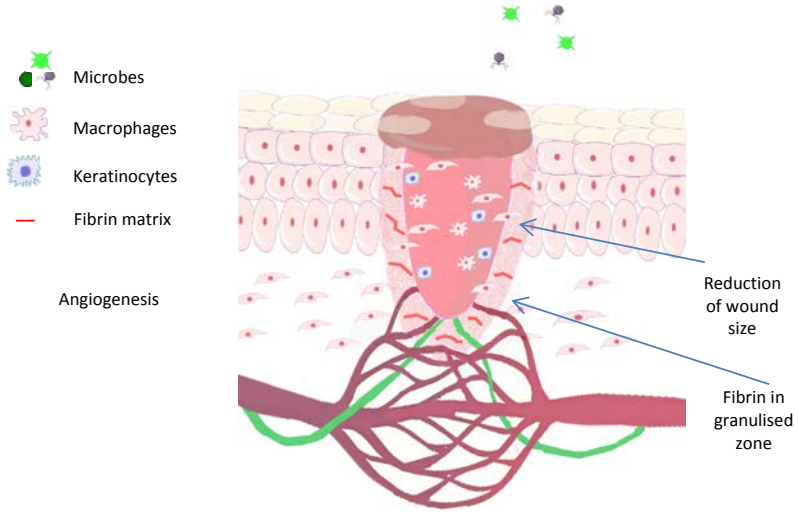
(a) Exudative stage



(b) Inflammatory stage



(c) Proliferative stage



(d) Regenerative stage

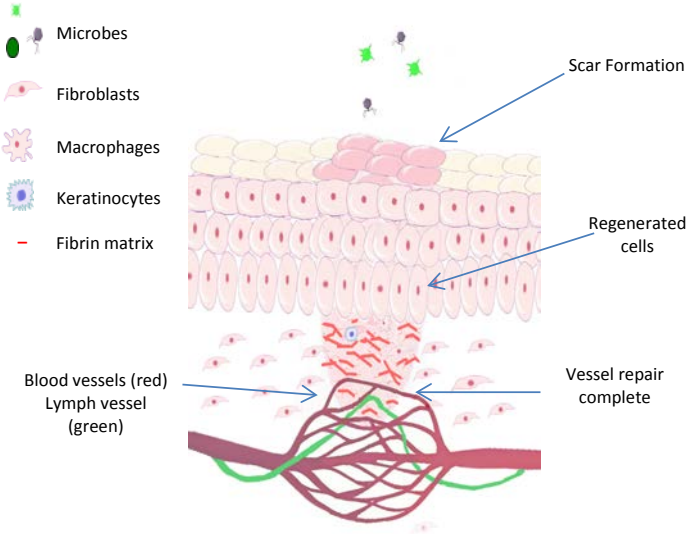


Table 1. Important mediators in wound healing process with their respective receptors, cell sources, targets and roles in wound healing.

Factor	Family	Receptors	Cells	Function	Level in acute wounds	Level in chronic wounds	Reference
PDGF	PDGF-BB **Additional:** PDGF-AA PDGF-AB PDGF-CC PDGF-DD)	Tyrosine kinase: α-receptor β -receptor	Platelets Fibroblasts Endothelial cells Macrophages Keratinocytes	Chemotaxis Proliferation of fibroblasts Promote blood vessel maturation Matrix deposition Reepithelialisation	Increased levels	Decreased levels	14,26,27,28,29,30
FGF	FGF-2 or bFGF **Additional:** FGF-7 FGF-10 KGF Total: 23 members	Tyrosine kinase: FGFR 1-4	Keratinocytes Mast Cells Fibroblasts Endothelial cells	Angiogenesis Formation of granulation tissue Reepithelialisation	Increased levels	Decreased levels	14,26,31,32,33,34
EGF	EGF TGF-α HB-EGF **Additional:** Amphiregulin Epiregulin Betacellulin Neuregulins	Tyrosine kinase: EGFR HER2 HER3 HER4	Platelets Macrophages Fibroblasts	Formation of granulation tissue Reepithelialisation Increases tensile strength in wound	Increased levels	Decreased levels	14,26,31,32,35,36,37 ~~26~~ ~~31~~ ~~32~~ ~~35~~ ~~36~~ ~~37~~
VEGF	VEGF-A **Additional:** VEGF-B VEGF-C VEGF-D VEGF-E PLGF	Tyrosine kinase: VEGFR-1 VEGFR-2 VEGFR-3	Platelets Endothelial cells Macrophages Lymphocytes Neutrophils Keratinocytes	Vasculogenesis Angiogenesis	Increased levels	Decreased levels	14,26,28,30,32,35,38,39 ~~26~~ ~~28~~ ~~30~~ ~~32~~ ~~35~~ ~~38~~ ~~39~~
TGF-β	TGF-β1	Serine-threonine kinases:	Platelets Macrophages	Angiogenesis Chemotaxis	Increased levels	Decreased levels	14,26,35,39,40 ~~26~~

	Additional: TGF-β2 TGF-β3	TGFβRI TGFβRII	Fibroblasts Keratinocytes	Reepithelialisation Anabolism of ECM Collagen production by stimulating fibroblasts Cellular proliferation and differentiation			~~35~~ ~~39~~ ~~40~~
Proinflammatory cytokines	IL-1 IL-6 **Additional:** TNF-α IL-8 IL-11 IL-27	ICAM-1 IL-6Rα	Monocytes Neutrophils Macrophages Keratinocytes	Chemotaxis Inflammation (except IL-27) Reepithelialisation Collagen synthesis Synthesis and breakdown of ECM Regulation of immune response	Increased levels at initial healing stages	Persistent Increased levels	14,26,39,41,42 ~~26~~ ~~39~~ ~~41~~ ~~42~~

Abbreviations: PDGF: Platelet-Derived Growth Factor, FGF: Fibroblast Growth Factor, KGF: Keratinocute growth factor, EGF: Epidermal Growth Factor; TGF-α: Transforming growth factor-alpha; HB-EGF: Heparin binding EGF, VEGF: (Vascular Endothelial Growth Factor), PLGF: Placenta growth factor, TGF-β: (Transforming Growth Factor- β); IL: (Interleukin); TNF-α: Tumor necrosis factor-alpha

1.2. Wound Dressings

Historically, wound dressings were designed to protect the wound site from external environment and played a passive role in healing process [43]. The range of available passive barrier-type wound dressings, *e.g.* gauze and tulle, increased as medical understanding of the wound healing process improved [44]. Such dressings undoubtedly are inexpensive and provide some protection, but being passive, cannot respond to changing wound conditions or deliver medicaments in a controlled or sustained manner to enhance the healing process. For wounds that follow the normal healing process, conventional, barrier-type dressings may be effective; conversely, chronic non-healing wounds can easily become infected thereby failing to progress through the normal stages of healing. Correct clinical management thus becomes imperative to minimise complications during wound healing [1,45].

Ideal dressings not only cover and protect the affected area, but can also create optimal moist environment at the wound site and facilitate healing [46,47,48,49,50]. Advanced wound management strategies involve non-invasive monitoring of healing, pain management and the controlled release of agents capable of promoting regeneration, repair and scar minimisation [51].

The concept of moist healing, as proposed by George Winter, revolutionised the field of wound management, and the focus of wound dressing changed from conventional dry passive products, to responsive moisture-promoting materials [52,53]. Dressing types used to achieve a moist wound healing environment include films, hydrocolloids, foams and hydrogels (Table 2).

Table 2. List of commercially available dressings based on the concept of moist wound healing environment.

Type of dressing	Characteristics	Cautions	Proprietary products	Reference
Film dressings	• Polyurethane films with an adhesive to hold the dressing • Create moist healing environment • Elastic, durable and conformable • Waterproof and transparent • Semi-permeable to water vapour and gases • Impermeable to bacteria • Impervious to liquids such as wound fluid • No secondary dressing required	• Being non-absorbent, limited use for highly exuding wounds • Being adhesive, newly formed epithelium could be disrupted during removal • Frequently develop leakage channels	Opsite® Films (Smith & Nephew) Tegaderm™ (3M™, UK Plc.) Mepitel® Film (Mölnlycke Health Care Limited)	45,50 ~~50~~
Hydrocolloid dressings	• Moist wound dressing • Capable of absorbing wound exudate • Usually made of polyurethane film with an adhesive mass • Adhesive mass is often composed of gelatin, pectin and sodium CMC which swells on absorbing exudate • Impermeable to water and gases	• Not indicated for infected or heavy exudating wounds • Being opaque difficult to follow the healing process without prior removal • May produce a distinct odour at wound site	DuoDERM® (ConvaTec Inc,) 3M™ Tegaderm™ hydrocolloid dressing (3M™, UK Plc.) Replicare® (Smith and Nephew)	55,56,57,58 ~~56~~ ~~57~~ ~~58~~
Foam dressings	• Bilaminate (or trilaminate) moist wound dressing with varying thickness • Excellent absorption capacity • Can expand and conform to wound shape • Easy to remove • Can be loaded with antimicrobials and other active agents	• Not suitable for low exudating wounds • Frequent change may be required for heavy exudating wounds • May cause maceration on saturation with exudate	Mepilex® and Mepilex Ag® (Molnlycke Health Care) Allevyn (Smith and Nephew) Aquacel® (ConvaTec Inc.) Cutimed® Siltec B (BSN medical Inc.) Biatain® Silicone Ag (Coloplast Ltd.)	59,60,61 ~~60~~ ~~61~~
Hydrogel dressings	• Insoluble aqueous gels as moist wound dressing • Moisture retention and donation properties • Usually non-adhesive	• Some hydrogels are mechanical weak in swollen state but mechanical properties can be enhanced by	Purilon® Gel (Coloplast Ltd) Derma-Gel (Medline Ind. Inc.) Intrasite® Gel (smith &	3,61,62,63 ~~61~~ ~~62~~ ~~63~~

	so easy to remove • Can be loaded with antimicrobials and several active wound healing agents • Can be smart and stimuli responsive • Can be injected • Can be crosslinked *In situ*	copolymerisation with appropriate polymer(s). • May cause maceration after accumulation of exudate • May require secondary dressing	Nephew)

