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The Use of Poly(vinyl alcohol)-based Hydrogels in Biomedical Applications

Deepak Adarsh Subramanian

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Submitted to:

Nicholas A. Peppas, Sc. D.

McKetta Department of Chemical Engineering

The University of Texas at Austin

Supervising Professor

Delia Milliron, Ph. D.

McKetta Department of Chemical Engineering

The University of Texas at Austin

Second Reader

ABSTRACT

Author: Deepak Subramanian

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Supervising Professors: Nicholas A. Peppas, Sc. D., Delia Milliron, Ph. D.

Polymers have found increasing favor in biomedical applications due to the greater control that researchers can exert over their properties. Researchers have focused on the development of therapies using biologically compatible polymers due to their ability to limit potentially harmful interactions with the body. This research has led to advances in tissue engineering, controlled and targeted drug delivery, and other biomedical fields, with the goal of improving both the effectiveness and accessibility of health care.

Poly(vinyl alcohol) (PVA) hydrogels possess several chemical properties that make them well suited for biomedical applications. These include inertness and stability, biocompatibility, and pH-responsiveness. As a result, PVA based materials have been studied for potential applications in areas of biomedicine such as targeted drug delivery, tissue engineering, and wound healing.

This thesis examines the properties of PVA and seeks to understand how the chemical and physical structure affects their properties. It then examines how these properties enhance their utility in potential biomedical applications. Finally, it reviews the research into development of PVA based materials for three different biomedical applications.

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DEDICATIONS

I would like to dedicate this thesis to my family for their encouragement and support throughout my life. They have always been behind me, and I really appreciate their support through all of my endeavours including this thesis.

CHAPTER ONE

Introduction

In the medical field today, there is growing emphasis on harnessing the power of polymers and other biomaterials to develop solutions that are easy to synthesize, effective in dealing with the issue, and do not present any other potential issues to the patient. Researchers, favoring treatments that are more effective and safer for the patient, are leveraging the unique properties of biomaterials to develop new techniques for the diagnosis and treatment of various ailments (both disease and injury) in the body.

Biomaterials are defined as materials that are engineered to interact with biological systems, generally for a medical purpose [1]. As strategies for combating disease and trauma have developed, biomaterials have generally been used for two main purposes. The first is as a diagnostic. Biomaterials have been used in numerous ways (such as cell and tumor imaging agents) to identify characteristics of different diseases and ailments [2][3], which can ultimately lead to the prescription of more accurate therapies to treat the ailment. This use of biomaterials is important from a clinical perspective because of the greater accuracy in diagnosis of the type, extent and locality of the ailment and, consequently, improved efficacy of prescribed treatments.

The second application of biomaterials is as a therapeutic. Biomaterials can be used to treat, augment, repair, or replace a tissue function in the body that has been compromised because of disease or trauma. Biomaterials are finding increasing use in treatment in several different areas, such as wound healing, tissue engineering, drug delivery, tissue replacement therapies (such as artificial joints and prosthetic limbs), and medical devices (such as pacemakers and stents) [1]. Biomaterials have been increasingly used in many of these applications, as researchers have begun

to take advantage of the unique properties of these materials to design therapeutic solutions to many health issues [4][5]. Using biomaterials as therapeutics is attractive because their unique properties can allow for more innovative therapies to be devised and used in practice; this can lead to the development of more effective therapies and, ultimately, better treatment of diseases and ailments that affect people.

Biomaterials used for diagnosis or therapeutic application are broadly classified as either natural and synthetic-based biomaterials. Natural biomaterials, as the name indicates, are materials that are primarily isolated from compounds found in nature [6]. These are preferred in applications that are particularly sensitive and require a higher degree of biocompatibility (in order to prevent a harmful immune response from being triggered), as well as in applications in which the material has an inherent benefit in enhancing treatment. Examples of these applications that have been explored include wound healing [6], nerve repair [6], and urology [7]. Types of natural polymers that have been used in biomedical applications include alginate, chitosan, gelatin, fibrin, glucan, hyaluronan, and silk fibroin.

Synthetic-based biomaterials are generally synthesized in the lab rather than being obtained from natural sources. While these materials may not be as biocompatible as the natural-based biomaterials, researchers have begun investigating synthetic-based biomaterials due to their unique and tunable properties, which make them very versatile for biomedical applications. Synthetic biomaterial research has focused on two main areas - synthetic polymers and inorganic nanomaterials. Synthetic polymers (in contrast to the natural polymers such as alginate and chitosan) are generally synthesized from their component monomers in the lab through a defined synthetic route; as such, properties such as molecular weight, composition, and branching can be controlled. This allows for control over the chemical and physical properties of these synthetic

polymer materials, making them ideal for more specialized applications in which their properties can be exploited to improve the accuracy and efficacy of their function. Synthetic polymers have been used in applications such as 3D scaffolds for tissue engineering [8] and controlled drug delivery [9]. Examples of synthetic polymers that have been explored as biomaterials for these applications include poly(ethylene glycol) (PEG), poly(acrylic acid) (PAA), polyethylene, polyurethanes, and poly(D,L-lactide-co-glycolide) (PLGA).

Inorganic nanoparticles used in biomedical applications are generally either composed of metals, metal oxides, or semiconductor materials. As nanoscale materials, these inorganic materials have unique properties that allow the materials to either work as standalone biomaterials (generally in diagnostics and cellular imaging, due to their unique optical properties) or in concert with natural or synthetic polymer biomaterials for other applications such as controlled drug delivery [10]. Examples of these inorganic nanoparticle-based biomaterials include nanoscale organoclays, zinc oxide, and graphene oxide.

In this thesis, I examine the biomedical applications of poly(vinyl alcohol) (PVA), which is a synthetic polymer. I specifically focus on the applications of PVA-based hydrogels in wound dressings, tissue engineering, and controlled drug delivery. In my analysis, I examine the properties of these hydrogels, with special focus on the physical and chemical properties of PVA hydrogels that make them most useful for these three applications. I review current research into developing these hydrogels for their applications. This includes research into the use of pure PVA hydrogels for these applications, as well as research that has focused on the development of PVA-based composite hydrogels that incorporate other types of biomaterials (including other natural biomaterials, synthetic polymers, and inorganic nanoparticles) for each of these applications and compares the properties and use of these hydrogels with those of pure PVA hydrogels. My goal in

this thesis is to present a comprehensive review of research into the use of PVA-based hydrogels as biomaterials in these three biomedical applications and determine their suitability for these applications.

CHAPTER TWO

Background

2.1 PVA Hydrogels

Poly(vinyl alcohol)-based biomaterials (henceforth abbreviated as PVA) are currently being researched for biomedical applications due to their biocompatibility and sensitivity to changes in pH, as well as their ready availability and relatively simple processing. Unlike other delivery devices in which the monomers undergo a polymerization reaction before being crosslinked, PVA is available commercially, making it easier to synthesize the gels.

Poly(vinyl alcohol) is a polymer consisting of repeat vinyl alcohol units. However, this polymer is not made through direct polymerization of vinyl alcohol monomer; instead, the monomer vinyl acetate is polymerized to form poly(vinyl acetate), and this polymer undergoes a saponification reaction to form PVA [11]. This results in the synthesis of a polymer with a very high polydispersity index; however, the molecular weight of the PVA used in creating these hydrogels is generally relatively constant.

