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Hydrogels for delivery of bioactive agents: A historical perspective ☆

Sang Cheon Lee [a], Il Keun Kwon [a], Kinam Park [a,b,c,*]

[a] Kyung Hee University, School of Dentistry, Department of Maxillofacial Biomedical Engineering and Institute of Oral Biology, Seoul, Republic of Korea
[b] Purdue University, Departments of Biomedical Engineering, West Lafayette, IN, USA
[c] Purdue University, Department of Pharmaceutics, West Lafayette, IN, USA

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ABSTRACT

Since 1960 when the history of modern hydrogels began significant progress has been made in the field of controlled drug delivery. In particular, recent advances in the so-called smart hydrogels have made it possible to design highly sophisticated formulations, e.g., self-regulated drug delivery systems. Despite intensive efforts, clinical applications of smart hydrogels have been limited. Smart hydrogels need to be even smarter to execute functions necessary for achieving desired clinical functions. It is necessary to develop novel hydrogels that meet the requirements of the intended, specific applications, rather than finding applications of newly developed hydrogels. Furthermore, developing smarter hydrogels that can mimic natural systems is necessary, but the fundamental differences between natural and synthetic systems need to be understood. Such understanding will allow us to develop novel hydrogels with the new, multiple functions that we are looking for.

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1. Research on hydrogels

The number of references published under the research topic of "hydrogel" has increased exponentially during the last decade. According to SciFinder®, the first reference on hydrogel appeared in 1894. Although the hydrogels described during that time period was a colloidal gel of inorganic salts, which are not exactly the same type of hydrogels we are dealing with nowadays, the use of the word "hydrogel" in as early as 1894 is very interesting. Since then, the term "hydrogel" was used to describe a 3-dimensional network of hydrophilic natural polymers and gums, in which the network is formed chemically or physically. The hydrogel of current understanding for biological use was first developed by Wichterle and Lim in 1960 [1]. Although the usefulness of hydrogels in biomedical applications was recognized, the number of publications on hydrogels was still under 100/year until 1974. As shown in Fig. 1A, the number of references on hydrogel took off in the middle of 1970s and grew exponentially 20 years later. Since 2000, the yearly publication surpassed 1000, and the number is close to 5000 for the last two years. Fig. 1B describes relative numbers of publications under the topics of "drug delivery," "nanotechnology," and "smart hydrogels". The "drug delivery" term was further refined into "protein" and "gene" for estimating the relative research efforts on protein delivery and gene delivery. As shown in Fig. 1B, the number of publications on smart hydrogels is about the same as that of gene delivery. On the other hand, research on protein delivery has been much more active due to the longer history of protein drugs resulting from advances in genetic engineering. The number of references on nanotechnology skyrocketed from the middle of 2000s, reflecting the research trend in the last decade.

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* Corresponding author at: Purdue University, Departments of Biomedical Engineering and Pharmaceutics, 206 S. Martin Jischke Drive, West Lafayette, IN 47907, USA. Tel.: +1 765 494 7759.
E-mail address: kpark@purdue.edu (K. Park).

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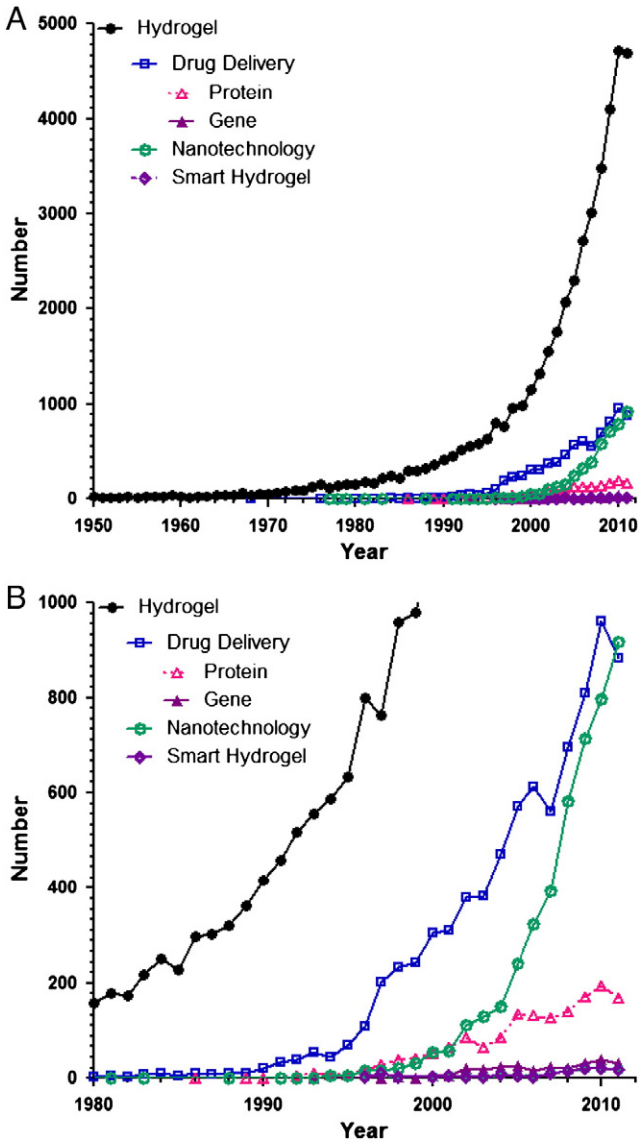