In addition to the above examples of commercially available dressings, there is a plethora of wound dressing products available on the market today, aiming at promoting wound healing, including Adaptic Touch® (a non-adhesive silicone dressing by Systagenix Wound Management Limited), ALGICELL® and Algosteril® (an alginate dressing by Derma Sciences Inc. and calcium alginate dressing by Smith & Nephew, UK respectively), Altrazeal™ (by ULURU Inc., a white wound filler powder dressing that transforms into a malleable protective dressing on contact with the exudate that fills the wound,), BIOSTEP™ (by Smith & Nephew, UK, a collagen matrix dressing that optimises wound closure by deactivating excess matrix matalloproteinases) and Drawtex® (hydroconductive dressing by Beier Drawtex Healthcare, featuring LevaFiber™ technology works by capillary, hydroconductive and electrostatic action).

In addition to these dressings, hydrogel dressings are one of the most versatile advanced form of moist wound dressings [64] that are commercially available in different forms. AmeriGel® (Amerx Health Care Corp., a hydrogel dressing with moisture sustaining properties), ActiGuard™ (by Dynarex Inc., a hydrogel sheet dressing that is permeable to air and water vapours enhancing wound breathe) and Intrasite® gel (smith&nephew Inc., an amorphous hydrogel dressing that helps in optimising wound environment for re-epithelialisation), are some of the proprietary

hydrogel dressings. The current review would give readers a comprehensive overview of hydrogels as wound dressings. Moreover, the routine scientific approaches of preparing hydrogels for wound management applications, forms of commercially available hydrogel wound products, and the material aspect of hydrogel production with their laboratory characterisation tests are discussed using up-to-date literature.

1.3. Hydrogel Dressings

Hydrogels are composed of water insoluble, cross-linked polymers with a high affinity for aqueous media. These three dimensional polymeric gels have a hydrophilic, porous structure that permits a massive degree of water absorption, several times greater than the original dry weight [3,65,66]. The hydrophilic properties of hydrogels are related to the cross-linking density of polar functional groups such as amide, amino, carboxyl and hydroxyl in the polymer structure [67,68,69,70,71]. Hydrogels offer the unique properties of high water content (up to 99.5%), non-adhesive nature, malleability and a resemblance to living tissues in terms of their biocompatibility [43,63,65,72,73]; all combine to make them an ideal dressing candidate. Moreover, hydrogels display the property of swelling and de-swelling reversibly in aqueous solutions, hence their application in a range of sectors including regenerative medicine, drug delivery and the focus of this review, wound management.

Hydrogels help promote wound healing [74] *via* their moisture exchanging activities that develops an optimum microclimate between the wound bed and the dressing [67, 75]. Due to their high moisture content, these dressings also provide a cooling, soothing effect; reduce the pain associated with dressing changes [76]. In addition,

the limited adhesion of hydrogels means that they can be easily removed from the wound, without causing further trauma to the healing tissue [77]. The transparent nature of some hydrogel dressings also allows clinical assessment of the healing process, without the need to remove the dressing.

Hydrogels can be formulated to behave in a stimuli responsive manner [74] so that when loaded with a drug or active biomolecule they are able to control diffusion and release, thus making them truly interactive dressings [78,79]. Some healing agents are hydrophobic in nature and their delivery in hydrophilic environment (wound dressing hydrogel) can be achieved by using solubility enhancing drug carriers like cyclodextrins (CDs) [80]. CDs, a family of cyclic truncated-cone shaped oligosaccharide offers heterogeneous environment *i.e.* hydrophilic outer surface and hydrophobic inner cavity [80,81]. CDs have wide pharmaceutical applications in view of their biocompatibility and solubility enhancing properties [82]. In addition, the inclusion of drug in the hydrophobic cavity of CDs, leading to the inclusion complex (IC) formation, offers protective and release modulating properties [83,84]. CD containing hydrogels can be produced in different ways; loading the pre-formulated CD-drug IC during or after crosslinking, grafted on the hydrogels [85] or cross-linking with diglycidyl-ethers [84]. The first approach is a simple but it may have a limitation of unmodulated drug release. In contrast, the release can be controlled with the other approaches [84,86,87]. Modern therapies where more than one medication with different hydrophilic/hydrophobic nature may benefit, development of CD-based hydrogel with dual drug delivery of hydrophobic drug (attributed to CDs) and hydrophilic compound (selecting polymers with hydrophilic active substance like chitosan), has opened a new scope [82]. The efficacy of these CD-based hydrogels has demonstrated enhanced therapeutic capacity for wound dressing applications