PVA hydrogels have desirable physical properties that make them ideal for biomedical applications. First, PVA hydrogels demonstrate good biocompatibility when implemented *in vivo*, indicating that using these hydrogels will not have any adverse effects on normal body cells when ingested into the body [12]. In addition, these hydrogels have physical properties such as microstructure, Young's modulus, and deformation properties that are comparable to biological tissues, meaning that these hydrogels are ideal for tissue substitutes and other biomedical applications [13]. Finally, and of most importance to this study, PVA hydrogels demonstrate some

sensitivity to the pH of their surroundings, indicating that they can be used as stimuli-responsive biomaterials for controlled drug delivery [5]. Because of these desirable properties, PVA hydrogels are being investigated for numerous biomedical applications, including use as controlled drug delivery devices.

2.2 Crosslinking of PVA Hydrogels

PVA hydrogels can be crosslinked in a few ways: physical crosslinking, chemical crosslinking, and radiation-initiated crosslinking [14]. Physical crosslinking involves the formation of crystalline regions in the PVA solution through repeated freezing and thawing cycles; in this way, a tough, elastic gel can be formed. Figure 1, below, shows the process by which the freezing and thawing process produces a PVA hydrogel [15].

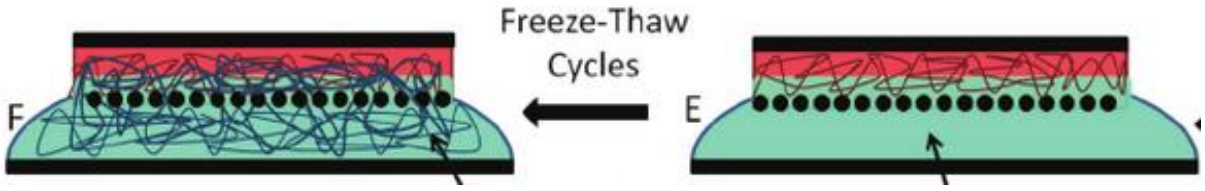

Figure 1 – Freeze-thaw cycles to produce a PVA hydrogel. This process is used to create a physically crosslinked PVA hydrogel without using any chemical agents.

This technique has been used by Yokoyama *et al.* and Peppas *et al.* to produce PVA hydrogels that possess greater strength and elasticity than PVA gels produced at room temperature [16][17]. One benefit to using this procedure is that there is no risk of retaining potentially harmful reagents after the gel is synthesized. However, these gels do not have the same mechanical strength of gels that are crosslinked chemically.

Creating chemically crosslinked PVA gels, on the other hand, requires the use of a crosslinker that can react with the available hydroxyl groups present from the vinyl alcohol repeat unit structure. For PVA gels, the most common crosslinkers are bifunctional aldehydes such as glutaraldehyde (the crosslinking agent that will be used in this experiment), as they can react with the hydroxyl groups to form covalent acetal bonds between PVA chains, improving the mechanical strength of the gel [14]. This reaction requires low pH conditions (supplied by an acid catalyst), a quenching agent (methanol), and a solvent to proceed. Figure 2, below, shows the mechanism of aldehyde-based chemical crosslinking of PVA to form hydrogels [18].

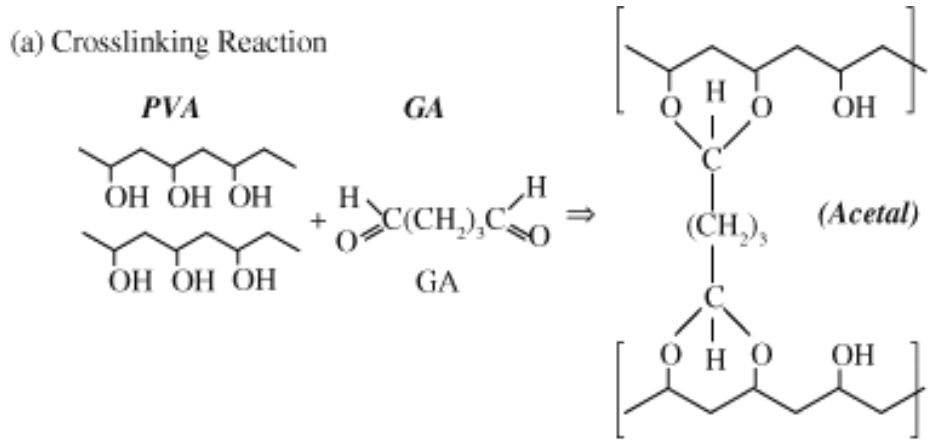

Figure 2 – Chemical crosslinking of PVA to form hydrogels. This figure shows the mechanism through which glutaraldehyde crosslinks PVA chains together to form hydrogels.

This technique was used by Zu *et al*. to create chemically crosslinked PVA hydrogels with applications in transdermal drug delivery of insulin, showing that this procedure can be used to synthesize gels capable of performing controlled drug delivery [19]. One disadvantage of this procedure is that some residual acid or methanol may stay trapped within the gel, which could lead to some possible toxic side effects.

2.3 PVA-based Composite Hydrogels

In addition to the chemical and physical crosslinking of PVA chains to form PVA hydrogels, other materials can be incorporated into the framework to form composite hydrogels. Composite materials, are amalgams of two or more different materials that each retain their own properties. Figure 3, below, shows a schematic of a composite material [20].

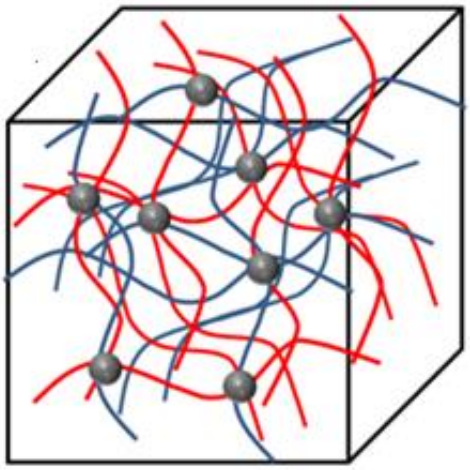

Figure 3 – Schematic of composite material. The schematic in this figure shows the composite material as a combination of different materials in the same framework, with both polymer-based materials (in red and blue) and inorganic materials (gray spheres) indicated.

Composite hydrogels are of interest because of their ability to incorporate the properties of each of the component materials into the framework of the hydrogel, allowing researchers to take advantage of the properties of multiple types of materials to design hydrogels that can more effectively serve as biomaterials for different applications. These materials can both augment the strengths of PVA and ameliorate some of the weaknesses that PVA has as a biomaterial. As a result, PVA-based composite hydrogels have been studied as a way to utilize the versatility of

PVA while taking advantage of the unique properties of other types of biomaterials such as natural polymers, synthetic polymers, and inorganic nanoparticles.

CHAPTER THREE

Objectives

The objectives of this thesis are to:

1) Provide an overview of the different applications of PVA-based hydrogels (wound dressing, tissue engineering, and drug delivery).
2) Identify the relevant properties of PVA-based hydrogels and analyze their applicability to these applications.
3) Review the current research into applying pure PVA-based hydrogels and PVA-based composite hydrogels for these applications.

This is done by analyzing each application individually and looking at the potential of using PVA hydrogels in each context. This is important because not all applications require biomaterials with the same properties, and looking at each potential application on its own ensures that the applicability of PVA-based materials is analyzed in the proper context. Ultimately, the goal of this thesis is to determine whether PVA-based hydrogels (either pure PVA or composite hydrogels) are suitable biomaterials for wound dressing, tissue engineering, and drug delivery applications.

