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Hydrogel Polymer: A Unique Material for Bio-Separation, Bio-Sensing and Drug Delivery

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Abstract: Hydrogel products made up of a group of polymeric materials, the hydrophilic structure of which renders them capable of holding large amounts of water in their three-dimensional networks. Extensive application of these products in a number of industrial and environmental areas of application is considered to be of prime importance. As expected, natural hydrogels were gradually replaced by artificial types due to their higher water absorption capacity, long service life, and wide varieties of raw chemical resources. Literature on this subject was found to be expanding, especially in the scientific fields of research. However, a number of publications and technical reports dealing with hydrogel products from the engineering points of view were examined to overview technological aspects covering this growing multiple professional fields of research. The primary objective of this article is to review the literature concerning classification of hydrogels on different bases, physical and chemical characteristics of hydrogel, and technical feasibility of their utilization. An innovated category of recent generations of hydrogel materials was also presented in some detail.

Keywords: Hydrogel preparation, processing, application.

I. INTRODUCTION

The terms gels and hydrogels are used interchangeably by food and biomaterials scientists to explain polymeric cross-linked network structures. Gels are defined as a substantially dilute cross-linked system, and are categorised principally as weak or strong depending on their flow behaviour in steady-state (Ferry, 1980). Edible gels are used mostly in the food industry and mainly refer to gelling polysaccharides (i.e. hydrocolloids) (Phillips & Williams, 2000). The term hydrogel describes 3-D network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain sensible amount of water (Rosiak & Yoshii, 1999). The hydrogel structure is made up of the hydrophilic groups present in a polymeric network upon the hydration in an aqueous environment. This chapter reviews the preparation methods of hydrogels, additionally, methods to characterize these hydrogels and their proposed applications are also reviewed.The three classical phases of matter on Earth are solid, liquid or gas. Phase transitions occur with sufficient change in pressure and/or temperature. For example, water (liquid) transitions to ice (solid) with a drop in temperature. Gelatin powder, such as Kraft Foods' Jell-O, is a solid. Empty a packet of Jell-O into a mixing bowl and add boiling water. Stir until dissolved and then chill. Now the material in the bowl is neither solid nor liquid nor gas; it's a hydrogel.

Like a solid, hydrogels do not flow. Like a liquid, small molecules diffuse through a hydrogel. Hydrogels are currently viewed as water insoluble, cross-linked, three-dimensional networks of polymer chains and water that fills the voids between polymer chains. Crosslinking facilitates insolubility in water and provides required mechanical strength and physical integrity. Hydrogel is essentially water (the mass fraction of water is much greater than that of polymer). The ability of a hydrogel to hold significant amount of water implies that the polymer chains must have at least balanced hydrophilic character.

II.CLASSIFICATION

The hydrogel products can be classified on different basis as given below:

Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins.

Figure 1: Hydrogel

Classification according to polymeric composition

The method of production leads to formations of some important classes of hydrogels. These can be exemplified by the following:

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(a)Homopolymeric hydrogels are referred to polymer network obtained from a single species of monomer, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization process.
(b)Copolymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network.
(c)Multipolymer Interpenetrating polymeric hydrogel (IPN), an important class of hydrogels, is made of two different cross-linked synthetic and/or natural polymer component, contained in a network form. In semi-IPN hydrogel, one component is across-linked polymer and other component is a non-cross-linked polymer.

Classification based on configuration
The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

(a)Amorphous (non-crystalline).
(b)Semicrystalline: A complex mixture of amorphous and crystalline phases.
(c)Crystalline.

Classification based on type of cross-linking
Hydrogels can be divided into two classes based on the chemical or physical nature of the cross-link junctions. Chemically cross-linked networks have permanent junctions, while physical networks have transient junctions that arise from either polymer chain complexity or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

Classification based on physical appearance
Hydrogels appears as matrix, film, or microsphere depending on the technique of polymerization involved in the preparation process.