Comment [GA2]: Gupta et al., 2018 ISBPPB 2018 abstract

Comment [GA3]: Sun et al., 2014

Comment [GA4]: Barragan et al., 2018

Comment [GA5]: Rakmai et al., 2017

Comment [GA6]: Jeong et al., 2018

Comment [GA7]: Lee et al., 2012

Comment [GA8]: Jeong et al., 2018

Comment [GA9]: Jeong et al., 2018

Comment [GA10]: Hoare and Kohane, 2008 not 96 any more

Comment [GA11]: Pinho et al., 2013

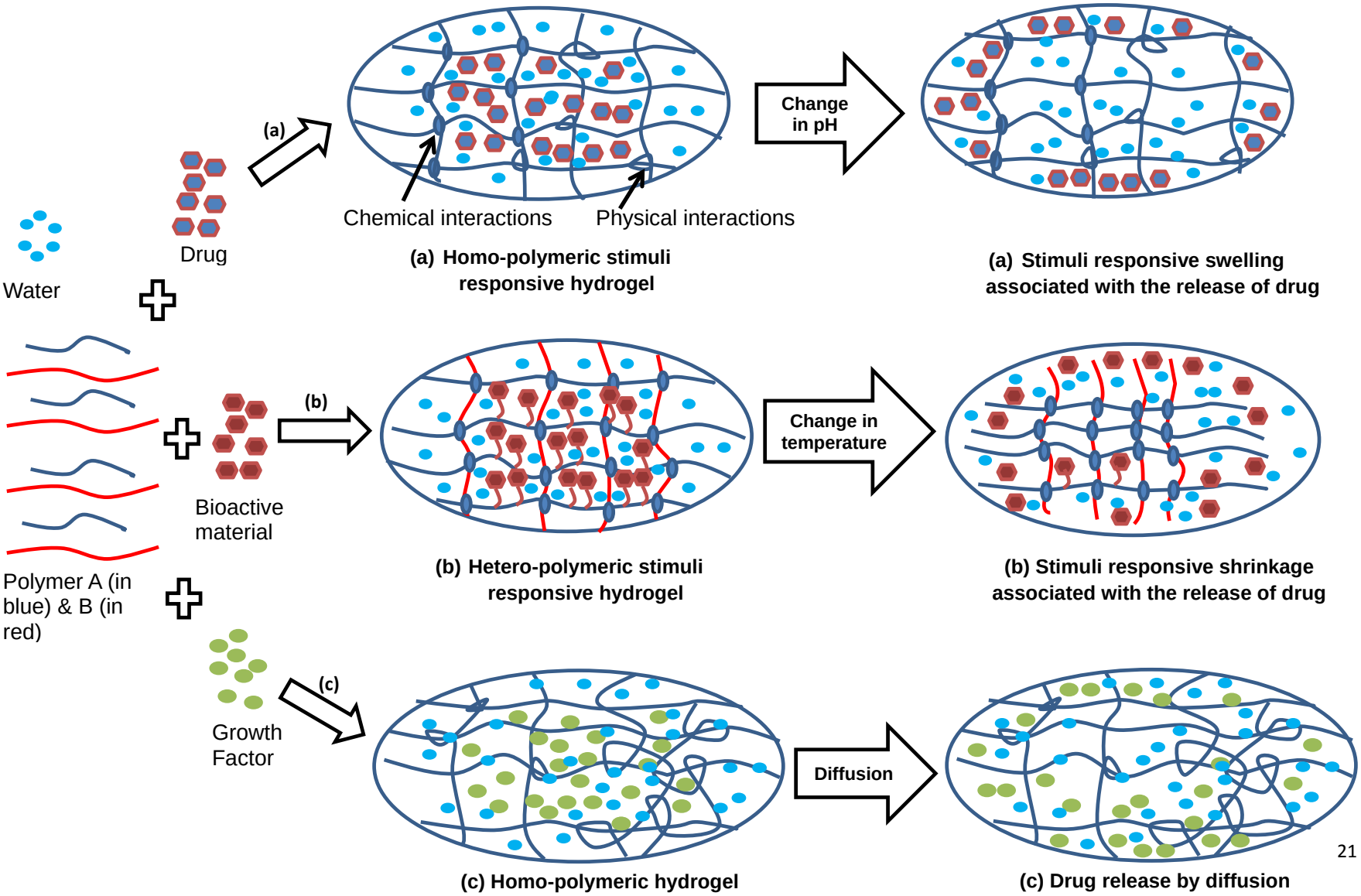
Comment [GA12]: Barragan et al., 2018

[84,85,87]. Moreover, hydrogel have been successfully used as a matrix for the fabrication of dressings for the sustained delivery of essential growth factors (Table 1) and healing agents to facilitate wound healing [28,29,31] (Figure 2). All these properties resulted into several proprietary hydrogel wound dressings used in clinical practice for wound management all over the globe. Due to their unique properties, hydrogel dressings are indicated for use in variety of wounds such as, but not limited to, dry wounds with necrotic tissue, burn wounds, diabetic foot ulcers, pressure ulcers, chronic leg ulcers and low to moderately exudating wounds **[**56,88,89,90**]**. In spite of the various hydrogel dressing products already in the market, there is still an ongoing research in the area with the aim to further improve the hydrogel dressings covering patient comfort, clinical efficacy and multiple aspects of wound healing.

Comment [GA13]: Lee et al., 2012, Pinho et al., 2013, Jeong et al., 2018

Comment [GA14]: 80,81,82

Figure 2. Schematic illustration of (a) Drug loaded homo-polymeric pH responsive hydrogel (b) Hetero-polymeric bioactive material loaded temperature responsive hydrogel (c) Growth factor loaded homo-polymeric hydrogel, with their release trends.


Water
Drug
(a)
Chemical interactions
Physical interactions
(a) Homo-polymeric stimuli responsive hydrogel
Change in pH
(a) Stimuli responsive swelling associated with the release of drug
Polymer A (in blue) & B (in red)
Bioactive material
(b)
(b) Hetero-polymeric stimuli responsive hydrogel
Change in temperature
(b) Stimuli responsive shrinkage associated with the release of drug
Growth Factor
(c)
(c) Homo-polymeric hydrogel
Diffusion
(c) Drug release by diffusion

2. Preparation of Hydrogels

Hydrogels can be prepared from various natural and synthetic polymers, using a range of different compositions as well as physical and chemical cross-linking techniques. The crosslinks in hydrogels can be due to covalent bonds, ionic interactions, chain entanglements, *etc.*, leading to a variety of physical configurations, chemical arrangements and interactions. Interestingly, it is the very nature of the cross-linkage that determines much of the hydrogel's physicochemical properties and hence eventual applications.

2.1. Physically crosslinked hydrogels are formed by the physical linking of polymer chains *via* molecular entanglement, ionic interactions, hydrogen bonding or hydrophobic association [~~83~~91]. Several thermodynamic changes *e.g.* heating or cooling of polymer solutions, freeze-thawing, lowering pH, selection of anionic and cationic polymers can result in physical crosslinking between polymeric chains [69, ~~84,85,86~~92,93,94]. Preparation of these hydrogels involves relatively mild conditions and simple purification procedures as no toxic chemical crosslinking agents are required during their synthesis; offering them exceptional biological nontoxic, biocompatible properties thus making them ideal matrix for the delivery of therapeutic agents at wound site [66,~~87~~95].

2.1.1. *Ionic interactions*:

These hydrogels are formed between ionic polymers crosslinked with multivalent, counter charged species. Polyanionic polymers that are complexed with polycationic polymers form hydrogels by a process of polyelectroyte complexation, which is also referred to as complex coacervation [~~88~~96]. Alginate hydrogel dressings using

divalent calcium cations ($CaCl_2$) are commonly synthesised by this technique [~~89,90~~97,98].

2.1.2. *Crystallisation*:

Hydrogels for wound management applications can also be synthesised by freeze-thawing. During freeze-thawing of an aqueous polymeric solution, water freezes causing phase separation which leads to the formation of microcrystals [~~91,92~~99,100]. Repeated freeze-thaw cycles facilitate reinforcing existing crystals within the structure and offers higher crystallinity and added stability upon swelling [~~87,93~~95,101]. Physically crosslinked biocompatible and elastic hydrogels using PVA/PEG polymers [~~92~~100] and PVA/sodium alginate [~~94~~102], fabricated by consecutive freeze-thaw cycles as a potential wound dressing formulation are examples of this type of gelation.

2.1.3. *Hydrogen bonding between chains*:

This class of hydrogels can be produced by lowering the pH of aqueous polymer solutions, when carboxylic groups are present on the chains. At acidic pH aqueous polymer solubility is reduced which promotes hydrogen bonding and the formation of hydrogels [~~95~~103]. However, these physical networks can easily disperse with the influx of water therefore in addition to these other type of crosslinking can be considered to hold the hydrogel constituents [~~96~~86]. Hydrogels with pH sensitive gelation (around pH 6.5) of chitosan can be produced by these physical interactions [~~97~~104].

2.1.4. *Amphiphilic block copolymers*:

These physical hydrogels are made from two chemically different homopolymer blocks one of which is hydrophobic and the other is hydrophilic. These copolymers self-assemble in aqueous media forming hydrogels due to thermodynamic incompatibility between the blocks [~~98,99~~105,106]. Moreover, drugs like antimicrobials can be incorporated in these copolymers and sustained release can be achieved for wound management applications [~~100,101~~107,108]. Thermoresponsive poly(Ɛ-caprolactone)-poly(ethylene glycol) block copolymer hydrogels with potential wound dressing applications are a good example of this category [~~101,102,103~~108,109,110].

2.1.5. *Protein interactions*:

With the advancement in biotechnology, hydrogel synthesis by engineering of recombinant proteins has become possible. This new development in the field of material chemistry pioneered by Tirrell and Cappello [~~104,105~~111,112] allows to control the structural and functional design of protein block thus preparing the physically crosslinked hydrogels with desirable biological, physical and mechanical properties. These biopolymeric protein based hydrogels primarily assemble by protein-protein interactions or aggregation of polypeptides by phase (temperature) transitions [~~106~~113]. It can be foreseen that these hydrogels hold a strong potential in wound management. Fabrication of protein engineered bioactive collagen-mimetic protein ($eCol_{GFPGER}$) with PEG based matrix hydrogel dressings with a potential of wound healing in humans is an innovative approach in the field of wound management [~~107~~114].

2.2. Chemical crosslinked hydrogels are formed by covalent linkages resulting in high mechanical strength networks. These can be synthesised by chain growth

polymerisation, addition and condensation polymerisation and high energy irradiations (gamma ray or electron beam).

2.2.1. Crosslinking by chain growth polymerisation:

It includes three stages: initiation, propagation and termination. Generation of free radical site by suitable reaction initiator initiates the polymerisation process followed by chain elongation by the addition of low molecular weight monomeric building blocks. The elongated polymer chains are randomly crosslinked by the cross-linking agent leading to the hydrogel formation [~~108~~115]. Hydrogel of 2-acrylamido-2-methylpropane sulfonic acid sodium salt (AMPS-Na^+) using potassium persulfate as a free radical initiator and ethylene glycol dimethacrylate as a crosslinking agent can be synthesised by redox initiation via free radical polymerisation for wound dressing applications [~~109~~116]. Chemically crosslinked hydrogel of AMPS with AMPS-Na^+ prepared by using 4,4-azo-bis(4-cyanopentanoic acid) as photo-initiator and N,N'-methylene-bisacrylamide as a cross-linking agent demonstrated optimum water absorption and retention properties for wound management applications. Moreover, their flexible and transparent nature with good skin adhesion properties advocates their potential biomedical applications [~~110~~117].

2.2.2. Crosslinking by chemical reactions of complementary groups:

Hydrophilic polymers have functional groups like COOH, OH and NH_2 which can be utilised for the hydrogel formation. These pendant functional groups with complementary reactivity (amine-carboxylic acid or isocyanate-OH/NH_2 reaction or Schiff base formation) can establish covalent linkages between polymer chains leading to the hydrogel formation using crosslinking agents [~~111,112,113~~118,119,120]. Antibacterial alginate-chitosan hydrogel wound dressings

can be synthesised by the Schiff based reaction between aldehyde group of oxidized alginate and amino group of carboxymethyl chitosan [~~111~~118]. Injectable *in situ* chitosan-hyaluronic acid hydrogels [~~114~~121] for wound applications are another example with gelation attributing to Schiff base between amino group of carboxymethyl chitosan and aldehyde group of aldehydic hyaluronic acid. Being injectable, these hydrogel dressings hold an added advantage of easy and comfortable application with high conformability without wrinkles which could lead to improved patient compliance.