CHAPTER FOUR

PVA Hydrogels in Wound Dressing Applications

4.1 Introduction to Wound Dressing Applications

Wound dressings help to accelerate and improve the process of wound healing; this includes protecting the wound from pathogens that could enter the wound and infect the source as well as promoting the growth and regeneration of cells to "heal" the wound. While wound dressings were originally used as passive supports to merely prevent infections, developments in wound dressing development have focused on the creation of an optimal healing environment that can enhance the healing process as well.

These "functionally active" wound dressings interact with the wound (and surrounding skin and tissue) to promote the action of growth factors and cell regeneration, while reducing the negative effects of fluid buildup and potential infection. Figure 4, below, shows how a wound dressing system can influence the wound healing process [21].

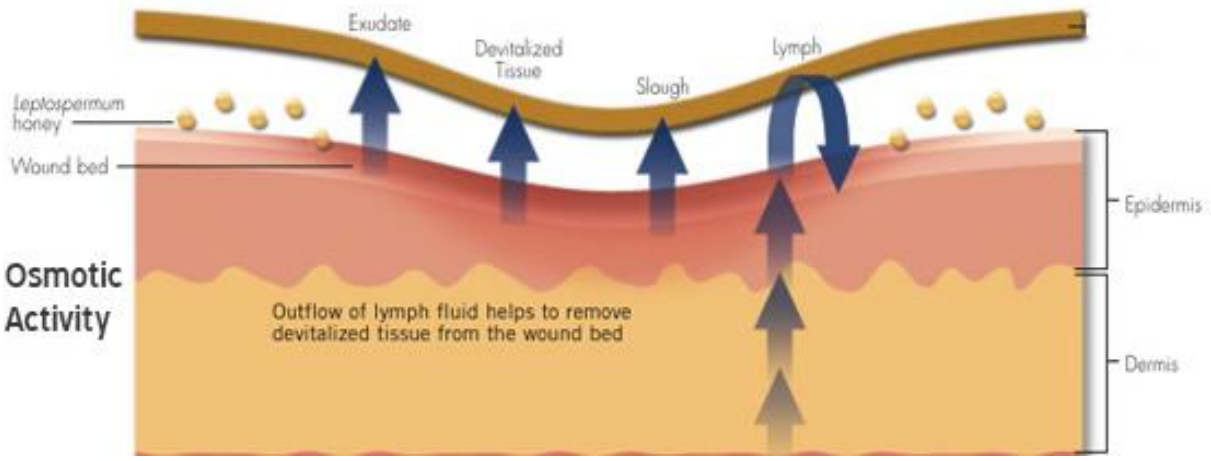

Figure 4 – Accelerated wound healing with "functionally active" wound dressing. This figure shows some of the effects of using a functionally active wound dressing on the healing process.

Ultimately, a good wound dressing should keep a moist environment around the wound (since dryness slows down the growth of epithelial cells on the wound surface), prevent contamination by external pathogens, allow for gas exchange with the environment, reduce adhesiveness to skin over time (so that the dressing fits tightly to the wound soon after application before being easily removed after a period of time), absorb fluids produced around the wound (to prevent fluid buildup and its potential consequences), remain elastic, and demonstrate biocompatibility [22][23]. Hydrogels possess these properties and are thus well suited for use in wound dressings [22].

4.2 Useful Properties of PVA Hydrogels

PVA hydrogels have chemical properties that allow them to perform the desired functions of wound dressings. As stated before, PVA hydrogels have good biocompatibility with the human body [12], meaning that they will not react negatively with the body. These hydrogels specifically do not demonstrate any significantly harmful effects on tissue, indicating that they can be used in wound dressings [24]. This is especially true when the gels are prepared using physical crosslinking techniques rather than chemical crosslinking techniques, as this avoids the use of chemical crosslinking agents that could be toxic to living cells [25].

In addition, PVA hydrogels show very high hydrophilicity, which allows them to absorb aqueous fluids very well; as most bodily fluids are aqueous, these hydrogels can therefore remove fluids from wound sites more effectively and thus prevent fluid buildup at the wound site. Fluid buildup is problematic because it can lead to bacterial growth at the wound site, which could lead to infection and a delay in wound healing [27]. PVA, as a material, has one hydroxyl group per repeat unit, which means that a polymer strand of sufficiently high molecular weight will have a large number of hydroxyl groups that can form hydrogen bonds with water [26]. A PVA hydrogel,

which contains many of these polymer strands, can therefore interact with water very well and allows water to diffuse into the hydrogel [28]. As a result, aqueous fluids can diffuse into the hydrogel very readily, which removes them from the wound site to a greater extent [26].

Finally, PVA hydrogels have the capability to resist external environmental stresses (from pathogens and other sources), thus protecting the wound site from further damage and infection. This capability is the result of the mechanical strength of PVA hydrogels. Singh *et al.* have shown that PVA hydrogels have the requisite tensile strength and burst strength to endure the frictional stresses of day-to-day life by absorbing the energy without breaking [27]. Additionally, PVA hydrogels have shown the ability to resist bacterial penetration, and therefore can protect the wound site from external infection (in addition to their prevention of internal infection through fluid removal) [27]. Both of these properties allow wound dressings prepared from PVA hydrogels to provide a strong wound covering that prevents outside stresses from interfering with wound healing.

4.3 Uses of PVA Hydrogels in Wound Dressings

As described earlier, hydrogels (and PVA hydrogels in particular) are ideally suited for use in wound dressings; therefore, it is not surprising that these materials have been the target of a lot of research in this area. PVA hydrogels for wound dressing applications can be categorized into three areas: pure PVA hydrogels, PVA hydrogels crosslinked with biological polymers, and PVA composite hydrogels containing embedded nanoparticles. These approaches are covered in the following sections.

4.3.1 Pure PVA Hydrogel-based Wound Dressings

Winter *et al.* demonstrated that wound healing was accelerated in the presence of a moist environment when compared to a dry environment [29]. Since PVA hydrogels provide this optimal environment for cell growth and regeneration, different groups have attempted to synthesize PVA hydrogels for wound dressing purposes. Oliveira *et al.* [30] recently synthesized PVA gels containing the antimicrobial agent UK propolis, and demonstrated both the desirable chemical properties of the PVA gel and the antimicrobial action of the UK propolis.

However, pure PVA hydrogels do not have all the necessary characteristics of a good wound dressing material. Without blending or modification, PVA hydrogels do not possess the elasticity or thermal stability necessary to serve as stand-alone wound dressings [31][32]; therefore, most research into using PVA as a wound dressing material involves combining PVA with other materials improve the elasticity and provide more thermal stability.

4.3.2 PVA-Biopolymer Crosslinked Wound Dressings

One approach that has been researched is to crosslink PVA with natural biopolymers such as glucan, alginate, and hyaluronan, among others [31]. Utilizing natural biopolymers is attractive for a couple of reasons. First, natural biopolymers are very readily available when compared to other materials or synthetic polymers; this makes their preparation easier and less expensive. Also, natural biopolymers can be easily modified, allowing researchers to develop functional biopolymers with different properties. Finally, natural biopolymers (that are generally found in biological tissue such as human tissue) are generally very biocompatible, meaning that addition of these polymers would not risk triggering an immune response from the body [31].

