Polymer chemistry and hydrogel systems

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1. Introduction
Hydrogels are a class of polymer materials that can absorb large amounts of water without dissolving. The latter is due to physical or chemical crosslinkage of the hydrophilic polymer chains. Hydrogels can be prepared starting from monomers (A), prepolymer (B) or existing hydrophilic polymers (C).

1.1. Synthesis of hydrogels from monomers (figure 1A)
Copolymerisation of hydrophilic monomers and polyfunctional comonomers, acting as crosslinkers, leads to the formation of hydrophilic network structures. Most commonly used monomers are hydrophilic (meth)acrylates and (meth)acrylamides [1–4]. One of the first examples reported in the literature [1] was a copolymer of (2-hydroxyethyl) methacrylate (HEMA) and ethyleneglycol bismethacrylate (EGDMA). The resulting hydrogel has been used for the production of soft contact lenses and as reservoir for drug delivery. Crosslinked copolymers of acrylamide and methylene bisacrylamide are daily used to prepare gels for electrophoresis. Polymerization of vinyl monomers is most frequently initiated via radical initiators (peroxides, azo-compounds). Radicals are generated by heating, by the use of a redox initiator (e.g. ammonium persulfate + N,N’-tetramethyl ethylene diamine, TEMED) or a photoinitiator. An alternative way to initiate the radical polymerisation process is by high energy irradiation.

1.2. Synthesis of hydrogels from prepolymer (figure 1B)
Hydrogels have been prepared by crosslinkage of low molecular weight hydrophilic polymers or oligomers. One example is the reaction of α,ω-hydroxy poly(ethylene glycol) with a diisocyanate in the presence of a triol as crosslinker [5,6]. This reaction leads to the formation of crosslinked hydrophilic polyurethanes. An alternative approach is the conversion of the hydroxyl end groups of poly(ethylene glycol) into (meth)acrylate which can then be crosslinked via radical polymerisation [7].
1.3. Synthesis of hydrogels from polymers (figure 1C)

Chemical crosslinkage of hydrophilic polymers results in the formation of a hydrogel. There are numerous examples described in the literature. Well known is the preparation of stationary phases for gel filtration chromatography. As an example: Sephadex® is a network of dextran crosslinked with epichlorohydrin. Other examples are proteins crosslinked with formaldehyde, gluteraldehyde or a polyaldehyde [8,9]. Ionic polymers can be crosslinked by the addition of di- or tri-valent counterions. An example is the gelation of sodium alginate by addition of Ca\(^{2+}\)-ions (figure 2).
Other polymers like gelatine and agarose can form hydrogels upon cooling from an aqueous solution. The gelation is due to helix-formation and association of the helices, forming junction zones (figure 3).

These physically crosslinked hydrogels have a sol-gel transition temperature. Permanent crosslinkage can be achieved by subsequent chemical crosslinkage. This is described below as an approach to gelatine-based hydrogels for wound treatment applications.
2. Gelatin-based hydrogels

Vandenbulcke et al have reported on the preparation of gelatine hydrogels crosslinked with partially oxidised dextrans [10–12] (figure 4).

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\text{gelatine} + \text{dextranaldehyde} \Rightarrow
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**Figure 4.** Preparation of gelatine hydrogels crosslinked with partially oxidised dextrans.

The materials were developed with the aim to use them as wound dressing. For that purpose, growth factors were incorporated at the stage of the crosslinking. It turned out that they were partially trapped in the gelmatrix via covalent linkage. Therefore, an other approach was worked out. Gelatin was chemically modified with methacrylamide side groups which could subsequently be polymerised by radical initiators or high energy irradiation [13–15].
The methacrylamide side groups are introduced by reaction with methacrylic anhydride with the ε-amino groups of lysine residues (figure 5). The degree of modification, which can be varied by controlling the reaction conditions, determines to a large extent the mechanical properties of the resulting hydrogel. This can be demonstrated by rheological measurements. The G’-modulus for gels prepared from gelatin derivatives with different degree of substitution is shown in figure 6.

**Figure 5.** Chemical modification of gelatin with methacrylamide side groups.
Figure 6. The G’-modulus for gels prepared from gelatine derivatives with different degrees of substitution (SG).

In the experiment described above, crosslinkage was performed using water soluble photo-initiators. However, crosslinkage by electron beam and x-ray irradiation was done as well. The advantage of this method is that the gelatine derivatives are crosslinked and sterilised in one step. In order to minimize degradation of the gelatine, irradiation was performed on deaerated (oxygen-poor) solutions of the gelatine derivative.

In vitro degradation studies in presence of collagenases indicated that the rate of gel degradation, measured by the gel-fraction, decreased with increasing degree of substitution (figure 7).

Figure 7. Gel degradation decreases with increasing degree of substitution (SG).
The gelatine-based hydrogels have been tested in vitro and in vivo on their biocompatibility. No serious adverse reactions were observed. Subsequently, the hydrogels were tested for the treatment of wounds, using the pig model with full thickness wounds. The gelatine gels proved to lead to rapid re-epithelialisation and good wound repair. Finally, it was also demonstrated that biologically active compounds, like growth factors and growth factor stabilisers can be easily incorporated into the hydrogel without substantial loss of activity.

3. Conclusions

Hydrogels are an interesting class of materials that can be prepared by a variety of methods. The properties of these materials depend on their building blocks and the preparation procedures and can be largely varied.

Among the various classes of hydrogels, are the gels based of physically structuring biopolymers, like gelatine. By chemically modifying these biopolymers, hydrogels with a dual crosslinkage (physical and chemical) can be prepared.

Hydrogels serve a broad range of applications, including biomaterials, matrices for drug delivery and scaffolds for tissue engineering.

References

[1] Wichterle O and Lim D 1960 Nature 185 117–8
[2] Moynihan H 1987 Hydrogels in Medicine and Pharmacy vol. 2 ed Peppas N A (CRC Press, Boca Raton) chapter 2
[3] Kopecek J and Bazilova H 1974 Poly[N-(2-hydroxypropyl)methacrylamide]—iii : Crosslinking copolymerization Eur. Polym. J. 10 465–70
[4] Schacht E 1987 Int. Pharm. J. 1 3
[5] Van Bos M, Schacht E 1987 Acta Pharm. Technol. 33(3) 120
[6] Graham N B 1987 Hydrogels in Medicine and Pharmacy vol. 2 ed Peppas N A (CRC Press, Boca Raton) chapter 4
[7] Kelner A 2000 PhD thesis, Ghent University
[8] Schacht E, Nobels M and Vansteenkiste S 1993 Polym. Gels Netw. 1 213
[9] Schacht E, Vandenheede C, Lemahieu A, De Rooze N and Vansteenkiste S 1993 Encaps. Control. Release 18 18
[10] Schacht E, Bogdanov B, Van den Bulcke A and De Rooze N 1997 React. Funct. Polym. 33 109
[11] Bogdanov B, Schacht E and Van den Bulcke A J 1997 Thermal Anal. Calorim. 49 847
[12] Draye J P, Delay B, Van de Voorde A, Van den Bulcke A, Bogdanov B and Schacht E 1998 Biomaterials 19 99
[13] Van den Bulcke A, Bogdanov B, Schacht E, Draye J P and Delay B 1999 Proc. Int. Symp. Controlled Release Bioactive Materials 26 232
[14] Van den Bulcke A, Bogdanov B, Schacht E, Draye J B and Delay B 1999 Proc. Int. Symp. Controlled Release Bioactive Materials 26 246
[15] Van den Bulcke A, Bogdanov B, De Rooze N and Schacht E 2000 Biomacromol. 1 31