2.2.3. Crosslinking by using high energy radiations:

Cross-linking by radiations is widely used to polymerise unsaturated compounds for hydrogel synthesis since it is devoid of the use of toxic chemical crosslinking agents and is a cost effective technique as separate sterilisation of hydrogel formulation can be avoided. On exposure to high energy radiations, radicals are formed on polymer chains in an aqueous solution which initiates free radical polymerisation. Recombination of these radicals on different polymer chains lead to the formation of covalent crosslinked hydrogels [66,~~88~~96]. Silver nanoparticles loaded AMPS-Na^+ hydrogels [~~115~~122], PVA/gum acacia [~~116~~123] and nanosilver/gelatin/carboxymethyl chitosan hydrogels synthesised by gamma (cobalt-60) irradiation technique are examples of potential antimicrobial hydrogel wound dressings [~~117~~124].

Comment [GA15]: Hennink and Nostrum 2012

2.2.4. Crosslinking by thiol-ene click reaction:

The reaction of thiols (nucleophile) to electron-rich alkenes leading to the production of thioether polymer networks is a weapon of choice for hydrogel preparation owing

to their biological inertness, rapid reaction rate and controlled release properties. Dictated by the functional groups and reaction conditions, the reaction mechanism could be thiol-Michael click reaction or radical-mediated thiol-ene reaction [125]. Synthesis of gelatin/poly(ethylene glycol) hydrogels for the delivery of immunomodulatory molecules like cytokines and growth factors through mesenchymal stem cells (MSC) carriers [126], epidermal growth factors loaded heparin-based hydrogels [127], and poly(urethane-acrylate) based antimicrobial hydrogel wound dressings [128] for wound management applications are good examples of thiol-ene reactions.

Comment [GA16]: Kharkar et al., 2016

Comment [GA17]: Xu et al., 2013

Comment [GA18]: Goh et al., 2016

Comment [GA19]: Gharibi et al., 2017

3. Hydrogel dressing products:

There are many different types of wounds with multitude of different symptoms, including necrotic, sloughy, granulating and epithelialising that vary in size, shape and thickness. Understanding the purpose and principle of dressing formulations for these differing applications helps to match the correct dressing and wound combination.

Hydrogel dressings are indicated for the treatment of a variety of wound types, with precise selection of formulation ultimately based on clinical application:

3.1. Amorphous hydrogels:

Lacking a fixed shape, these hydrogels can be evenly applied over the wound using an applicator and being amorphous, these would mould into the shape of wound defect easily. These are specifically indicated in the treatment of uneven or cavity wounds that cannot be easily covered with fixed, definite shape dressings. Examples of commercially available products include: 1) Aquasite®, an amorphous, glycerine-

based hydrogel dressing [Derma Sciences Inc.], and 2) Intrasite® gel, a partially hydrated, amorphous propylene glycol hydrogel [Smith & Nephew, UK].

3.2. Impregnated hydrogel gauze dressings:

Used for partial or full thickness wounds where sterile packing of the wound bed is required, these formulations combine the advantages of hydrogels with non-woven dressings. Impregnated gauze dressings are saturated and/or permeated with an amorphous hydrogel and are commercially available as gauze pads, non-woven sponges and strips of different sizes. Commercially available products under this category are: 1) Aquasite® impregnated gauze dressing, a 100% cotton gauze pads incorporated with a hydrogel [Derma Sciences Inc.], and 2) Intrasite® conformable, hydrogel impregnated gauze dressings [Smith & Nephew, UK]. These dressings are available in various sizes and are indicated for use in necrotic, sloughy and granulating full thickness wounds.

3.3. Sheet hydrogel dressings:

Consisting purely of hydrogel, these dressings can be cut into the required size and shape to fit the wound. Hydrogel sheet dressings are indicated for the treatment of deep cavity and partial thickness wounds (*e.g.* ulcers, including venous and arterial, pressure sores, skin donor sites, surgical incisions, 1st and 2nd degree burns). Aquasite® hydrogel sheet dressing, glycerine based hydrogel formulations [Derma Science Inc.] and Flexigel® sheet, polyacrylamide based hydrogel sheet dressings [Smith & Nephew, UK] are commercially products available in different sizes (e.g. 2”x2” and 4”x4”) and can be easily cut to fit wound. These act as advanced wound dressing by keeping the wound bed moist thus offering soothing effect and facilitate wound healing as well as providing physical barrier between wound and external

environment. Moreover, being transparent, these sheet dressings allow easy monitoring of healing process.

4. Polymers suitable for hydrogel wound dressings:

Some polymers due to their physicochemical and biocompatible properties are extensively used in biomedical applications. Most commonly used polymers used for fabricating hydrogel for wound dressing applications are discussed below. Moreover, other commonly used polymers with wound dressing applications are listed in Table 3.

4.1. Poly(vinyl alcohol) (PVA)

PVA being biocompatible, transparent and capable of maintaining moist environment has attracted application in wound care [~~118,119~~129,130]. PVA chains can be crosslinked to produce PVA hydrogels by variety of techniques including freeze-thawing cycle, electron beam irradiation and using cross linkers like glutaraldehyde [53]. Hwang *et al*., (2010) [~~120~~131] employed a freeze-thaw technique to produce a gentamicin-loaded PVA-dextran hydrogel dressing. The authors suggested that the presence of dextran in the hydrogels enhanced the elasticity, swelling ability and water vapour transmission rate (WVTR) of hydrogel. Moreover, dextran favours the crystallisation of PVA, thus producing a more uniform, homogenous gel structure. *In vitro* test results confirmed the hydrogel formulated with 2.5% PVA, 1.13% dextran and 0.1% gentamicin was haemocompatible thus suitable for wound management applications. Moreover, *in vivo* (rat model) tests revealed enhanced healing with greater wound size reduction of a full thickness surgical excision wound of the dorsum with gentamicin-loaded-PVA-dextran hydrogels compared to the foam dressing (Medifoam^{TM}) and gauge dressing. The re-epithelialisation rate of

gentamicin loaded resulting hydrogel was significantly higher (98±2%) than conventional foam dressing (74±14%) which supporting its potential wound dressing application.

Sodium ampicillin containing PVA-Sodium Alginate (PVA-SA) hydrogel membranes for wound dressing applications were synthesised by Kamoun *et al*., (2015) [~~94~~102]. The authors achieved physical crosslinking (entanglement) between PVA and different content of SA by repeated freezing-thawing cycles. *In vitro* protein adsorption test was performed to determine the ability of the hydrogels with regards to cleansing the secreting lesions and the results suggested an increase in bovine serum albumin (BSA) adsorption from 0.7-1.8mg/cm^2 with an increase in SA content from 0-75% (w/w). These membranes demonstrated high haemocompatibility and broad antibacterial activity suggesting their potential application as an active biodegradable hydrogel dressing in wound care. In another study, PVA based hydrogel dressing was developed *in situ* by co-enzymatic reaction using glucose present in wound exudate to trigger crosslinking. Glucose oxidase (GOx) and horseradish peroxidase (HRP) were used to catalyse the hydrogelation process. GOx oxidised glucose to H_2O_2 which in the presence of HRP was taken by phenolic hydroxyls of the PVA derivative (PVA-Ph) leading to the hydrogel formation. The authors presented *in vivo* findings suggesting significantly faster cure of full-thickness wounds (rat model) with 77% and 96% wound closure at 7 and 10 days of treatment, respectively compared to only 27% at day 7 and 70% at day 10, with commercially available hydrogel dressing [~~121~~132].

Comment [GA20]: Kamoun *et al*., (2015)

4.2. Poly(N-vinyl-2-pyrrolidone) (PVP):

PVP, a well-known synthetic polymer due to its biocompatible nature has attracted several biomedical applications including wound management. Nu-Gel® (Systagenix) and Neoheal® (Kikgel) are PVP based proprietary hydrogel products indicated for use in first and second degree burns, severe sun burns, partial thickness wounds, ulcerations and bedsore. PVP undergoes crosslinking under ionising radiation, resulting in transparent hydrogels but these hydrogels have poor mechanical properties with limited swelling. It's swelling behaviour and mechanical properties can be enhanced by blending it with other polymers such as polysaccharides [~~122,123,124,125,126~~133,134,135,136,137]. The use of ionizing radiations is considered to be a favourable tool, wherever feasible, for hydrogel formation (and sterilisation) due to easy process control, minimal wastage, low cost and no chemical crosslinkers requirement [~~123,127~~134,138].

