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Polymeric biomaterials and nanomedicines

Jiyuan Yang [a], Jindřich Kopeček [a, b, *]

[a] Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA
[b] Department of Bioengineering, University of Utah, Salt Lake City, UT 84112, USA

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ABSTRACT

This overview intends to demonstrate the close relationship between the design of smart biomaterials and water-soluble polymer–drug conjugates. First, the discovery and systematic studies of hydrogels based on crosslinked poly(meth)acrylic acid esters and substituted amides is described. Then, the lessons learned for the design of water-soluble polymers as drug carriers are highlighted. The current state-of-the-art in water-soluble, mainly poly[*N*-(2-hydroxypropyl)methacylamide (HPMA), polymer –drug conjugates is shown including the design of backbone degradable HPMA copolymer carriers. In the second part, the modern design of hybrid hydrogels focuses on the self-assembly of hybrid co-polymers composed from the synthetic part (backbone) and biorecognizable grafts (coiled-coil forming peptides or morpholino oligonucleotides) is shown. The research of self-assembling hydrogels inspired the invention and design of drug-free macromolecular therapeutics – a new paradigm in drug delivery where crosslinking of non-internalizating CD20 receptors results in apoptosis in vitro and in vivo. The latter is mediated by biorecognition of complementary motifs; no low molecular weight drug is needed.

1. Introduction

In this overview we intend to demonstrate the close relationship between the design of biomaterials and the design of nanomedicines as experienced in our research. One of us (JK) was a graduate student at a laboratory where hydrogels, the first rationally designed biomedical polymers, were discovered by Drahoslav Lím [1,2] and soft contact lenses designed by O. Wichterle [3] in the 1950s. These discoveries initiated biomaterial and nanomedicine research worldwide and for many remain an inspiration today.

Original hydrogels were synthesized by traditional radical copolymerization of vinyl and divinyl (crosslinker) compounds. The first hydrogels were based on hydrophilic esters of methacrylic acid – e.g. the first soft contact lenses were a copolymer of 2-hydroxyethyl methacrylate (HEMA) with ethylene dimethacrylate (EDMA). Numerous hydrogel structures followed [2] and a detailed study of the relationship between the composition of hydrogels and their biocompatibility [4] was the driving force for the design of water-soluble polymeric carriers based on *N*-substituted methacylamides and development of polymer–drug conjugates, one of the most promising nanomedicines.

Our recent hydrogel research focuses on the self-assembly of hydrogels from hybrid block or graft copolymers driven by the interaction of complementary biorecognition motifs [5]. Both peptide/protein [6,7] and oligonucleotide [8] motifs have been used in hydrogel design. For example, two distinct pentaheptad peptides (CCE and CCK) were designed to create a dimerization motif and serve as physical crosslinkers. Indeed, graft copolymers, P-CCE and P-CCK (P is the *N*-(2-hydroxypropyl)methacylamide (HPMA) backbone), self-assembled into hybrid hydrogels. The hydrogel formation was mediated by the formation of antiparallel coiled-coil CCK/CCE heterodimers [6,9]. This research was the motivation for the design of "drug-free macromolecular therapeutics" [10]. Formation of coiled-coil heterodimers at B-cell surface resulted in the crosslinking of CD20 (non-internalizating) receptors and initiation of apoptosis [10,11].

The above two examples indicate the close relationship between biomaterials research and the design of nanomedicines. In this report we shall try to make this connection more clear.

* Corresponding author. Center for Controlled Chemical Delivery, 20 S 2030 E, BPRB 205B, University of Utah, Salt Lake City, UT 84112-9452, USA.
E-mail address: jindrich.kopecek@utah.edu (J. Kopeček).

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2. Traditional hydrogels and water-soluble polymeric drug carriers

2.1. Discovery, early research and clinical applications of hydrogels

Hydrogels were systemically studied by Lím and Wichterle in the 1950s in Prague. They have chosen methacroylated derivatives because the structure of the polymer reflects a pivalic (trimethylacetic) acid structure. The latter is stable to pure hydrolysis and no similar structure in the nature was known, making enzyme-catalyzed hydrolysis less probable [12]. After trying the methacroylated polyvinyl alcohol and partially substituted mannit [13], Lím hit the jackpot when he left the transesterification of methyl methacrylate with triethylene glycol overnight in the middle of the work-up; he added water to separate the triethylene glycol dimethacrylate layer from water soluble components. However, during night the water layer turned into a clear hydrogel. Obviously it was a copolymer of triethylene glycol monomethacrylate and triethylene glycol dimethacrylate [12]. A detailed evaluation of similar crosslinked copolymers from monoglycol and diglycol led to the selection of monoglycol (copolymer of HEMA and EDMA) for the synthesis of first soft contact lenses [1,14].

Parallel with the development of soft contact lenses other medical applications commenced – glaucoma microcapillary drains [15], augmentation of vocal cords [16], restoration of detached retina [17], preventing scar formation after surgery [18], and covering for perforated ear drums [19]. There are numerous excellent reviews that describe the early work on hydrogels [2,14,20–24].