Glucan is a water-soluble biodegradable polymer that is generally derived by fermenting incubated plants [31]. As a polymer, it is of interest because of its antimicrobial and antiviral properties, which come about due to its stimulation of macrophages in the immune system [33]. Blending PVA with glucan to create a crosslinked gel can allow for the creation of a wound dressing material with the useful properties of PVA and the antimicrobial properties of glucan. Huang *et al.* [34] synthesized a PVA/glucan blend hydrogel by adding glucan stock solution to a 16 wt.% PVA solution (in water) at room temperature, and casting to a film with thickness 30 μm. Wound dressing made from this material was tested under *in vitro* conditions to determine the dressing's properties as well as *in vivo* testing on Wistar rats to check for wound healing. The results of the *in vitro* experiments indicated that adding glucan increased the elasticity of the hydrogel (which was a drawback of pure PVA hydrogels) while maintaining the material's biocompatibility and lack of skin irritation. The results of the *in vivo* wound healing experiments showed that the blend hydrogel accelerated healing (due to the release of glucan from the gel over time and the facilitation of fibroblast growth on the wound tissue). Ultimately, they concluded that a PVA/glucan blend hydrogel would improve the properties of a hydrogel when compared to a pure PVA hydrogel (particularly elasticity) while accelerating wound healing through the release of glucan over time.

Alginate is a salt of the natural linear polysaccharide alginic acid, which is generally extracted from brown marine algae such as different types of seaweed [31]. As a polymer, alginic acid has good wound healing properties such as improving the hemostatic, adhesion, and cell proliferation properties of a wound site [35], thus making it a potentially useful copolymer for PVA-based wound dressing materials. Kim *et al.* [36] synthesized a crosslinked PVA/sodium alginate hydrogel using the freeze-thawing method of physical crosslinking and performed both *in*

vitro testing of the hydrogel's absorptive and mechanical properties and *in vivo* testing of the wound dressing's healing capabilities using male SD rats. They found that adding sodium alginate to the hydrogels increased their elasticity and did not affect adhesion of platelets to the hydrogel surface, while the *in vivo* studies showed that the hydrogel wound dressing accelerated inflammatory cell growth and epithelial tissue regeneration. From these results, they concluded that using the freeze-thawing physical crosslinking method to produce a PVA/sodium alginate hydrogel allowed for the development of a material that is more elastic than a pure PVA hydrogel while maintaining its biocompatibility and ability to accelerate wound healing.

Hyaluronan (or hyaluronic acid) is a naturally occurring biodegradable polymer that is generally derived from the connective tissues of mammals [31]. A unique property of hyaluronan-based materials is that they can directly interact with proteins and growth factors in tissues to facilitate the healing rate and tissue repair at wound sites [37], meaning that using hyaluronan-based materials allows the material to directly contribute to the wound healing process instead of merely providing the optimal environment for this process to take place. Fahmy *et al.* [38] used a freeze-thawing process to physically crosslink PVA and hyaluronan chains, creating a PVA/hyaluronan blend hydrogel. They performed *in vitro* mechanical strength, absorptivity, and biocompatibility testing to determine the properties of the synthesized hydrogel, as well as *in vivo* antimicrobial testing to determine the effect of adding the hyaluronan on the antimicrobial properties of the hydrogel. They found from the *in vitro* testing that adding hyaluronan increased the mechanical flexibility and water absorptivity of the hydrogels (when compared to pure PVA hydrogels) while maintaining biocompatibility at lower levels of hyaluronan. From the *in vivo* testing, they found that increasing the amount of hyaluronan provided better resistance against the growth of *Candida albicans* (one of the most common microbes in wound infections), thus

demonstrating its antimicrobial capabilities. They concluded that the physically crosslinked PVA/hyaluronan blend hydrogel demonstrates better wound dressing properties than a pure PVA hydrogel, while also providing the benefit of antimicrobial actions towards microbes that commonly infect wound sites.

4.3.3 PVA-Nanoparticle Composite Wound Dressings

Inorganic nanoparticles and fibers have also been used to create composite gels with PVA hydrogels to improve their properties [31]. These particles enhance the mechanical and thermal stability of these hydrogels, especially in the area of most stress. However, since these materials are not biodegradable, the wound dressings are normally used for superficial and shallow wounds. Three common types of inorganic nanoparticles that are introduced to PVA hydrogels are clays, metal oxides, and carbon-based materials.

Nanoscale organoclays are of particular interest because of their intercalation properties in polymeric matrices and their nanoscale basal space, meaning that they can be incorporated into the PVA hydrogel matrix and serve as reinforcing agents [22]. They can also be biofunctionalized to improve gas transfer and antimicrobial activity [31]. Gonzalez *et al.* [39] synthesized PVA hydrogels that contain bentonite nanoparticles and tested their water absorption, water vapor transmission rate (a method of measuring gas transfer into and out of the wound dressing), and antimicrobial properties. They found that incorporating the bentonite nanoparticles improved the strength of the composite hydrogel, as well as providing a water vapor transmission rate that is similar to that of healthy skin. They demonstrated sensitivity and antimicrobial activity for *L. monocytogenes* bacteria and concluded that incorporating bentonite organoclay nanoparticles into the PVA hydrogel matrix led to an improvement of the mechanical, gas transfer, and antimicrobial properties of the hydrogel.

Another approach is to incorporate metal oxide nanoparticles such as zinc oxide (ZnO) into the PVA hydrogel matrix. ZnO nanoparticles are of interest for PVA hydrogels because they can improve the mechanical and thermal stability and provide antimicrobial properties for the hydrogel [31]. This would improve the suitability of PVA hydrogels as wound dressings. Chaturvedi *et al.* [40] used freeze-thawing physical crosslinking methods to synthesize PVA cryogels, incorporated ZnO nanoparticles to create a cryogel composite, and tested the cryogel's mechanical properties, biological fluid absorption, and antibacterial properties. They found that the composite cryogel had sufficient tensile strength for wound dressing applications as well as increased elasticity. They also found that the cryogel was able to absorb a large quantity of biological fluid, making it good for absorbing excess fluid at the wound site. The composite cryogel also demonstrated greater antibacterial activity due to the action of the nanoscale ZnO. They concluded that incorporating ZnO nanoparticles to create a physically crosslinked PVA composite cryogel allowed them to create a material that is more well suited for wound dressing applications.

Another approach that's been attempted is to incorporate carbon-based nanoscale materials such as graphene oxide into PVA-based hydrogels, in order to utilize the antimicrobial properties of graphene oxide in addition to the useful properties of PVA hydrogels [31]. Graphene oxide also has good mechanical strength and can be used to reinforce PVA hydrogels in wound dressings. Carbon-based nanoscale materials therefore would improve the applicability of PVA composite hydrogels in wound dressings. Shi *et al.* [41] used freeze-thawing physical crosslinking methods to synthesize PVA/graphene oxide composite hydrogels and used γ-irradiation to reduce graphene oxide into graphene. They found that adding graphene oxide to the PVA hydrogel improved the mechanical properties (while also reducing crystallinity, which improved the flexibility of the material), while also improving the thermal stability of the hydrogel. They concluded that adding

graphene oxide improved the mechanical and thermal properties of a PVA-based composite hydrogel. Usman *et al.* [42] have showed that adding graphene oxide to PVA-based composite hydrogels also improved their antimicrobial properties.

CHAPTER FIVE

PVA Hydrogels in Tissue Engineering Applications

5.1 Introduction to Tissue Engineering

Tissue engineering is a broad field that generally focuses on using biomaterials and cells from the body to enhance tissue growth and regeneration [43]. This typically involves using a 3D porous scaffold (seeded with cells and growth factors) to stimulate cell growth and serve as a template for tissue regeneration. Figure 5 shows a schematic that illustrates the necessary components for a tissue engineering system [43].