Fechine *et al*., 2004 [~~128~~139] reported an approach to synthesis PVP hydrogel using safer, portable and less expensive UV radiation (**λ**max 254nm) technique. They produced hydroxyl radicals from the photolysis of H_2O_2 and these radicals were reacted with PVP giving rise to macroradical polymer chains which underwent recombination leading to the hydrogel formation. The hydrogel produced demonstrated *in vivo* cytocompatibility with satisfactory low inflammation index in rabbit model (72hr direct contact with rabbit skin) hence classified as non-irritating material for wound management purposes.

Jovanovic *et al*., (2011) [~~129~~140] reported an approach to synthesise antimicrobial PVP hydrogels using gamma radiation to achieve gelation. Antimicrobial properties in these hydrogels are attributed to silver nanoparticles produced *in situ* in PVP hydrogel matrix by reduction of silver nitrate with radiolytic products of water up on gamma irradiation. These nanocomposite hydrogels exhibited high elasticity, good

mechanical properties and good swelling capacity and may be tailored for potential wound dressing applications.

Another attempt of fabricating antimicrobial silver nanoparticles (AgNP) loaded PVP based blend hydrogel using gamma radiations was made by Khampieng *et al*., 2018 [~~130~~141] for wound management of chronic wounds. The blend of PVP with alginate and chitosan in the ratio of 10:1.2:1.8 respectively enhanced the swelling and mechanical properties making these hydrogels suitable for dressing applications. When compared to three commercially available dressings (Acticoat™, Algivon® and Suprasorb® A + Ag), these hydrogels (10mM AgNP concentration) showed superior cytocompatibility with higher cell viability against mouse (112.64±4.66%) fibroblasts (L929), human dermal fibroblast (89.47±1.11%) and human keratinocytes (HaCaT) cells (105.35±4.52%). Moreover, the maximum swelling behaviour (2267±109%) of these resulting hydrogels was superior to Acticoat™ (362±66%). These findings suggested their greater capability of absorbing wound exudate thus making them a potential candidate for chronic wounds including pressure ulcers.

4.3. Poly(ethylene glycol) (PEG):

PEG is a polyether which attracted a wide interest in the biomedical applications including wound management due to its transparent, non-toxic, non-immunogenic, biocompatible and biodegradable properties [~~131, 132~~142,143]. PEG fumarate [~~133~~144] and PEG acrylates like PEG diacrylate (PEGDA) [~~134,135~~145,146], PEG dimethyacrylate (PEGDMA) [~~136~~147] and PEG methyl ether methacrylate (PEGMEMA) are some of the commonly used acrylates in hydrogel formation for biomedical applications. Due to its featured biological properties, PEG has been

used in proprietary products like Aquaflo™ (Covidien), Neoheal® (Kikgel) and AmeriGel® (Amerx Health Care Corp.) hydrogel wound dressings.

Since chronic wounds are associated with alkaline pH, with an aim to restore the elevated pH to the physiological pH (7.4), in order to facilitate healing, Koehler *et al*., 2017 [~~131~~142] fabricated a pH-modulating acidic PEGDA/Alginate hydrogel dressings containing acrylic acid (AA). In addition to controlling the alkaline pH neutralisation, AA enhanced the swelling capacity of the hydrogels. PEGDA/AA/alginate hydrogels with 0.25%AA demonstrated superior mechanical strength, biocompatibility and enhanced cell migration velocity (19.8 ± 1.9µm h^{-1}) in a 2D cell migration assay leading to a complete wound closure. Also, the ingrowth of keratinocytes increased by 164% (3D Human skin constructs and Healing assay) compared to untreated control. Chen *et al*., 2013 [48] prepared a PEG/chitosan hydrogel dressing by using PEG diacid (PEG with carboxylic acid groups at both ends) crosslinked to chitosan by way of ester and amide linkages. Authors reported that PEG/chitosan with the mole ratio of carboxylic acid from PEG diacid (PEG molecular weight 1000Da) to amine group from chitosan of 90/10 offered good mechanical properties and appropriate degradation rate. Also, *in vivo* wound treatment studies (mice model) revealed the capability of these hydrogels to suppress inflammation, with fewer inflammatory cells, enhance re-epithelialisation and increased angiogenesis thus supporting their potential use as a biomaterial for wound dressings.

Comment [GA21]: Koehler *et al*., 2017

In another study, Dong *et al*., 2014 [~~137~~148] formulated a wound dressing hydrogel using PEG-based multifunctional hyperbranched copolymer crosslinked with thiolated hyaluronic acid (HA-SH) with adipose-derived stem cells (ADSC). These polymers stay as a solution at room temperature while they undergo in situ

crosslinking (thiol-vinyl Michael addition between vinyl groups on copolymer and thiol on HA-SH) at body temperature, forming a stable, non-adhesive and bioactive hydrogel (within 8 minutes) at the wound site. Being injectable, these can be easily and effectively applied to any wound shape and size. Although *in vivo* studies (rat model) revealed that these hydrogels resisted wound contraction to some extent but there was a strong evidence of their angiogenesis enhancing ability.

4.4. Poly(2-hydroxyethyl methacrylate) (PHEMA):

PHEMA was the first hydrogel used in the production of soft contact lenses due to its inert nature, biocompatibility, excellent mechanical strength and high water imbibing properties [~~138~~149]. In addition to its biomedical application as a contact lens material, due to its exceptional physicochemical properties and accepted *in vivo* tolerance, it has attracted its use in wound management as a hydrogel dressing material [~~139~~150].

Halpenny *et al*., 2009 [~~140~~151] reported the use of PHEMA in the fabrication of the bactericidal light sensitive hydrogel wound dressing. With inherent would healing properties and to avoid potential emergence of antibiotic resistance, nitric oxide (NO) was selected as an antimicrobial agent. In order to deliver NO to a desirable site with controlled release, authors developed photoactive NO donors (nitrosyls) which were incorporated into polyurethane that was covalently incorporated into pHEMA hydrogel. In order to enhance the antimicrobial activity of these hydrogels, H_2O_2 or methylene blue were used as auxiliary growth attenuators. When these hydrogels were tested against *P. aeruginosa and E. coli,* significant antimicrobial activity was recorded. Authors proposed that this approach was superior to washing the wound site with 3% H_2O_2 solution. This study demonstrates the futuristic approach of

fabricating hydrogels with an added advantage of controlled release of antimicrobial by illuminating (stimuli) the dressing (exposure to light) from time to time to maintain antiseptic conditions at the wound site.

Singh and Dhiman, 2015 [75] produced antibiotic (moxifloxacin) containing PHEMA-based copolymeric hydrogel dressings using carbopol and gum acacia by free radical polymerisation method, with potential wound dressing applications. The permeability test results showed that these are permeable to oxygen and impermeabile to microbes present in open environment. Moreover, their high fluid uptake (7.22±0.26g per gram of gel) and retaining property makes these hydrogel dressings suitable for application in moderate to high exudative wound with potentially 3-5ml exudate per $10cm^2$ per day. These hydrogels have been proposed to be haemocompatible (0.95% haemolytic effect) thus validating their wound management applications. Their low albumin absorption (0.19±0.02mg cm^{-2}) which could be attributed to highly hydrophilic nature of gum acacia, also favours its wound dressing application. Formulations with antioxidant activity may help to reduce oxidative stress at the chronic wound site thus promote healing. The results from the antioxidant activity [Folin–Ciocalteu (F–C) reagent assay] and superoxide radicals scavenging ability (64.21±2.70%) were found promising. *In vivo* test (mouse model) results revealed that unlike gauge dressings, the resulting hydrogels could be removed easily removed from wound site without causing trauma. Moreover, wounds treated with these hydrogels revealed enhanced healing with well organised fibroblasts and angiogenesis compared to open untreated wounds. All these properties advocate their wound management applications as wound dressings.

Controlling the microbial bioburden is a major challenge in chronic wound healing and the introduction of antimicrobial agents in the polymeric materials with potential

biomedical applications is a common practice to tackle this challenge. Amongst different antimicrobial agents, silver is widely used due to its strong antimicrobial activity [3]. Several methods have been reported in literature to produce silver nanoparticles [~~141,142,143,144~~152,153,154,155]. Siddiqui *et al*., 2016 [~~145~~156] made a successful attempt to produce antimicrobial nanocomposite PHEMA hydrogels with silver nanoparticle (AgNPs) using *in situ* radical polymerisation. These hydrogels exhibited good thermomechanical properties with potential wound management applications. In another study, with the aim of controlling bacterial bioburden at the wound site whilst maintaining the moist environment, Di *et al*., 2017 [~~146~~157] synthesised transparent antimicrobial PHEMA based hydrogels coated with AgNPs reduced by sodium hydrogen borate. Authors added bacterial cellulose to PHEMA to improve its flexibility and hydrophilic properties. These hydrogels were tested against two opportunistic microbial strains, *Escherichia coli* (*E. coli) and Staphylococcus aureus (S. aureus).* Disc diffusion results revealed antimicrobial activity with clear zone of inhibitions (ZOI) measuring 0.25±0.15cm and 0.50 ±0.15cm respectively for the tested strains. Moreover, these finding were confirmed with colony forming unit (CFU) method with 99% and 90% reduction in CFU count against the respective tested strains, after 24h. Furthermore, these hydrogels exhibited rapid water absorption which would minimise the detrimental effect of exudate on wound site. Being transparent, these hydrogels would allow monitoring of the healing process without the need of removing the dressing. All these properties, along with low toxicity results advocate its potential application in wound management.