Classification according to network electrical charge
Hydrogels may be categorized into four groups on the basis of presence or absence of ionic charge located on the cross-linked chains:

(a)Nonionic (neutral).
(b)Ionic (including anionic or cationic).
(c)Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.
(d)Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

Hydrogel-forming natural polymers include proteins such as collagen and gelatine and polysaccharides such as starch, alginate, and agarose. Synthetic polymers that form hydrogels are traditionally prepared using chemical polymerization methods.

III. APPLICATIONS OF HYDROGEL

Hydrogel of many synthetic and natural polymers have been produced with their end use mainly in tissue engineering, pharmaceutical, and biomedical fields (Hoare & Kohane, 2008). Due to their high water retaining capacity and biocompatibility they have been used in wound dressing, drug delivery, agriculture, sanitary pads as well as trans-dermal systems, dental materials, implants, injectable polymeric systems, ophthalmic applications, hybrid-type organs (encapsulated living cells) (Benamer et al., 2006; Nho et al., 2005; Rosiak et al., 1995; Rosiak & Yoshii, 1999). A list of hydrogels with their proposed corresponding applications is shown in Table No.1.

APPLICATIONS IN BIO-SEPARATION, BIO-SENSING AND DRUG DELIVERY:
Hydrogel membrane for Bioseparation:
Recently, major attention has been focused towards developing stimuli sensitive hydrogels and membranes for selective separations. Membranes are semipermeable barrier materials, which are the main components of a separation process. The separation through porous membranes is mainly due to sieving mechanism of membranes and therefore, the efficiency of selective separation depends upon the size of the pores, chemical nature of membrane and the interaction between membrane and the permeate. Because of the unique properties, membranes have found large number of applications in bio-separation processes.

Table(1): Applications of hydrogel & types of polymers

Application	Polymer
Wound care	polyurethane, poly(ethylene glycol), poly(propylene glycol), poly(vinylpyrrolidone), polyethylene glycol and agar, Xanthan, methyl cellulose, carboxymethyl cellulose, alginate, hyaluronan and other hydrocolloids
Drug delivery, pharmaceutical	poly(vinylpyrrolidone), starch, poly(vinylpyrrolidone), poly(acrylic acid), carboxymethyl cellulose, hydroxypropyl methyl cellulose, polyvinyl alcohol, acrylic acid, chitosan, acrylic acid, 2-acrylamido-2-methylpropanesulfonic acid, acrylic acid, carboxymethyl cellulose.
Dental materials	Hydrocolloids (Ghatti, Karaya, Kerensis gum)
Tissue engineering, implant	poly(vinylalcohol), poly(acrylic acid), Hyaluronan, collagen

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Injectable polymeric system	polyesters, polyphosphazenes, polypeptides, chitosan.
Technical products (cosmetics, pharmaceuticals)	Starch, gum Arabic, xanthan, pectin, carrageenan, gellan, welan, guar gum, locust bean gum, alginate, starch, heparin, chitin and chitosan.
Others (agriculture, waste treatment, separation, etc.)	Starch, xanthan, polyvinyl alcohol, poly (vinyl methyl ether), poly (N-isopropyl acrylamide).