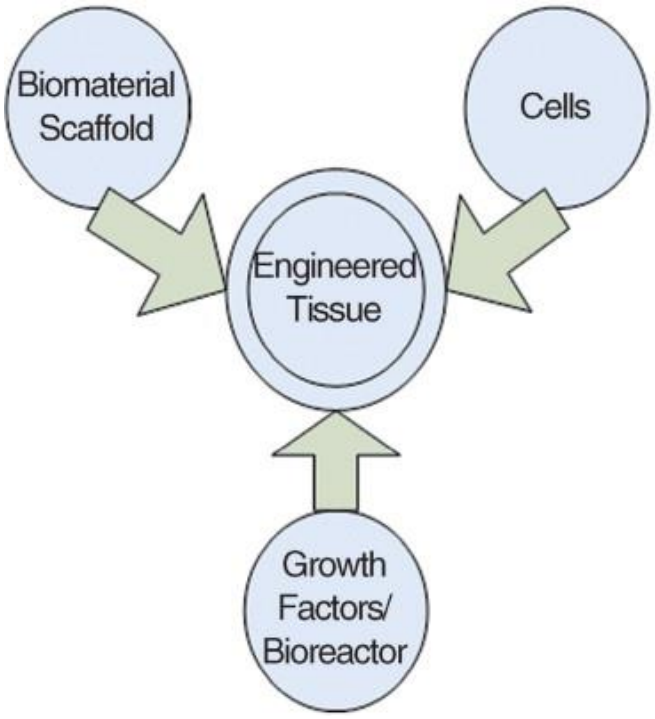

Figure 5 – Necessary components of tissue engineering. This figure shows the three main components – scaffold, cells, and growth factors – required for successful tissue engineering.

The major application of biomaterials in tissue engineering lies in the choice of scaffold, as other factors are largely tissue-dependent. A good scaffold for tissue engineering should exhibit biocompatibility (so that it does not interact harmfully with the body and provoke an immune response). It should also be biodegradable (because the goal of the scaffold is to promote tissue regeneration rather than tissue replacement, and so the scaffold should degrade over time as the new cells grow and the tissue regenerates). It should also have the required mechanical strength and properties for the particular tissue application (which is especially important and challenging for bone and cartilage tissue engineering), while containing a porous scaffold architecture (so that cells can penetrate and diffuse through the scaffold, and allow waste products and byproducts to diffuse out of the scaffold and into the excretory system) [43]. Hydrogels (due to their porosity and good biocompatibility) have been explored as potential options for scaffolds in tissue engineering.

5.2 Useful Properties of PVA Hydrogels

PVA hydrogels have chemical and physical properties that make them suitable for tissue engineering applications. First, PVA hydrogels show good biocompatibility with the human body [12], and therefore can be used in biomedical applications without presenting an immune response. As indicated before, this biocompatibility is enhanced when the gels are prepared using physical crosslinking techniques rather than chemical crosslinking techniques, due to the lack of potentially toxic crosslinking agents [25].

In addition, PVA hydrogels can demonstrate good biodegradability in the presence of some special enzymes, due to the hydroxyl groups in the monomer structure and ester groups in the polymer structure. These ester linkages can be broken via the hydrolysis mechanism in synthetic polymers (such as PVA), thus making them easy to degrade over time; the rate of degradation can

be controlled by controlling the structure of the polymer [44]. The byproducts of PVA hydrogel degradation generally maintain the biocompatibility of the hydrogel, meaning that this degradation process does not produce any toxic by-products that could be harmful to the body [45]. Thus, PVA can be used as a promoter for tissue regeneration without having to serve as a permanent tissue replacement.

PVA hydrogels also have good mechanical strength, comparable to that of tissue [46]; therefore, these materials can be used in tissue engineering applications, as they can withstand the stresses and strains that normal tissues face without failure. Having comparable mechanical strength is extremely important because failure under normal physiological conditions could end up stunting tissue growth and regeneration rather than enhancing it. Finally, PVA hydrogels can be synthesized with good porosity using physical freeze-drying methods [47], indicating that these hydrogels can allow for tissue growth without the issue of excess material build-up at the growth site. Ultimately, these four characteristics of PVA hydrogels allow the material to serve as a good tissue engineering scaffold for various applications.

5.3 Current Uses of PVA Hydrogels in Tissue Engineering

Just as with wound dressing applications, PVA hydrogels have been used in a variety of different ways in tissue engineering applications. To enhance the properties of PVA hydrogels, researchers have explored different combinations of PVA with other natural and synthetic materials (in addition to pure PVA hydrogels) to see how the addition of these materials affects the properties of the hydrogel [48]. This section details the ways that pure PVA hydrogels, PVA-natural polymer composite hydrogels, and PVA-synthetic polymer composite hydrogels have been used in different tissue engineering applications.

5.3.1 Pure PVA Hydrogels in Tissue Engineering

Pure PVA hydrogels have been synthesized using a couple of different techniques, and these hydrogels were shown to possess optimal properties for tissue engineering applications. Researchers have used physical cross-linking techniques to synthesize the hydrogels and found that their mechanical properties were on par with those of healthy tissue (in addition to the necessary biocompatibility and cell adhesion for tissue engineering applications).

For example, Jiang *et al*. [46] synthesized pure PVA hydrogels using a system of freeze-thawing (FT) cycles and found that the synthesized hydrogels showed similar microstructure and mechanical properties to healthy tissues. This indicates that the material has good tissue-mimetic properties that would allow it to withstand some of the pressures from day-to-day life. In addition, Gupta *et al.* [49] demonstrated that mechanically strong freeze-thawed PVA hydrogels exhibit good cell adhesion and promote the growth of human fibroblast cells, indicating that these hydrogels can be used to promote cell growth and tissue regeneration.

To improve the properties of PVA hydrogels, some researchers have chemically modified the structure of the hydrogel using different techniques. For example, Luo *et al.* [50] used highly concentrated aqueous solutions of CO_2 to partially hydrolyze PVA hydrogels and create a highly porous hydrogel structure. This structure enhances the hydrogel's ability to allow cell diffusion into and out of the hydrogel, as well as extracellular products and necessary fluids such as water and air.

The hydrogels were also exposed to human fibroblast cells, and they demonstrated the ability to promote cell growth, indicating that they have promise in tissue engineering applications. In addition, Curley *et al.* [51] used FT methods to prepare a salt-modified PVA hydrogel, which

demonstrated superior thermal stability and mechanical strength when compared to pure PVA hydrogels.

While these hydrogels show some ability to serve as good scaffolds in tissue engineering applications, they do not have optimal properties for tissue engineering. To improve the properties of these hydrogels, researchers have investigated composite hydrogels containing natural polymers or synthetic polymers in addition to PVA.

5.3.2 PVA-Natural Polymer Composite Hydrogels in Tissue Engineering

As explained in the previous chapter, natural polymers have a number of useful properties that allow them to complement PVA in composite hydrogels. They are more readily available than other materials, are easily modified, and do not introduce potential cytotoxicity concerns to the hydrogel system (as the materials are naturally occurring and biocompatible) [31]; thus, they are good candidates for tissue engineering applications. Researchers have taken advantage of these properties, and many types of PVA-natural polymer composite hydrogels have been synthesized and studied for tissue engineering applications. This section will focus on composites with alginate, chitosan, and fibrin.