4.5. Poly(n-isopropylacrylamide) (PNIPAM):

PNIPAM is a smart polymer with amide and propyl moieties in its monomeric structure responsible for its temperature dependent volume phase transition (VPT at 34ºC). Its lower critical solution temperature (LCST) is slightly lower (32ºC) than VPT temperature. Being nontoxic, biocompatible and with phase transition close to the human body, it has attracted wide biomedical applications [~~147,148,149~~158,159,160].

Jiang *et al*., 2012 [~~150~~161] synthesised thermoresponsive antimicrobial PNIPAM wound dressing hydrogels crosslinked using PEGDA by free radical polymerisation using ammonium persulfate (APS) and N,N,N',N'-tetramethylethylenediamine (TEMED) as initiators. Cell interaction properties of PNIPAM were enhanced by using acryoyl-lysine (A-Lys), which is known to improve cell adhesion and proliferation. Polyhexamethylene biguanide (PHMB) with low cellular toxicity and broad spectrum activity was used as an antimicrobial agent. *In vivo* wound healing studies (rat model) in normal and infected (with *Pseudomonas aeruginosa)* wounds demonstrated enhanced healing with accelerated wound closure on day 4, with 21.66±7.94% wound size reduction in PHMB–loaded hydrogels compared to untreated control (5.92±4.11%). Furthermore, decrease in surface bacterial concentration with PHMB-loaded-PNIPAM hydrogels was also observed as compared to untreated control group.

The bone marrow mesenchymal stem cells (BMSCs) are known to secrete growth factors like TGF-β and FGF and accelerate wound healing in healthy skin however due to increased protease secretion by high levels of cytokines in inflammatory environment of chronic wounds, their activity can be compromised. In order to fully harvest the benefit of delivered BMSCs at the wound site, chronic inflammation

needs to be controlled which would ultimately lead to protease inhibiting activity [~~151,152~~162,163]. Chen *et al*., 2015 [~~151~~162] designed thermosensitive biocompatible PNIPAM hydrogel dressings using poly(amidoamine) as a biodegradable cross-linker, to deliver the encapsulated BMSCs to the diabetic ulcers. *In vivo* (diabetic mice model) immuno-histochemical studies using CD86 to mark M1 macrophages and CD163 for M2 macrophages on day 5 and 7, revealed that the hydrogel treatment inhibited chronic inflammation at the wound site as compared to untreated control group. Moreover, the hydrogel enhanced the secretion of growth factors (TGF-β and FGF) by BMSCs resulting in the formation of granulation tissue, angiogenesis, ECM secretion and re-epithelialisation, leading to healing of wounds in diabetic mice model. These finding provide guidance and evidence of efficiency of these hydrogels in treating diabetic ulcers.

4.6. Alginate:

Alginate, a natural polysaccharide derived from marine brown algae and some soil bacteria has attracted wide biomedical application including wound management due to its hydrophilic, biocompatible and non-toxic nature [~~89,153,154,155,156~~97,164,165,166,167]. Its exceptional wound healing properties resulted in its use for fabricating commercially available hydrogel dressings like Purilon® Gel (Coloplast Ltd.) and Nu-Gel™ Hydrogel with Alginate (Systagenix Wound Management Ltd.). Alginate has an ability to form hydrogels by addition of divalent cations like Ca^{2+} which binds to guluronate blocks of alginate chains enabling ionic cross-linking between guluronate block of adjacent alginate chains in the so called egg-box cross-linking model leading to gel formation [~~157,158,159~~168,169,170]. In case of loss of the divalent cationic cross-linker, the alginate dressing can easily degrade but this issue is commonly overcome by cross-

Comment [GA22]: Rezvanian et al., 2016

linking (ionic or covalent) alginate with other polymers like PVA, gelatine, chitosan *etc*. [43]. Balakrishnan *et al*., 2005 [~~160~~171] made an attempt to synthesise a hydrogel wound dressings (in situ) by periodate oxidation of sodium alginate (SA) resulting in alginate dialdehyde (ADA) and subsequently reacting it with gelatine (G) using borax. Ɛ-amino groups of lysine or hydroxylysine groups of gelatine complexed with available aldehyde, facilitated by borax, resulting in a crosslinked hydrogel. In addition to accelerating this Schiff's base formation, borax acted as an antiseptic. This hydrogel formulation demonstrated optimum WVTR (2686 ± 124 g/m^2/day) and water absorptivity. Moreover, the rate of re-epithelialization, *in vivo* (rat model), was significantly enhanced (90.38±9%) in wound treated with hydrogel dressings compared to gauge dressings (81.65±9%). Furthermore, wound size was significantly reduction in wounds treated with these dressings (95.3±5%) compared to gauge dressings (75.5±5%), suggesting their potential application in wound management.

Comment [GA23]: Balakrishnan *et al*., 2005

In another study, Saarai *et al*., 2012 [~~161~~172] selected SA and G polymers with the same objective of obtaining a moist, elastic and biocompatible hydrogel wound dressing. They used various SA and G concentrations to underpin the correct blend ratio of SA and G to produce hydrogel with optimum physicochemical properties for wound management applications. Based on the results findings, the authors proposed SA/G 50/50 ratio to be optimum producing a hydrogel with desirable viscoelastic and absorption properties for wound management application.

4.7. Chitosan:

Chitosan is a linear natural polysaccharide derived by alkaline N-deacetylation of chitin, obtained from exoskeleton of crustacean like crab, lobster and shrimp [~~162,~~

~~163, 164~~173,174,175]. Due to its biocompatibility, haemocompatibility, biodegradable nature and featured haemostatic, antimicrobial (bacteriostatic and fungistatic) and wound healing properties [48,~~165,166,167~~176,177,178], it is considered fit as wound dressing material. Chitosan can be used to produce membrane, sponge, scaffold and it also has hydrogel forming ability. However, a hydrogel formulation would be the most suitable form as it is able to protect, interact, contract the wound and facilitate wound healing by developing optimum moist healing environment [~~168~~179]. Chitosan can get deformed easily through external stress but this challenge can be overcome by blending it with suitable polymers to enhance its mechanical properties for fabricating wound dressing [48].

Ribeiro *et al*., 2009 [~~167~~178] developed an antimicrobial chitosan hydrogel dressing using lactic acid to induce stoichiometric protonation of the $–NH_2$ sites of chitosan followed by exposure to ammonia fumes (later removed). The hydrogel formation mainly involved hydrogen bonding and physical entanglement of polymer chains. The hydrogel produced was claimed to be porous, favouring gaseous (O_2 and CO_2) exchange and preventing build-up of exudate. *In vitro* and *in vivo* experiments confirmed the cytocompatibility and histocompatibility (local and systemic) of the biomaterial. MTT assay results using fibroblasts cells from rat skin seeded with the resulting hydrogel for 24h confirmed cytocompatible nature of this biomaterial. The application of these hydrogels in dermal burn wounds was evaluated by inducing full-thickness transcutaneous dermal wounds in rats. *In vivo* histological studies further confimed the biocompatibility of these hydrogels as no inflammation or specific pathological abnormalities were observed during the test period. Macroscopic analysis results of wounds treated with these hydrogels revealed considerably smaller wound bed compared to control (PBS treated). Clinical application potential

of these hydrogels for wound management needs to be further evaluated by undertaking advanced studies.

In another study, Wang *et al*., 2012 [~~168~~179] reported the development of chitosan, honey and gelatine hydrogel sheets for burn wounds. The authors produced sheets by varying content of chitosan (not more than 0.5 wt%) and honey (not more than 20 wt%) but keeping the amount of gelatin constant (20 wt%) and studied the physicochemical and functional characterisation of these hydrogel sheets on burn wounds. Chitosan and honey showed a positive synergistic effect as antibacterials in these dressings. Hydrogel formulation with chitosan (0.5 wt%), honey (20 wt%) and gelatin (20 wt%) was reported to be the optimal dressing due to its soft moist nature and excellent *in vitro* antimicrobial activity (100% inhibition rate) against *E. coli* and *S. aureus*. Biocompatibility of the resulting hydrogels was established by *in vivo,* acute oral toxicity study (mouse model) and dermal irritation test (rabbit model) with no noticeable toxic symptoms or skin irritation during set time points of upto 48h. Wound healing study (rabbit model) revealed that throughout the study at each set time point (on day 4, 8 and 12) hydrogel formulations demonstrated higher wound contraction compared to commercially available MEBO® ointment and untreated control. The complete recovery of the burn wound was achieved in around 12 days with hydrogel dressings compared to 14 days with MEBO® treated group and 17days in the control group concluding a faster healing with the hydrogels.