Hydrogels are hydrophilic polymers and have three dimensional network structures. These hydrogels are insoluble in water but exhibit swelling/shrinking depending on various external stimuli such as temperature, pH, electric field, magnetic field, light, etc. Therefore, they have been termed as stimuli responsive gels. The combination of hydrogels and membranes provide hydrogel membranes with synergistic properties of membranes and hydrogels with a good mechanical strength. Furthermore, these membranes mimic the biological tissues and exhibit excellent biocompatibility. The swelling and shrinking property of hydrogels can be used to adjust the pore size/mesh size of membranes. Hydrogel membranes are generally characterized by swelling properties as well as the molecular weights between crosslinks (mesh size/crosslinking density). Permeation through hydrogel membranes not only depends on the molecular structure but also on the external conditions. Such membranes have applications in bio-separation, controlled drug delivery, bio-hybrid artificial organs and multi-component separations and also used as sensors and chemical valves. Hydrogel membranes can be synthesized either by chemical crosslinking wherein, the covalent bonds are present between different polymer chains or by physical crosslinking, wherein the dissolution of polymer is prevented by physical interactions between polymer chains. In this work, we have applied both the methods for the synthesis of novel hydrogel membranes. We have selected chitosan [CS] and poly (vinyl alcohol) [PVA] due to their hydrophilic nature, biocompatibility and excellent film forming properties. The membranes, which show discontinuous volume transition in water as a function of temperature, have potential applications in drug delivery system. So the work was undertaken to design and develop the thermosensitive membranes, which exhibit discontinuous volume transition in water as a function of temperature. Poly (N-isopropyl acrylamide) [PNIPAm], is the most commonly used thermosensitive polymer exhibiting the lower critical solution temperature [LCST] in the range of 31- 33°C. Thermo- and pH-sensitive hydrogel membranes were synthesized based on chitosan and PNIPAm. It is well established that, the appropriate balance between hydrophilic and hydrophobic interactions lead to discontinuous phase separations. Therefore, the study was undertaken to synthesize thermosensitive hydrogel membranes whose homopolymers do not show LCST at an observable temperature range. In order to develop such thermosensitive hydrogel membranes without chemical crosslinker, n-tertiary butyl acrylamide [NTBA] monomer was grafted onto PVA. Moreover, post crosslinking of PVA film can be easily done by simple techniques like heat treatment/annealing of membranes at high temperature. In order to improve the mechanical strength of these membranes, water swellable nano-clay was incorporated and properties of the membranes were studied. It is well established that the presence of nano-clay in polymer system increases the mechanical property of the system. The irreversible adsorption of PVA onto hydrophobic membranes such as polyvinylidene fluoride [PVDF] has been studied using XPS, water contact angle, etc. The molecular origin of the wettability of PVDF surface by hydrophilic PVA has been deduced by XPS and EDAX measurements.

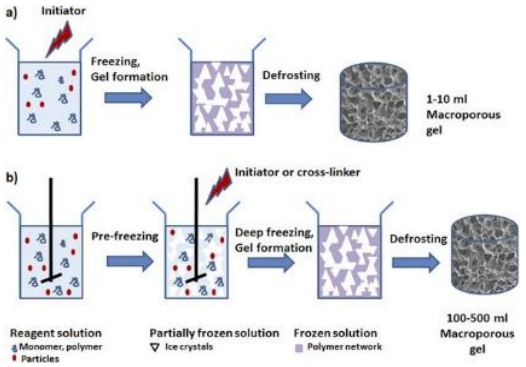

Figure 2: (a) The schematic representation of the method of preparation of macroporous gel for bioseparation and (b) The novel (pre-freezing) approach outlined herein.

The major emphasis is given on the synthesis and characterization of hydrogel membranes by different techniques. The swelling properties of these hydrogel membranes were carried out as a function of pH and temperature. Permeation studies through hydrogel membranes were undertaken using biomacromoles. The incorporation of nano fillers into hydrogels was performed to obtain nanocomposite hydrogel membranes with varying properties. The entire work is presented in seven chapters and the outline of each chapter is given in the foregoing. The major focus of this work is to design and develop hydrogel membranes whose properties can be controlled by external conditions. This chapter highlights the objectives of the present work such as different strategies for synthesis of hydrogel membranes, nanocomposite gel membranes, adsorption of hydrophilic polymers onto hydrophobic membranes and characterization in terms of swelling, permeability, etc.

Hydrogels as a drug delivery system:

Much work on bioresponsive hydrogels for drug delivery relates to the release of insulin in response to raised blood sugar levels. In one approach, glucose oxidase molecules

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are attenuated onto a basic polymeric carrier. Following the enzyme reaction that converts glucose to gluconic acid, thereby temporarily lowering the pH, the basic groups on the polymer are protonated, inducing swelling and increase the release profile of insulin. This system works as a feedback loop, upon release of insulin the sugar levels drop, resulting in a pH increase that stops the release of further insulin.