As mentioned before, alginate is a natural polysaccharide that is extracted from brown algae [48]. Due to its biocompatibility, ability to gel under mild conditions, and good cell adhesion properties, alginate is a popular choice for creating a composite hydrogel with PVA. This composite hydrogel may be used for craniofacial tissue regeneration as a superior alternative to autologous tissues or porous polyethylene (due to its mechanical properties and biocompatibility) [48]. Bichara *et al.* [52] synthesized PVA-alginate composite hydrogels and evaluated their effect on the growth of chondrocyte cells. They found that adding alginate to the hydrogel structure

significantly improved the hydrogel's compressive strength and facilitated the growth of the chondrocyte cells. In addition, Stone *et al.* [53] prepared 1/1 PVA/alginate hydrogels using citric acid *in situ* crosslinking and demonstrated that the hydrogel's thermal stability and mechanical performance did not decay over time and exposure to water, indicating that the hydrogels had the ability to withstand *in vivo* stresses. Overall, PVA-alginate composite hydrogels have shown the ability to perform both mechanically and biologically, meaning that they would be suitable for tissue engineering applications.

Chitosan is a derivative of the common linear polysaccharide chitin and has been commonly used in other biomedical applications such as wound dressings [48]. Due to its biocompatibility and elasticity, chitosan has been studied as a potential additive to PVA hydrogels to enhance their properties. Gomez *et al.* [54] used epichlorohydrin to crosslink PVA-chitosan composite hydrogels and tested their properties in biocompatibility and cell growth promotion. They found that these crosslinked composite hydrogels enhanced the growth of chondrocyte cells and formation of neotissue that exhibited similar characteristics to elastic cartilage, making it a potential scaffold for cartilage tissue regeneration. In addition, the gels demonstrated high biocompatibility and cell viability. Pandele *et al.* [55] used graphene oxide to prepare PVA-chitosan composite hydrogels and tested their mechanical and biological properties. They found that the composite hydrogel showed significantly improved mechanical strength (particularly elastic modulus) and allowed proliferation of osteoblastic cells, indicating its potential application in bone tissue regeneration. Overall, PVA-chitosan composite hydrogels have shown the necessary mechanical properties and cell proliferation enhancement to serve as promising scaffolds for tissue engineering applications.

Fibrin is another natural biomaterial that has recently been adapted for tissue engineering applications. It is a biodegradable polymer and can generally be isolated from a patient's blood [48]. Fibrin itself is manufactured by the body during the wound healing process [56], and as such fibrin-based materials exhibit exceptional biocompatibility (due to the material being synthesized in the patient itself) and cell adhesion (as platelets need to bind to the fibrin during the normal wound healing process). In addition, fibrin gels have very high porosity and good mechanical strength, making them ideal additives to PVA hydrogels [56]. Bichara *et al.* [57] used PVA-fibrin composite hydrogels as a biosynthetic cartilage scaffold for tissue engineering. They demonstrated that this material showed enhanced cell adhesion and allowed cell growth in the material's pores; in addition, the mechanical properties of the hydrogel were consistent with healthy cartilage (and were actually enhanced by cell growth in the material). Based on these results, PVA-fibrin composite hydrogels show promise as scaffolds in cartilage tissue engineering applications.

5.3.3 Synthetic PVA Composite Hydrogels in Tissue Engineering

In addition to using natural polymers in composite hydrogels, some researchers have synthesized composite hydrogels using synthetic polymers [48]. While these polymers are not as widespread as natural polymers, and do not always exhibit the same biocompatibility as natural polymers, they possess very tunable physical and chemical properties that allow for increased customization of the composite hydrogel [48]. There have been a number of different composites that have been synthesized and studied; this paper will focus on composite hydrogels of PVA with ultra-high molecular weight polyethylene (UHMWPE), polyurethanes, and poly(D,L-lactide-co-glycolide) (PLGA).

Ultra-high molecular weight polyethylene (UHMWPE) is a synthetic polymer that exhibits hydrophobic behavior [48]. It has previously been used in orthopedic biomedical devices such as

artificial joints due to its low friction coefficient and has been explored as a tissue engineering scaffold for orthopedic tissue regeneration [58].

Holloway *et al.* [59][60] synthesized two types of PVA-UHMWPE composite hydrogels and examined their chemical and mechanical properties when in contact with orthopedic tissue. They used a grafting technique to synthesize UHMWPE fiber-reinforced PVA hydrogels and found that the grafted hydrogels demonstrated superior interfacial adhesion and shear strength [59]. They also incorporated polypropylene (PP) fibers to reinforce PVA-UHMWPE composite hydrogels and found that this material had material properties that closely resembled those of the meniscus, indicating that this material could be used as a temporary meniscus replacement during tissue growth [60].

Polyurethanes (PU) are a class of polymers that are characterized by the presence of carbamate bonds between the monomer chains [48]. Due to their good biocompatibility, relatively easy chemical modification, and susceptibility to hydrolytic degradation, these materials have been explored as potential scaffolds for tissue engineering [61]. Bonadkar *et al.* [62] synthesized PVA-PU crosslinked hydrogels and examined their mechanical and biological properties. They found that the swelling ratio and elastic behavior of these hydrogels closely mirrored that of natural cartilage, while chondrocyte cell viability and expression was enhanced in the crosslinked hydrogel [62]. This indicates that PVA-PU composite hydrogels have potential as scaffolds for cartilage tissue engineering applications.

Poly(D,L-lactide-co-glycolide) (PLGA) is a copolymer of lactic acid and glycolic acid in which the two monomer subunits are joined by ester linkages [48]. The hydrolytic degradation rate of this polymer can be controlled by adjusting the concentration of monomers in the polymer, while the polymer also maintains the properties of its component monomers; this makes it an

attractive scaffold for bone tissue engineering [63]. Nie *et al.* [64] prepared PVA-PLGA composite hydrogels containing different growth factors and observed their capacity to promote cell growth. They found that using the composite hydrogel enhanced chondrocyte cell adhesion and proliferation, as well as having sufficient porosity to allow delivery of the growth factors to the growing tissue [64]. These results indicate that PVA-PLGA composite hydrogels can serve as good scaffolds for tissue regeneration.

CHAPTER SIX

PVA Hydrogels in Drug Delivery Applications

6.1 Drug Delivery and Controlled Release Systems

Drug delivery research involves investigating strategies to safely deliver drugs inside the body in a controlled and/or targeted manner. *Oral drug delivery* (in which an encapsulated drug is ingested orally and allowed to diffuse into the bloodstream via the digestive system) and *intravenous drug delivery* (in which the drug is directly injected into the bloodstream) are used to deliver a variety of therapeutic drugs into the body, such as insulin for diabetic patients and chemotherapeutics in order to treat different types of cancers.

One of the most significant issues with the field of therapeutic delivery today involves the inability to control the level of a drug in the bloodstream. With oral or intravenous delivery currently, the initial concentration of the drug in the bloodstream is very high (potentially toxic), and the concentration decreases rapidly over time due to metabolism of the drug by the human body. The concentration eventually reaches a level in which the drug is no longer effective, in providing the intended therapeutic benefit. The range of drug concentration in the bloodstream between the effectiveness level at the low end and the toxic level at the high end is referred to as the therapeutic window, and the issue with conventional drug delivery techniques is that the drug concentrations are too often outside the therapeutic window, and therefore the drug cannot effectively treat the disease [65].

One method of improving the drug delivery process is controlled drug delivery, in which the drug transport is delayed or controlled by the use of a polymeric carrier. This carrier creates conditions of slower release because of molecular (drug) diffusion via the pores or microviods of

the polymer. In a special case of drug delivery commonly known as “intelligent drug delivery”, the release of the drug into the bloodstream is triggered and controlled by various physiological stimuli. Currently, research is being conducted into developing delivery devices (generally in the form of nanoparticles that encapsulate the drug) that can respond to temperature changes, pH changes, and the presence of an oscillating magnetic field [66][67]. In the presence of the stimulus, the particles undergo a structural change that causes pores in the nanoparticle to expand. As these pores become larger, the drug can diffuse out of the nanoparticle in larger quantities and enter the bloodstream. When the stimulus is removed, the pores in the nanoparticle shrink, preventing additional drug diffusion from taking place. It is thus possible to control the amount of drug in the bloodstream at any point in time by controlling the stimulus that opens or closes the pores in the nanoparticle shell that the drug is encapsulated within.