Fig. 1. The number of references published under the research topic of "hydrogel" in SciFinder®. The total number of papers on hydrogel from 1950 to 2011 is 43,764. Of these, 8554 references were on the topic of drug delivery. In the drug delivery topic, the search for subtopics on protein and gene resulted in 1674 and 284 references, respectively. Of the 43,764 hydrogel references, the search for topics on nanotechnology and smart hydrogels resulted in 1246 and 130 references, respectively.

2. Hydrogels for drug delivery

Analysis of the references on drug delivery by the index terms resulted in more than 1000 different terms. The most widely used index terms include pharmaceutical hydrogels, dissolution, physical swelling, and controlled release. Despite a large number of references related to hydrogel-based drug delivery systems, however, the actual number of hydrogel-based drug delivery systems or devices approved by the Food and Drug Administration (FDA) is extremely small. The clinically used hydrogel-based drug delivery systems or devices are mostly for contact lenses, intraocular lenses, wound dressing, surgical tissue sealant, anti-adhesive of tissues, hydrogel tissue expander, and transdermal patch containing hydrogels for drug delivery.

Research on hydrogels for drug delivery has been focused on developing advanced drug delivery systems, such as self-regulated insulin delivery systems and artificial pancreas. These systems are based on the so-called smart hydrogels which respond to a minute change in environmental conditions with a large change in physicochemical properties, degradation, sol–gel phase transition, and shape transformation [2]. In comparison with smart hydrogels, ordinary hydrogels undergo only the swelling–deswelling process depending on the availability of water in the environment. It is the additional properties over the basic swelling–deswelling property that makes a hydrogel smart. The environmental factors, also referred to as external stimuli, can be physical (temperature, electricity, magnetic field, ultrasound, and pressure), chemical (pH, ion type, ionic strength, and solvent) and biological (enzyme, antibody, and glucose).

Applications of smart hydrogels have been divided into four broad areas, such as drug delivery, bioseparation, biosensor, and tissue engineering. Here we focus on drug delivery. As pointed out above, we need to understand the reasons for the lower number of hydrogel products that are in clinical use, despite the rather extensive research activities. We need to ask ourselves why we do what we do, i.e., why do we do research on hydrogels? There may be various valid answers, and research on hydrogels does not always have to lead to clinically useful products, as long as scientific advances are made. But, one of the ultimate goals of researchers in the drug delivery field is to provide new drug delivery systems or devices treating diseases and helping patients. In this sense, it is time to examine why translational research has not been as successful as expected.

Hydrogel properties need to be optimized for developing advanced drug delivery systems. The properties to be optimized are safety, biodegradability, drug loading capacity, and control on drug release kinetics. The safety of any materials is the first concern that has to be answered. Unless a hydrogel material has been used for extended periods of time without any serious side effect, its safety has to be proven before clinical use. This is not a trivial matter, and for this reason, hydrogel materials that have been previously used in FDA-approved products are widely chosen. For implantable devices, biodegradable hydrogels are preferred because it does not require surgical removal. For example, histrelin hydrogel implant, which is implanted just under the skin of children's inner upper arm to release luteinizing hormone-releasing hormone (LHRH) for a year, requires surgical removal [3]. It is made of the same material as a soft contact lens, which does not degrade, and thus, it has to be removed after a year by a surgical procedure.

Controlling drug loading and subsequent release is also critical for intended applications. For implantable drug delivery systems, sustained drug release for months, is required. Yet, most hydrogel formulations cannot release a loaded drug for such a long period of time. This is mainly due to the nature of hydrogels which swell in the presence of water, resulting in fast drug release. Many papers on smart hydrogels have been published [4–7]. Smart hydrogel drug delivery systems include enzyme-sensitive hydrogel nanoparticles, magnetic hydrogels, drug-sensitive hydrogels, and hydrogels for dual protein delivery. The duration of drug release in most studies is usually limited to a few days maximum. For practical applications the duration of drug delivery needs to be much longer, especially when the hydrogel system is to be implanted. The point of using smart hydrogels is not just to make a new, unique formulation. Rather, it should be to make better formulations than the existing ones in their functions and properties, e.g., release for extended periods of time with controllable release kinetics or self-regulated release.

3. Self-regulated drug delivery systems

One of the holy grails of controlled drug delivery is self-regulated insulin delivery systems. Insulin delivery is not like any other drug delivery where a sustained, long-term release can achieve an intended goal. Insulin release has to occur at the right time in the right amount. Insulin delivery starts with measuring the glucose concentration in the blood or in an environment in equilibrium with that of the blood. Once the glucose level increases, the right amount of insulin has to be released to lower the glucose concentration. Once the