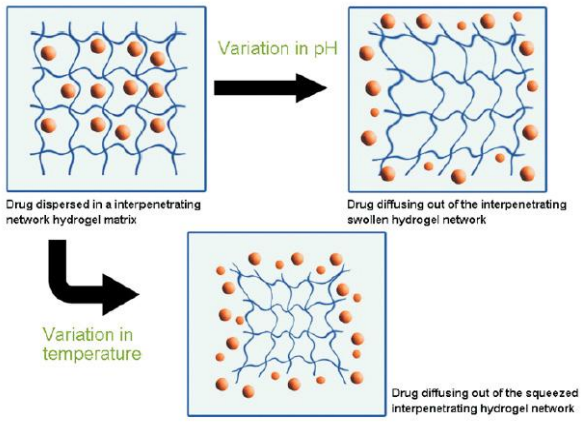

Figure3: Swelling and deswelling behavior of interpenetrating hydrogel network with variation in temperature and pH for drug delivery system.

Ishihara et al. combined a copolymer membrane of N, N-diethylaminoethyl methacrylate (DEA) and 2-hydroxypropyl methacrylate (HPMA) with a cross-linked poly (acrylamide) membrane, in which glucose oxidase was immobilized. The glucose-susceptible insulin permeation was achieved based upon the combination of an enzymatic reaction with a pH-sensitive swelling. In this, glucose diffuses into the membrane and is catalyzed by glucose oxidase, resulting in the conversion of glucose to gluconic acid. The micro environmental pH in the membrane becomes low, due to the production of gluconic acid. Swelling of the membrane results from ionization of the amine groups by the lower pH, insulin permeability through the membrane is enhanced. Thus, insulin transport through the membrane is strongly dependent upon the glucose concentration. Further, Ishihara et al. investigated insulin release from polymer capsules containing insulin and glucose oxidase, which were produced by a conventional interfacial precipitation method. Insulin release was inhibited in the absence of glucose, but was strongly enhanced in the presence of glucose. In case of site-specific discharge explains the catalytic action of disease-specific enzymes to trigger drug release from polymeric prodrug carriers. Prodrugs are inactive precursors of drug molecules that are activated in vivo, usually through enzymatic hydrolysis. E.g, a cancer-specific enzyme secreted by tumor cells can be used to trigger the release of a therapeutic agent to prevent or reduce metastasis. This objective may be achieved by immobilizing drug molecules linked to a polymeric backbone (such as polyethylene glycol, or PEG) via enzyme-cleavable linkers. Rein V.ULijnl et al. developed a nondissolving, enzyme-responsive hydrogel with physically entrapped guest molecules. Macromolecule release is determined by charge-produced hydrogel swelling, which is controlled enzymatically. A cleavable peptide chain is modified to respond to a particular protease.

Hydrogel microparticles for biosensing:

In recent years, there has been vast development of hydrogel-based technologies for a range of biotechnology applications including diagnostics, drug delivery, and tissue engineering. Hydrogels are adaptable materials due to their hydrophilic, biofriendly, and highly tunable nature, making them applicable in this varied range of contexts. Recent significant advances in types of gel materials, microfabrication techniques and biosensor development have come together to assemble the key components for fabrication of encoded hydrogel particles for biosensing. This introduction will enumerate the chemical advantages of hydrogels and their initial success in being used in a microarray format, which led to the gel bead-based advances that we will describe later.

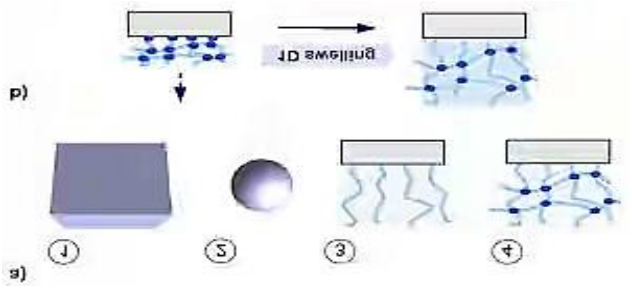

Figure 4: Schematic representation of (a) in-situ crosslinking polymerization (1) and surface attachment of the hydrogel in the swollen state, and (b) post-synthetic crosslinking by first immobilizing an adhesion-promoting molecule (2), followed by deposition of a prepolymer (3), crosslinking of the dry layer (4), and subsequent swelling of gel of the gel (5).