Controlled drug delivery systems such as the one described above are generally composed of stimuli-responsive materials that can change structure when exposed to a specific type of stimulus. These materials are generally polymers (due to their unusual stimuli-responsive nature and tunability), and are synthesized either in the nanoparticle form or as gels. Synthesis generally involves creating a mesh-like structure by “crosslinking” the monomers together using a crosslinking agent. Figure 6, below, shows the crosslinking [68] in a stimuli-responsive material.

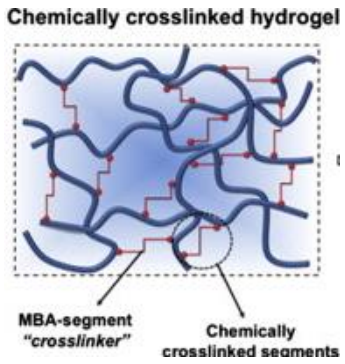

Figure 6 – Crosslinked hydrogel for drug delivery. In this figure, different monomer chains (shown in blue) are crosslinked together using a crosslinking agent. This creates a "mesh-like" porous structure that encapsulates the drugs to be loaded and released from the polymer.

In addition to the stimuli responsiveness shown by controlled drug delivery systems, the materials that make up the drug delivery system should also be biocompatible (in order to more effectively resist the immune response and thus avoid being immediately cleared from the body). They should also present no toxic effects (either from the materials themselves or any potential degradation products), as well as having the requisite swelling ability to allow drugs to diffuse out of the material upon exposure to the stimulus.

6.2 Useful Properties of PVA Hydrogels

PVA hydrogels have chemical and physical properties that make them useful for controlled drug delivery applications. They demonstrate sensitivity to the pH of their surroundings and show a change in hydrogel structure in response to a change in environmental pH [69]. This makes them well-suited for application in oral drug delivery, in which the PVA hydrogel would "shrivel" in the low pH environment of the stomach (protecting the drug from the highly degradative stomach acids) while "swelling" in the neutral pH environment present in the small intestine and allowing the drug to be absorbed into the bloodstream. While this pH-responsiveness is not as strong as that

of other materials such as poly(ethylene glycol) or poly(acrylic acid), PVA hydrogels are responsive to changes in this stimulus.

As mentioned before, PVA hydrogels are also biocompatible and will not trigger a very severe immune response when exposed to the body [70]. This is especially important with controlled drug delivery systems because their effectiveness is in part dependent on the amount of time that they are in the body – if they are cleared too quickly by the immune system, then they will not be able to deliver the drug at the level that it needs to be delivered. In addition, PVA itself is a non-toxic material, and any possible degradation products such as vinyl acetate monomers are generally non-toxic as well [71].

Finally, PVA hydrogels demonstrate good swelling behavior upon exposure to changes in environmental pH. This swelling is especially present in chemically crosslinked PVA hydrogels, as the chemical crosslinks are more robust and do not lead to the presence of crystalline blocks (unlike physical crosslinking methods) [71]. However, both methods of crosslinking produce gels that can swell and shrink when exposed to different pH, and thus have potential applications in controlled drug delivery.

6.3 Current Uses of PVA Hydrogels in Drug Delivery

6.3.1 Pure PVA Hydrogels in Drug Delivery

There are a few ways in which PVA hydrogels have been investigated for use in controlled drug delivery applications. Pure PVA hydrogels have been explored as oral drug delivery systems for a couple of different drugs [71]. Peppas and Mongia [72] used physical crosslinking techniques such as freeze-thaw cycles to prepare PVA cryogels for the delivery of smaller molecular weight drugs such as oxprenolol and theophylline. They examined the effect of the number of freeze-thaw

cycles on the release profile of these drugs from the hydrogels and found that increasing the number of freeze-thaw cycles led to a slower rate of drug release (probably due to the presence of more crystalline regions in the hydrogel structure). In addition, Kimura *et al.* [73] prepared PVA gel spheres for the delivery of insulin into the body. They used gel spheres due to their increased residence time in the body, which would improve the delivery of insulin over a prolonged period. They found that using these gel spheres resulted in successful delivery of insulin to diabetic rats and improved bioavailability of insulin.

However, pure PVA hydrogels (while good biomaterials for drug delivery) are not optimal for this application because of their limited pH-responsiveness (in comparison to other materials such as polyethylene glycol or poly(acrylic acid)) and relatively small swelling ability [71]. As a result, researchers have increasingly focused on investigating the use of PVA-based composite hydrogels in order to enhance properties such as pH-response., swelling, and biocompatibility [71]. The next two sections will cover the applications of PVA-natural polymer composite hydrogels and PVA-synthetic polymer composite hydrogels in controlled drug delivery.

6.3.2 PVA-Natural Polymer Composite Hydrogels in Drug Delivery

PVA-natural polymer composite hydrogels have been investigated for controlled drug delivery applications in order to enhance properties such as pH sensitivity and biocompatibility [71]. These polymers are readily available and generally do not have any effect on the cytotoxicity of the hydrogels, meaning that they can be incorporated cheaply without posing any new hazards towards the human body. A few types of natural polymers that are used in these composite hydrogel systems include alginate, gelatin, and silk fibroin.

Alginate, as described before, is a linear polysaccharide that is generally found in seaweed and brown algae [48]. Alginate is generally used as a composite material in PVA-based hydrogels because of its biocompatibility and ability to form interpenetrating networks with PVA; these interpenetrating networks have improved mechanical properties, making these hydrogels more suitable for biomedical applications. Xie *et al.* [74] used freeze-thaw cycles to physically crosslink PVA hydrogels before using Ca^{2+} ions to chemically crosslink alginate chains to form an interpenetrating network. The resulting hydrogel showed significantly improved swelling kinetics and pH sensitivity as compared to normally synthesized PVA hydrogels, as well as a relationship between the composition of the composite hydrogel and the pH sensitivity of the hydrogel [74]. This result shows that a functional PVA-alginate composite hydrogel can be synthesized with enhanced pH sensitivity and good mechanical properties (making it suitable for controlled oral drug delivery).

Gelatin is a water-soluble protein that is generally obtained by isolation and preparation from collagen [71]; its major uses are in the food industry as the foundation for jelly-based products. Gelatin has been examined as a possible biomaterial due to its good biocompatibility and hydrophilicity, which makes it good for biomedical applications. Pal *et al.* [75] used an esterification reaction to create a PVA-gelatin composite hydrogel membrane and tested the effect of the gelatin on the mechanical properties of the hydrogel and the diffusion of salicylic acid out of the membrane. They found that the mechanical properties and water absorption capabilities of the membrane were sufficient for an implantable drug delivery system. In addition, they observed that the diffusion coefficient of salicylic acid through the membrane was sufficient for drug delivery applications [75]. They concluded that using a PVA-gelatin composite hydrogel membrane showed promise as an implantable drug delivery system.

Silk fibroin is an insoluble protein that is made naturally by the *Bombyx mori* silkworm and has been used mostly as a surgical suture material [76]. Silk fibroin is being studied for possible biomedical applications due to its easy processability, biocompatibility, and mechanical strength; another advantage that makes it suitable for drug delivery applications is its stabilizing effect [76]. Kundu *et al.* [77] used photocrosslinking techniques to synthesize a PVA-silk fibroin composite hydrogel and tested the effects of silk fibroin on the gels' water uptake properties and dextran release profiles. They found that adding silk fibroin significantly increased the water uptake by the gels, while increasing the amount of silk fibroin in the gels allowed for greater and faster drug delivery over the same period [77]. They concluded that PVA-silk fibroin composite hydrogels had promise in controlled drug delivery.