2.1.1. Structure–biocompatibility relationship

Healing-in of hydrogel implants depends on the chemical structure, physical structure (porosity), and surface microarchitecture of hydrogels [25]. A systematic study of the biocompatibility of hydrogels based on esters and/or *N*-substituted amides of (meth)acrylic acid revealed no significant differences in the healing-in of hydrogels of different chemical compositions [4,26–29]. In contrast, significant differences have been observed for hydrogels with different porosity [30,31].

Hydrogels prepared by crosslinking copolymerization of HEMA with EDMA are an excellent model for the study of the relationship between porosity and biocompatibility. Due to the fact, that the interaction parameter (χ) polymer-water for this system is 0.7–0.8 (depending on crosslinking density) [32], phase separation may occur during copolymerization, which depends on the amount of water in the feed. Manipulating the water to monomer ratio in the feed permits the formation of homogeneous (transparent) hydrogels (<50% water in the feed), microporous hydrogels (pores are not interconnected; 50–70% water in the feed), and macroporous spongy hydrogels with interconnecting channels (>70% water in the feed) [31]. Thus, the biocompatibility of hydrogels with identical chemical structure, but differing in porosity could be evaluated [30,31]. The implantation of both homogeneous and heterogeneous hydrogels resulted in fibrous capsule formation. However, following implantation of porous hydrogels, in contrast to homogeneous hydrogels, newly formed blood capillaries and an eosinophil containing exudate penetrated into the implant. The intensity and the area of penetration were greater with higher hydrogel porosity [30,31]. An investigation of calcium deposits using von Kóssa staining revealed the dependence of the extent and localization of calcium deposits on porosity. There was only sporadic calcification in the margin of the implant following implantation of homogeneous or microporous hydrogels; however, with an increase in porosity, calcification occurred. The site of the deposition moved from the margin of the implant toward its center with increasing porosity [31]. Early studies on the biocompatibility of hydrogels have been summarized in ref. [4].

These results were corroborated in clinical settings. Implantation of homogeneous HEMA-based hydrogels to treat nasal malformation resulted in minor calcification at the margin of the implant (about 50% of patients evaluated after 3–10 years). Apparently, with scalpel damaged surface (due to surgeons modifying the size of the hydrogel implants in the operation room) connective tissue accumulated and initiated calcium deposition. Minor calcium deposition did not affect the biocompatibility or the final cosmetic effect (Fig. 1) [33,34].

2.1.2. Stimuli-sensitive hydrogels

Stimuli-sensitive polymers exhibit sharp changes in behavior in response to an external stimulus, such as pH, temperature, solvents, salts, electrical field, and chemical or biochemical agents. Such polymers may be used in numerous applications, including phase separations, affinity precipitations, bioactive surfaces, permeation switches, bioreactors, medical diagnostics, and drug delivery systems [35].

Upon a change in the environment, hydrogels swell or collapse. Environmentally induced changes in the transport properties of pH-sensitive hydrogels [36,37] or temperature-sensitive hydrogels [38] were studied several decades ago. Dušek and Paterson [39] predicted that changes in external conditions might result in abrupt changes of the hydrogel degree of swelling (phase transition). Tanaka et al. [40] and others [41,42] have verified the theory by experimental observations.

The majority of temperature-sensitive polymer hydrogels have an LCST, i.e., the gels collapse as the temperature increases. The process is thought being driven by entropy, which is supported by the observation that LCST transitions are endothermic. One widely accepted mechanism is based on disruption and re-establishment of a balance between hydrophobic and electrostatic interactions. Below the LCST, water molecules form hydrogen bonds with polar groups on the polymer backbone and organize around hydrophobic groups as iceberg water. As temperature increases past LCST, bound water molecules are released to the bulk with a large gain in entropy, resulting in the collapse of the polymer network [43].

Incorporation of enzyme-degradable peptide sequences [44] as crosslinks renders the hydrogels enzymatically degradable.

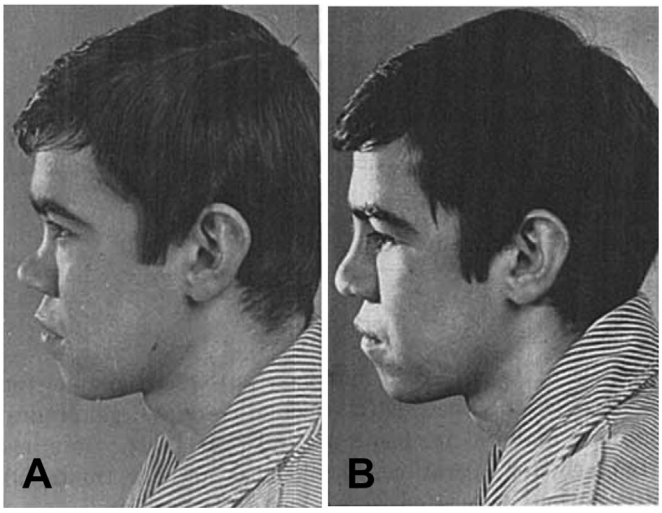

Fig. 1. The use of HEMA-based hydrogels (copolymers of HEMA with EDMA) in rhinoplasty. A) Patient before surgery; B) Patient after surgery. Reprinted from reference [33] with permission.