Hydrogels, made of cross-linked hydrophilic polymer chains, are readily functionalized with several biological entities such as nucleic acids or proteins. Thus, hydrogels can be engineered for capture and detection of clinically relative analytes including but not limited to proteins, DNA, mRNA, and microRNA (miRNA). Their solution-like environment, chemical tunability and nonfouling nature in biologically complex fluids (e.g. serum), further render hydrogels ideal candidates for diagnostic uses. The three-dimensional scaffold can be porosity-tuned to allow the diffusion and reaction of large biomolecules while remaining structurally stable under rough mixing or flow conditions.In a molecular diagnostic context, hydrogels were first utilized for the fabrication of hydrogel sensing planar microarrays. A wide range of hydrogel chemical compositions have been explored for DNA or protein microarrays, in particular polyacrylamide, polyethylene

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glycol, and alginate derivatives. Many methods to functionalize the gels have been explored, ranging from in situ functionalization at the time of synthesis to post-synthesis functionalization utilizing functional groups in the gel. In a series of studies where probe-functionalized polyacrylamide hydrogel pads were immobilized on a surface for DNA detection, hydrogels were found to be superior for biosensing relative to rigid two-dimensional planar surfaces. These pioneering studies demonstrated better thermodynamic association constants for nucleic acid hybridization inside the gel environment and proved that biological probes could be functionalized at considerably higher densities than possible on standard microarrays. Further studies extended to antibody-based protein detection revealed similar advantages with reard to probe-functionalization density. These favorable characteristics enabled higher specificity and detection sensitivity inside the gel environment. We note that the substrate used in those studies, polyacrylamide, has a small pore size (nm) and analytes showed significantly hindered diffusion inside the gels. Despite this compulsion, the gel microarrays had significant advantages over planar microarrays simply due to the unique chemistry inside the gel environment.

Most planar microarrays, however, suffer from inherent diffusional limitations that are difficult to overcome since these systems are not well mixed. These constraints apply to hydrogel planar arrays as well. For example, assuming solution diffusivity of a protein to be $100 lm^2/s$, the characteristic diffusion time across even 1 cm is on the order of days. This precludes the possibility of reaching equilibrium in a reasonable period of time. In addition, although microarrays can accommodate high-density multiplexing, there is low flexibility with regards to rapidly changing probe sets to tailor clinical panels, since probes are pre-immobilized on a single surface. Instead, beadbased suspension arrays can overcome mass transfer limitations by maintaining a well-mixed solution through shaking, thereby providing near-solution kinetics, and further offering high flexibility for rapid target panel modification. A natural advance in the field was thus to adapt hydrogel substrates in a particle-array format for solution-based detection.In the field of particle-based arrays, the very large majority of reported examples focus on polyethylene glycol derivedmaterials, while a few recent studies use alginate gels. After discussing the properties of those materials and the strategies for probe immobilization, we will review the methods for particle synthesis and encoding developed for these gels, ranging from graphical codes to spectral codes. Among the key contributions to the field that we will discuss in this article are novel methodologies to fabricate multifunctional hydrogel microparticles using lithographic processes (including replica molding and stop flow lithography) and spherical particles using droplet-based processes. In some applications, gels were synthesized, functionalized and encoded in a single step, while in others synthesis, encoding and functionalization took place at different times. We will review protocols for processing and reading the hydrogel particle array and examples of application for measurements of proteins, DNA, mRNAs and microRNA, in a range of sensing conditions. Finally, we will discuss the perspectives of hydrogel-based particle sensing, in particular how more recent analysis have begun to examine the utility of such microparticles in applications such as single-cell analysis.