6.3.3 PVA-Synthetic Polymer Composite Hydrogels in Drug Delivery

PVA-synthetic polymer composite hydrogels have also been developed as controlled drug delivery mechanisms [71]. While these polymers are not as common as the natural polymers, they can be tailored and functionalized to have specific properties that enhance their applications in drug delivery, such as enhanced stimuli-responsiveness and the ability to remain in the bloodstream without being removed by the immune system [71][82]. Two types of synthetic polymers that have been used in PVA-based composite hydrogels for controlled drug delivery applications are polyethylene glycol and poly(acrylic acid).

Polyethylene glycol (PEG) is a synthetic polymer composed of repeat ethylene oxide units [78]. This polymer, due to its high hydrophilicity, good biocompatibility, and pH-responsiveness, has been used in a variety of different biomedical applications [78]. In addition, it confers an additional benefit when used in controlled drug delivery systems due to its ability to inhibit a phenomenon known as "opsonization", which reduces blood clearance of the drug delivery

systems and thus improves the efficacy of drug delivery [78][83]. Gadea *et al.* [79] crosslinked PVA hydrogels with acyl chloride-modified PEG to form a crosslinked composite hydrogel. The group then tested the effect of PEG addition on the swelling capabilities and pH-responsiveness of the hydrogels. They found that the amount of PEG added to the hydrogels affects the water swelling properties and produces pH-sensitivity that is especially pronounced at higher pH [79]. These results indicate that a PVA-PEG composite hydrogel has potential benefits as a drug delivery system due to enhanced stimuli-responsiveness.

Poly(acrylic acid) (PAA) is a synthetic polymer composed of repeat units of acrylic acid; this polymer is known as a polyelectrolyte because at neutral pH, the acrylic acid units will lose a proton to the solution and carry a negative charge [80][84]. Due to its pH-sensitivity, biocompatibility, and temperature-sensitivity, PAA has been studied as a potential polymeric material for controlled drug delivery. Shin *et al.* [81] synthesized interpenetrating networks consisting of PVA and PAA chains to create a hydrogel system. They then tested the swelling capabilities, pH-responsivity, and temperature-sensitivity of the newly created system. They found that the hydrogel could change structure in response to changes in both buffer pH and the temperature of the surrounding environment, and this caused changes in the release of the encapsulated indomethacin drug [81]. They concluded that creating a PVA-PAA interpenetrating network hydrogel allowed for the possibility of a drug delivery system that was sensitive to multiple stimuli.

CHAPTER SEVEN

Conclusions

Biomaterials exhibit potential to address a number of different issues facing the medical field today. These include accelerating wound healing, regeneration of tissues and tissue replacement, and increasing the efficacy of drugs in the body through targeted and controlled delivery of therapeutics. Solving these problems could result in significantly improved treatment of diseases and other ailments, leading to a greater overall standard of living for people.

The development of novel biomaterials, especially the use of polymers with unique capabilities, has greatly improved the potential for solving these problems. One such polymer that has been widely investigated for use in biomedical applications is poly(vinyl alcohol). This polymer, which is generally synthesized by polymerizing vinyl acetate monomer and using transesterification to produce the final polymer, can form hydrogels through either physical crosslinking (which uses repeated freeze-thaw cycles to form cryogels) or chemical crosslinking through the use of difunctional crosslinkers such as glutaraldehyde. These hydrogels possess beneficial physical properties such as biocompatibility, mechanical properties and microstructure that closely resembles that of biological tissue, and a slight pH responsivity.

These properties make PVA hydrogels useful in biomedical applications, including wound healing, tissue engineering and drug delivery. Wound healing is enhanced by materials that promote cell growth at the wound site and prevent harmful infections during the healing process. Another application of PVA-based biomaterials is in tissue engineering, in which biomaterials serve as scaffolds that can promote cell growth and as temporary tissue replacements; these scaffolds degrade over time as the tissue regenerates. A third application is in controlled drug

delivery, in which PVA is used as a carrier or encapsulant. Then, the encapsulated drugs are released in the body at controlled rates as the drug delivery systems changes structural characteristics in response to the imposition of a certain stimulus, e.g., pH or temperature.

The properties of PVA hydrogels make them potential biomaterials for these applications. Researchers have investigated the potential for several PVA-based hydrogels for use in wound dressings, tissue engineering scaffolds, and controlled drug delivery systems. Pure PVA hydrogels have been studied as biomaterials for these applications, and the results demonstrate that these hydrogels have some promise. However, there are limitations in the properties of pure PVA hydrogels that make them less effective in these applications. To enhance the properties of PVA hydrogels, researchers have explored creating composite hydrogels containing both PVA and other materials such as natural polymers, synthetic polymers, and inorganic nanomaterials. These materials possess unique properties that can either complement or enhance the properties provided by PVA hydrogels, meaning that these composite materials can be even more effective as biomaterials for wound healing, tissue engineering, and controlled drug delivery. The research into creating composite PVA-based hydrogels with these different materials shows that the composite materials have enhanced properties that make them more suitable as biomaterials for these applications.

In summary, poly(vinyl alcohol)-based biomaterials have shown the properties that make them suitable for different biomedical applications, and PVA-based materials have been investigated for wound healing, tissue engineering, and controlled drug delivery applications. With the development of composite materials that combine the properties of PVA with the properties of other materials, the applicability of PVA in biomedical applications is further enhanced. Future work will focus on determining the optimal PVA-based material for each of these applications

(through experimenting with other potential composite materials with unique properties) and comparing them to materials derived from other sources to determine whether the PVA-based materials provide the most effective method of treating these problems. This will hopefully result in the identification of the most effective materials for solving different biomedical problems.

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BIOGRAPHY

Deepak Adarsh Subramanian was born and raised in Austin, TX, and graduated in 2014 from Westwood High School. He attended the University of Texas at Austin, pursuing a double major in Chemical Engineering (Honors) and Plan II Honors.

As an undergraduate, Deepak participated in several extracurricular activities. He worked as an undergraduate researcher under Dr. Nicholas Peppas (in the Institute for Biomaterials, Drug Delivery, and Regenerative Medicine) from August 2014 to May 2018. His research focused primarily on developing stimuli-responsive polymeric nanoparticles with applications in oral drug delivery (of insulin) and controlled drug delivery of chemotherapeutics. He also worked in Dr. Keith Keitz's lab for his senior design project, in which he optimized the conditions of a size exclusion chromatography column to most effectively separate differently sized oligomers of the amyloid β peptide.

Deepak was a member of the Omega Chi Epsilon (OXE), Tau Beta Pi (TBP), and Phi Beta Kappa (PBK) honor societies, serving as the Social Chair and Fundraising Coordinator for OXE. He also served on the Undergraduate Research Committee of the UT Senate of College Councils and was a cellist in the Engineering Chamber Orchestra (EChO) at UT. As a member of the UT team, Deepak participated in the ChemE Jeopardy! competition in 2016 and 2017 AIChE National conferences, with the team placing second in 2017.

After graduating from the University of Texas, Deepak will pursue a Ph. D. in Chemical Engineering at the Massachusetts Institute of Technology (MIT), where he intends to conduct research in the design and development of biomaterials for biomedical applications.