European Polymer Journal 72 (2015) 341–343

Contents lists available at ScienceDirect

European Polymer Journal

journal homepage: www.elsevier.com/locate/europolj

Editorial items

The past, present and future of hydrogels

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ARTICLE INFO

Article history:
Received 9 July 2015
Received in revised form 25 August 2015
Accepted 29 August 2015
Available online 29 August 2015

Keywords:
Hydrogel
Drug delivery
Tissue engineering
Self-healing

ABSTRACT

An overview of developments in the field of hydrogels is provided. The gradual increase in functionality and in complexity of hydrogels is highlighted in the light of the Special Issue on hydrogels. This contribution provides a concise overview of the majority of contributions to this Special Issue and aims to link it to historical developments in the field.

Hydrogels, a unique class of soft materials, consist of hydrophilic polymer networks that retain large amounts of water. These materials form 3D networks of polymer chains linked by either physical interactions or chemical bonds, and are often classified as physical or chemical gels, respectively. Physical interactions commonly include hydrophobic, hydrogen bonding and metal ion-ligand interactions, while chemically cross-linked hydrogels result from a broad spectrum of chemical reactions [1]. Over the past few decades, researchers made significant progress in developing hydrogels with greater sophistication and complexity to meet the demand for a wide range of applications. This is in contrast to the early days of hydrogel synthesis that used rather straightforward chemistry to crosslink hydrophilic polymers in the design of, for example, contact lenses [2]. Increasing demands on the properties and functionalities of such materials led to the development and design of new synthetic strategies. It provided the production of advanced materials that will be discussed later in this contribution. Two properties of hydrogels recognized early in their history are their soft nature and high water content, making them especially interesting for biomedical applications. In recent years, much emphasis of hydrogels is in the fields of drug delivery and tissue engineering [3].

The main reason for the popularity of hydrogels in biomedical applications is their bio-friendly nature, *i.e.* the function of biomolecules and cells is not impaired, even if they are encapsulated or otherwise in direct contact with the hydrogel. Looking at the two main biomedical application fields in more detail, we observe that the drug delivery field is increasingly moving toward micro- and nanosized designer hydrogel particles [4], while for tissue regeneration, mainly bulk hydrogels are being processed into well-defined 3D structures using state of the art techniques [5]. In order to facilitate the processing of hydrogels into defined shapes that retain their structure, the choice of polymer and cross-linking methods are receiving a lot of attention and many applications benefit from what are often called "smart" polymer properties. These "smart" polymers can respond to external triggers, such as changes in pH, temperature [6] or redox potential [7], resulting in *e.g.* reversible swelling and deswelling.

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http://dx.doi.org/10.1016/j.eurpolymj.2015.08.032
0014-3057/

Another property that is receiving significant attention in materials science in a general sense is self-healing. This concept has been implemented in traditional materials like metals and concrete [8], but also in polymers and composites [8a,9]. In recent years the concept of self-healing has been implemented in hydrogels [10].

From a biomaterials point of view, natural polymers, such as polysaccharides and protein-based polymers have gained interest due to their inherent advantageous properties regarding cell interactions. Especially polysaccharides such as hyaluronic acid, alginate and heparin are often used and depending on the cell type used, these polymers already showed their beneficial properties for tissue regeneration. Remarkably, relatively small modifications in hydrogel formulations (such as polymer concentration and method of crosslinking) can have a huge impact on the final performance. Therefore, there is still an urgent need for novel chemistry to facilitate this development of hydrogel biomaterials that are able to closely mimic the natural extracellular matrix (ECM). It is expected that a close mimic of the ECM will be superior in the field of tissue regeneration.

As mentioned, the design of small hydrogel particles for several applications is one of the major trends in the field. Examples are the developments in micro- and nanogels for biosensing [11], drug delivery in *e.g.* the gastro-intestinal (GI) tract [12] and for influencing cell microenvironments [13], which illustrate the broad spectrum of applications. Preparation techniques for these micro- and nanosized particles have evolved rapidly over the last decade from conventional methods such as emulsion polymerization [14] toward microfluidic and lithographic processes [15]. The result is that not only uniform spherical hydrogel particles can be obtained, but also specifically designed anisotropic particles with non-spherical shapes. Doyle et al. described the current trends in preparation of these anisotropic particles, which also allow for graphical encoding with applications in biosensing [11]. A technique that deserves specific attention is the recently developed 'stop-flow lithography', which enables high scale production of hydrogel particles of any shape and introduction of so-called complex graphical codes (barcodes) with a high resolution. Especially for biosensing, these versatile hydrogel particles have distinct advantages over surface-based systems such as planar microarrays because they offer a much higher capacity for bioprobe immobilization due to their 3D porous structure.

Nowadays also high tech methods are used to precisely design internal and surface structures of hydrogel materials on a micro scale level aimed to influence cell behavior. Depending on the cell type, choices in hydrogel properties such as stiffness and porosity are crucial to obtain the desired type of regenerated tissue. For example, polysaccharide-based hydrogels have been designed to yield a favorable environment for chondrocytes or mesenchymal stem cells for cartilage tissue formation [16], while neuronal cells benefit greatly from a hydrogel biomaterial having a spatial pattern that promotes effective neuronal guidance [17]. Especially patterning techniques resulting in micro patterns within or on the surface of 3D biomaterials have shown to contribute to better cell performance for specific types of cells. Seliktar et al. describe an elegant method to prepare microchannels in different types of hydrogels by a laser controlled photoablation technique. Control over the channel diameter showed to have a pronounced effect on neuronal cell behavior, and neurite ingrowth over several millimeters distance was observed, which is a step forward toward *in vivo* axonal regeneration [17].

Overall, we expect that the current developments toward highly designed and complex hydrogel materials will continue in the near future, which in turn is expected to create new application opportunities. Especially with the use of upcoming fabrication techniques of which a few examples are highlighted in this contribution, the complexity of materials may increase with limited or no increase in production costs. To conclude, we believe that the emerging micro- and nanoscale technologies will contribute to solving outstanding problems in the biomedical field and beyond.

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