IV.CONCLUSION

Recently, many hydrogel based networks have been designed and modified to meet the needs of different applications. The favorable property of these hydrogels is either ability to swell when put in contact with an aqueous solution. This review demonstrates the literature concerning classification of hydrogels on different bases, physical and chemical characteristics of these products and technical feasibility of their use. It also involved technologies used for hydrogel production together with its responses to environmental stimli like ph, temperature, etc. An innovated category of recent generations of hydrogel materials was also discussed in some details. Super-porous hydrogels are new materials that, regardless of their original size, rapidly swell to a large size. Different generations of SPHs developed to address the needs for certain applications.Based on the literature survey, it can be concluded that the specific requirements of advanced drug delivery could easily be met by hydrogels. Wide array of methods for the synthesis of these novel biomaterials has extended its application from drug delivery system to tissue engineering scaffolds, wound dressing material, bioseparators, gene delivery device and biosensors etc. Further delve into the fundamentals of multi-polymer based hydrogel and their properties, may give raise a novel approach for using the biomaterials in the biomedical field in a better way.

REFERENCES

1. Hydrogels: Methods of Preparation, Characterisation and Applications; Syed K. H. Gulrez, Saphwan Al-Assaf and Glyn O Phillips; Glyn O Phillips Hydrocolloids Research Centre, Glyndwr University, Wrexham, United Kingdom.
2. ISSN- 0975-1491; Vol 5, Issue 3, 2013; Review Article: "PREPARATION METHODS AND PROPERTIES OF HYDROGEL: A REVIEW", Nilimanka Das; Regional Institute of Pharmaceutical Science & Technology, Abhoynagar, Agartala 799 005, Tripura, India.
3. What are Hydrogels?; George A. Paleos, Pittsburgh Plastics Manufacturing, Butler, PA.
4. Polymer Hydrogels: Unique Material for Bioseparations, Biosensing and Drug Delivery; Dr. Aruna Nadarajah; January 30, 2009, Nitschke Auditorium, Department of Bioengineering University of Toledo, Toledo, Ohio.
5. Review article: Hydrogel microparticles for biosensing; Gaelle C. Le Goff , Rathi L. Srinivas, W. Adam Hill, Patrick S. Doyle; Novartis Institutes for Biomedical Research, 250 Massachusetts Avenue, Cambridge, MA 02139, USA; Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA.
6. Hydrogel Membranes For Bio-Separations: A Thesis; submitted to the University of Pune for the degree of doctor of Philosophy (In

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IARJSET

International Advanced Research Journal in Science, Engineering and Technology

AGNI-PANKH 16

Jawaharlal Darda Institute of Engineering and Technology, Yavatmal

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Chemistry); Shubhangi G. Gholap; April, 2005, Polymer Science & Engineering Division; National Chemical Laboratory (NCL) Pune – 411008, India.

7. Journal of Biomaterials and Nanobiotechnology, 2012, 3, 185-199; Published Online April 2012: Modular Hydrogels for Drug Delivery Susana Simões, Ana Figueiras, Francisco Veiga; Laboratory of Pharmaceutical Technology, University of Coimbra, Coimbra, Portugal; Pharmaceutical Studies Center (CEF), University of Coimbra, Coimbra, Portugal; Health Sciences Center (CICS), Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal.
8. "HYDROGELS AS A DRUG DELIVERY SYSTEM AND APPLICATIONS: A REVIEW"; Prashant P. Palshetti, Vivek V. Rajendra, Deepashree N. Dixit, Pranav P. Parekh; ISSN- 0975-1491; Vol 4; Issue 1, 2012; Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Rouza Bagh, Aurangabad 431001, Maharashtra, India, JSPM's Jayawantrao Sawant College of pharmacy and Research Hadapsar, Pune 411028.
9. Matsuyama, H.; Tamura, T.; Kitamura, Y. Separation and Purification Technology 1999, 16, 181.
10. Gaharwar, A.K.; Peppas, N.A.; Khademhosseini, A. Nanocomposite hydrogels for biomedical applications. Biotechnol. Bioeng. 2014, 111, 441–453.