Comment [GA24]: Wang *et al*., 2012

4.8. Starch:

Starch is one of the most abundant natural polysaccharide composed of two different polymers, namely amylose and amylopectin. Being economical, non-toxic, biocompatible and biodegradable, native starch has a potential as a wound

management material but its highly hydrophilic nature and relatively poor mechanical properties have limited its application. These problems can be overcome by either combining it with other polymer to make blend hydrogels [~~169~~180] or by chemically modifying native starch to improve its properties for biomedical applications. Oxidised starch [~~170,171~~181,182] and hydroxyethyl starch (HES) [85] are the common forms of modified starch used in the preparation of wound dressing. Bursali *et al*., 2011 [~~172~~183] prepared antimicrobial hydrogel films using potato starch-PVA complexed with boron using glutaraldehyde as a cross-linker. These hydrogels exhibited moderate antimicrobial activity (*in vitro*) against the tested bacterial and fungal strains, *E. coli (14mm ZOI)*, *S. aureus (13mm ZOI)*, *Pseudomonas aeruginosa* (*P. aeruginosa*) (12mm ZOI) and *Candida albicans* (*C. albicans*) *(14mm ZOI)* thus their potential wound management application could be further evaluated.

Kenawy *et al*., 2014 [~~85~~93] synthesised biodegradable hydrogel membranes for wound dressing purposes using HES, PVA and ampicillin. Physical crosslinking between HES and PVA was achieved by consecutive (three) freeze-thaw cycles. Use of HES in these hydrogels enhanced the swelling ability, capability of protein (BSA) adsorption and thermal stability of the formulation. The release (*in vitro*) of ampicillin in phosphate buffer at 37ºC (pH 7.5) from the hydrogel formulation increased with an increase in HES content (0-75%). These hydrogel membranes exhibited improved physicochemical, mechanical, thermal, degradation and drug release properties, attributed to the addition of HES to PVA and have a potential in wound management applications.

Comment [GA25]: Kenawy *et al*., 2014

Timmons *et al*., 2008 [~~173~~184], reported the effect of Aquaform® hydrogel dressing, (a modified starch copolymer with glycerol by Aspen Medical Europe Ltd) on the patient who developed moderate excoriation of the peri-anal area and multiple

superficial breaks around the anal and vulval region due to the faecal management system to deal with faecal incontinence. They found that Aquaform hydrogel therapy reduced pain and inflammation and prevented cutaneous infection resulting in complete healing of all the wounds. Askina® Gel (B.Braun Medical Ltd.); Flexigran (A1 Pharmaceuticals) and Iodosorb®, a Cadexomer iodine wound dressing (smith&nephew) are other commonly used starch based proprietary hydrogel dressings.

4.9. Bacterial Cellulose (BC):

BC, a biosynthetic cellulose is produced by several bacteria (Rhizobium, Agrobacterium, Alcaligenes *etc.*) but *Gluconacetobacter xylinus*, a Gram negative rod shaped obligate aerobe, is the best known source for BC production [~~174,~~ ~~175~~185,186]. BC being hydrophilic, highly pure, biocompatible, nonpyrogenic [187, ~~176, 177, 178~~188,189,190] and transparent material has resulted in its use for fabrication of proprietary (XCell®, Bioprocess®, Dermafill™, Gengiflex® and Biofill®) wound dressings with the clinical rationale being to facilitate autolytic debridement. Portal *et al*., (2009) [~~179~~191] published their findings of a sequential paired comparison of the rate of healing (75% reduction in wound size set as a primary outcome) during treatment of chronic non-healing lower extremity ulcers with standard dressings (gauze, foams and alginates) and commercially available BC dressing, Dermafill™. Wounds were initially treated with standard dressings and only the ones that failed to heal following 60 days or more were selected to be treated with BC dressing. The authors reported a significant improvement in chronic wounds,

Comment [GA26]: Gupta et al., 2017

achieving the primary outcome, with the use of Dermafill^{TM} dressings, in a shorter period of time confirming that BC hydrogel dressings enhances wound healing.

Being interwoven nanofibrillar network structure, BC allows encapsulation of small molecules and this property has attracted vast research interest of loading different molecules in BC to tailor the properties of BC wound dressing [~~180,181,182,183~~192,193.194,195]. Gupta *et al*., (2016) [3] reported the synthesis of broad spectrum antibacterial BC hydrogel. Whilst not antimicrobial itself, BC was loaded with two forms of silver (Ag): silver nitrate ($AgNO_3$) and silver zeolites (AgZ). The authors reported prolonged *in vitro* antibacterial activity (*S. aureus* and *P. aeruginosa*) with BC-AgZ formulation attributed to the double control system: first layer of control of Ag^+ release from zeolite cage structure and a second layer of controlled release by the BC hydrogel itself. Contrary to this, BC-$AgNO_3$ formulation, release of Ag^+ was only controlled by the BC matrix, hence less prolonged. Moreover, authors reported that the controlled release properties of the BC-AgZ hydrogel formulation minimises the toxicity associated with high topical Ag content.

4.10. Carboxymethyl cellulose (CMC):

CMC is a semi-synthetic, water-soluble ether derivative of cellulose in which H atoms from the hydroxyl groups are replaced with carboxymethyl [~~184~~196]. CMC can be crosslinked to make biocompatible and biodegradable hydrogel with high water uptake capacity [65,~~185~~197]. Its unique properties resulted in its use in proprietary hydrogel dressing products like FlexiGel^{TM} and Regranex$^{®}$ gel (Smith & Nephew, UK) and Purilon Gel$^{®}$, a sodium carboxymethyl cellulose (NaCMC) based hydrogel dressing (Coloplast).

Namazi *et al*., (2016) [~~186~~198] fabricated a novel antibiotic loaded NaCMC/mesoporous silica nanoparticles [Mobile Composition of Matter No. 41 (MCM-41)] nanocomposite hydrogel with controlled release properties using citric acid as a crosslinker and glycerol as a plasticizer. Tetracycline was used as a broad spectrum antibiotic and methylene blue (cationic dye) were tested as antibacterial agents. The results suggested that MCM-41 in the NaCMC hydrogel enhanced the swelling properties and permeability of the formulation. With an increase of MCM-41 from 0-15%, the swelling ration doubled; water vapour and oxygen permeability increased dramatically. In another study, Rakhshaei and Namazi, (2017) [~~185~~197] synthesised a tetracycline-eluting nanocomposite bioactive hydrogel dressing using NaCMC/MCM-41 impregnated with zinc oxide (ZnO) as an antibacterial agent. Their findings suggest ZnO impregnation in MCM-41 enhanced the tetracycline (TC) loading due to the positive charge of ZnO nanoparticles attracting TC molecules (negative charge above pH 7.4) to the MCM-41 surface. Also, the release of TC improved from burst release in pure NaCMC films within the first 3 hours to sustained release with CMC/ZnO-MCM-41 nanocomposite hydrogel. The final formulation exhibited strong antimicrobial activity (in vitro) against *E. coli* and *S. aureus* due to combined antimicrobial activity of ZnO (antibacterial) and prolonged release of TC (antibiotic), supporting the potential use of this cytocompatible hydrogel formulation in wound management.

Comment [GA27]: Rakhshaei and Namazi, (2017)

Oliveira *et al*., 2017 [~~187~~199] fabricated PVA-sodium carboxy methyl cellulose (NaCMC) hydrogel containing Propolis, a resinous bees product known for its wound healing and antimicrobial properties, by freeze-thaw technique. The hydrogel dressing designed for second degree burns offered added mechanical and swelling properties of PVA with flexibility and high water uptake properties of NaCMC. PVA-

NaCMC hydrogel with >15% propolis was proposed to be effective for wound healing as increased quantities of propolis lead to inferior mechanical properties.

4.11. Poly (gamma glutamic acid) (PGGA):

PGGA is a bacterial derived natural anionic polymer of D- and L-glutamic acid with hydrophilic properties [200]. Due to its biocompatibility, non-toxic and biodegradable properties, it has attained a good prospect in the biomedical field including wound management applications. Although PGGA hydrogels have poor mechanical strength but this challenge can be encountered by using other polymers to tailor the physicochemical properties for wound dressing applications [200,201].

Comment [GA28]: Omowumi et al., 2014

Comment [GA29]: Khalil et al., 2017,

Shi et al., 2015 [202] fabricated biocompatible PGGA wound dressing hydrogels mixed with different weight ratio (0 (H-0), 5 (H-0.5), 10 (H-1) and 20(H-2) mmol) of silk sericin (biocompatible protein). Weight ratio of PGGA was kept constant (10mmol) in all hydrogels. Ethylene glycol diglycidyl ether (EGDGE) was used as a crosslinker in the production of hydrogels. The resulting hydrogels were easy to remove without damaging the healing tissue and demonstrated high swelling ratio with fluid absorption potential (mimicking wound exudate) which increased with the increase in the amount of silk serine. Moreover, cell proliferation study (by inverted light microscopy) confirmed that the addition of silk serine in PGGA hydrogels improved not only cell attachment but also its proliferation (L929) on the hydrogels. in addition, *in vivo* (rat model) experiments demonstrated that wound closure was accelerated in animals treated with PGGA based hydrogels (maximum closure in H-2) compared to the control (gauze). All these finding along with the histological results (significant granulation and capillary formation in wounds treated with H-2 on day 9) support the application of these novel hydrogel as wound dressing.

In another study, Zhang *et al*., 2018 [203] described a procedure of producing composite hydrogels of PGGA with chitosan and heparin (Chitosan/Hep/PGGA ratio 10:5:5) as wound dressing for chronic wounds. Chitosan (polycation) when mixed with heparin (Hep) and PGGA (polyanions) in the presence of acetic acid, lead to the formation of hydrogels resulting from electrostatic interactions from oppositely charged agents. These hydrogels were loaded with superoxide dismutase (SOD) which imparted anti-oxidant properties. *In vivo* study (diabetic rat model) demonstrated accelerated wound closure (re-epithelialisation) in test group [Chitosan/Hep/PGGA (89.8±2.8%) and SOD-Chitosan/Hep/PGGA (92.0±3.7%)] compared to the control [3M wound dressing and gauze (85.4±2.4%)]. Collagen deposition findings (Masson's trichrome staining) were consistent with the results of wound closure study. Therefore authors concluded that SOD-loaded PGGA composite hydrogels hold a good prospect as wound dressings due to their collagen deposition and re-epithelialisation properties.

Table 3. Other natural and synthetic polymeric material used individually or in combination with other polymers for the production of hydrogel wound dressings.

	Source	Properties	Model/Case Study	Results	Commercial products	References
Collagen	Bovine; Porcine; Avian Rodent Marine	Natural polymer, nontoxic, biocompatible, biodegradable, haemostatic, support fibroblast growth, creates wound healing environment, stimulate macrophages and fibroblast, promote cell attachment and proliferation, cellular migration and tissue development.	Wounds in diabetic mice [Moura et al., 2014] Burn wounds in male rats [Oryan et al., 2018]	Promotes wound healing and epithelialisation	Woun'Dres® (Coloplast) Regenecare® (MPM Medical Inc.)	204,205,206,207,208~~188~~ ~~189~~ ~~190~~ ~~191~~ ~~192~~
Gelatin	Partial denaturation of bovine or porcine collagen	Natural polymer, Type A and B gelatine, elastic, biocompatible, biodegradable, activate microphages, haemostatic, high water absorption capacity, forms thermally-reversible hydrogels	Wounds in diabetic mice [Yoon et al., 2016]	Chemokine-loaded gelatin hydrogel dressings promoted healing, enhanced re-epithelialisation, neovascularisation	HyStem®-C (BioTime Inc.) Extracel-HP ™ (Glycosan Biosystems)	172,209,210,211,212,213 ~~161~~ ~~193~~ ~~194~~ ~~195~~ ~~196~~ ~~197~~
Hyaluronic acid	Bacterial fermentation; Extraction from animal tissues	Poly anionic biological macromolecule, biocompatible, biodegradable, non-immunogenic, non-thrombogenic, hydrophilic, antioxidant activity by reacting with oxygen-derived free radicals, wound healing activity by stimulating inflammatory signals and facilitate cell motility and proliferation.	Wounds in diabetic mice [da Silva et al., 2017]	HA hydrogels accelerated wound closure and wound healing. When incorporated with stem cells increased neoepidermis thickness observed	Restore® Hydrogels (Hollister woundcare) Regenecare® HA HyStem™ (BioTime Inc.)	214,215,216,217 ~~198~~ ~~199~~ ~~200~~ ~~201~~
Dextran	*Leuconostoc spp* *Weissella spp* *Lactobacilli*	Bacterial polysaccharide, biocompatible, biodegradable, hydrophilic, stimulate wound healing, enhance angiogenesis, promote reepithelialisation	Burn wounds in mice [Sun *et al.*, 2011] Wounds in mice [Alibolandi et al., 2017]	Promotes wound healing, enables neovascularisation, promotes angiogenesis, accelerates epithelial maturation, dermal differentiation and skin regeneration Dextran hydrogels		131,218,219,220,221,222 ~~120~~ ~~202~~ ~~203~~ ~~204~~ ~~205~~ ~~206~~

				accelerate wound healing which was further improved by loading hydrogels with curcumin nanomicelles		
Glucan	Cell wall of bacteria, yeasts, algae, lichens, plants (oats and barley)	Polysaccharide, biocompatible, biodegradable, antibacterial, antiviral, anti-inflammatory, exhibits wound healing activity, immune enhancing ability, enhances tensile strength of scar tissue,	26 patients (human subjects) with Hard-to-heal wounds like leg ulcers, diabetic foot ulcers and pressure ulcers [King *et al*., 2017] Wounds in diabetic mice [Grip et al., 2018]	Beta-glucan based Woulgan was very easy to apply and remove, capable of restarting healing process in a range of stalled wounds with wound size reduction	Woulgan® [Biotec Betaglucans]	223,224,225,226 ~~207~~ ~~208~~ ~~209~~ ~~210~~
Guar Gum	*Cyamopsis tetragonolobus*	High molecular weight non-ionic natural hetero-polysaccharide, low cost, hydrophilic, nontoxic, biodegradable, biocompatible, FDA approved			ActivHeal® (Advanced Medical Solutions Ltd.) 3M™ Tegaderm™ Hydrogel Wound Filler (3M Health Care)	70,227,228,229 ~~211~~ ~~212~~ ~~213~~
Polyurethanes	Synthetic polymers with repetitive urethane groups produced by condensation and	Biocompatible, nontoxic, good strength, good toughness, tear resistance , abrasion resistance, non-allergenic, favours epithelialisation, allows oxygen permeability	81 patients (human subjects) with acute and chronic wounds [Zoellner *et*	Enhanced granulation and epithelialisation, reduction in wound surface slough, pain relief, wound size reduction	Hydrosorb® (Hartmann) Hydrosorb® Comfort (Hartmann)	230,231,232 ~~214~~ ~~215~~ ~~216~~

	polymerisation methods		*al.*, 2007] Wounds in rat model [Bankoti et al., 2017]	Enhanced wound healing, increased neovascularization; higher re-epithelialisation, increased collagen synthesis		
Poly(acrylic acid)	Synthetic polymer produced by polymerisation of acrylic acid	Biocompatible, biodegradable, hydrophilic, pH responsive polymer so can be utilised in producing smart hydrogels,anti-bacterial	Wounds in Swiss mice [Champeau et al., 2018]	Nitric oxide controlled release PAA hydrogels lead to increased angiogenesis, organised collagen and accelerated wound contraction		233,234,235 ~~217~~ ~~218~~ ~~219~~
2-acrylamido-2-methylpropane sulfonic acid (AMPS)	Commercially available or by Ritter reaction of acrylonitrile-isobutylene with sulphuric acid	Hydrophilic, non-toxic, biocompatible, thermal stability, pH independent swelling stability, good coherency with good skin adhesion, easy to remove from wound surface, high oxygen permeability, flexible	Porcine burn model [Boonkaew et al., 2014a]	Silver nanoparticle loaded AMPs hydrogels efficiently prevented bacterial colonisation of wound during healing process		117,122,236,237,238 ~~110~~ ~~115~~ ~~220~~ ~~221~~ ~~222~~

Comment [GA30]: Witthayapra..2012

Comment [GA31]: Wang 2007

5. Conclusion and further perspectives

Chronic wounds impose an immense socio-economic burden and if fail to respond to the available medical interventions, may lead to amputation, leading to severe physical trauma and emotional distress to patients and their families. Chronic non-healing wounds may take several months to heal leading to multi-fold financial expenditure on management compared to acute wounds. Although there is a plethora of proprietary wound dressing products already available in the market but due to the increase in ageing population and incidences of chronic diseases, there is a critical need to continue to develop improved advanced wound dressings. Advanced wound care that hydrogel dressings form part of, make up around $7.1 billion of the wound care market and to match the increasing treatment needs in this sector, it is growing at an annual rate of 8.3%. This review presents a brief description of wound healing process and current state of wound dressing products with the main emphasis on hydrogels as wound dressings. Hydrogels, due to their unique properties, are considered as one of the most promising candidates for wound management as dressings. Non-toxicity, biocompatibility, biodegradability, high water content, moisture-retentive property, soft texture, swelling and de-swelling behaviour, stimuli-responsive potential, interactive nature, controlled delivery of therapeutic agents and low cost are few of the many unique properties of hydrogel dressings. These dressings can be fabricated using several polymeric materials by variety of physical and chemical cross-linking techniques. Presented review also expands its focus on the material aspect of the natural and synthetic polymers used in hydrogel formation. From the evidence based on clinical case studies of the application of proprietary hydrogel dressing products in acute and chronic wound management; *in vitro* studies and *in vivo* biological models for testing new hydrogel

material with potential clinical applications, it can be concluded that hydrogels are one of the ideal candidates for wound management as dressing material. Further research progress leading to low cost proprietary hydrogel dressings to facilitate and accelerate chronic wound healing should be the focus for the future in the area of wound care.

Comment [GA32]: Kindly elaborate this section as recommended by Reviewer 2.

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