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Cover Story

Collective progress in drug delivery

1. Beginning of the Journal of Controlled Release

Since September 1984, the Journal of Controlled Release (JCR) has published 300 issues as of April 2019. The 300th issue is a momentous one celebrating the roles that JCR has played over the last 35 years in the drug delivery field. The first sustained release formulations were 12-hour oral formulations based on the Spansule® technology by Smith Kline & French in 1952 [1]. The new controlled release formulations developed for the next 30 years changed the pharmaceutical industry through a very large number of oral and transdermal drug delivery systems, and most of the drug release mechanisms were developed during the same time period. JCR has documented the progress of the drug delivery field from 1984, and its published research papers have become diaries of the drug delivery researchers.

Many scientists in different disciplines worked on the controlled release of active agents for agricultural, veterinary, and human applications, and they organized the first annual symposium on the topic in 1973. Shortly after, the Controlled Release Society (CRS) was established in 1978. Recognizing the need to have a forum to share the advances in the controlled drug delivery field, leading scientists at the time agreed on starting a new journal specializing in the drug delivery technology. JCR, as the official journal of the CRS, published its first issue in September 1984. The founding editors of JCR were Jorge Heller and Jan Feijen, two of the most respected and liked scientists in the drug delivery field at the time. In their first editorial, Jorge and Jan indicated that their goal was to make JCR the leading forum for high quality manuscripts dealing with controlled release and related subjects [2]. Indeed, JCR has become a journal that we are all genuinely proud of, as a result of authors who have submitted their highest quality research findings, reviewers who have provided critical, yet constructive comments strengthening the manuscripts, and the editors. Nicholas Peppas served as Book Review Editor from the first issue, and David Friend joined as Associate Editor in 1989. In 1998, Colin Pitt succeeded the Editor-in-Chief position, and other editors joined the team, including Tsuneji Nagai, Kozo Takayama, Kazunori Kataoka, Wim Hennink, Vladmir Torchilin, Lisa Brannon-Peppas, and Ronald Siegel. The current Editor-in-Chief succeeded Colin Pitt in 2005 with the most capable editorial team, including Thomas Kissel, Stefaan De Smedt, Jean-Christophe Leroux, Dan Peer, Twan Lammers, Paolo Caliceti, Steven Schwendeman, You Han Bae, Samir Mitragotri, Ick Chan Kwon, Hideyoshi Harashima, Akihiko Kikuchi, Yu-Kyoung Oh, Vladmir Torchilin, Wim Hennink, and Justin Hanes. The success of JCR is also due to huge support from the publishers over the years, Kim Briggs, Jaap van Harten, Maarten van Twisk, and Fernanda Ogochi.

JCR publishes research articles, review articles, concept papers, and perspectives. It has also published special issues based on annual meetings around the world, including the International Symposium on Recent Advances in Drug Delivery Systems (held in Salt Lake City, UT), the European Symposium on Controlled Drug Delivery (held in the Netherlands), the Symposium on Innovative Polymers for Controlled Delivery (held in Suzhou, China), and the International Nanomedicine and Drug Delivery Symposium (held in different cities in the U.S.A.). JCR has also been publishing a cover story for each issue since 2008. Each cover story highlights a selected article for its importance, usefulness, and implication for future research. A total of 215 cover stories have been highlighted as of March 2019.

2. The Year 1984

The year 1984 presents a number of reference events that can be compared with similar events in 2019 to appreciate the progress made during the last 35 years. On January 22, 1984 at the Super Bowl XVIII the Los Angeles Raiders defeated the Washington Redskins by 29-point margin, 38-9. During the Super Bowl, Apple introduced the first Macintosh computer with the now famous commercial featuring “Big Brother” of George Orwell’s 1984 [3]. The Apple Macintosh, as its predecessor the Apple Lisa, copied the mouse-driven computer with a graphical user interface from the Xerox Alto computer developed at Xerox Palo Alto Research Center in 1972 [4]. The original Macintosh 128K (for 128 KB RAM) consisted of a black & white, 9-inch (23 cm) cathode ray tube monitor with a keyboard and a mouse. Its initial price was $2,500 which is equivalent to $6,000 in 2019. In 2019, an Apple MacBook Pro has 32 GB RAM at the price of $3,400. This is a 250,000 times increase in RAM capacity at approximately half the cost. Wide distribution of personal computers has also boosted the formation of the World Wide Web at an unprecedented rate. The advance in speed and capacity of a computer over the years are quite stunning. The impact of the World Wide Web since its inception in 1989 in our daily life is immeasurable.

One of the most consequential events in 1984 relevant to the drug delivery field is the Drug Price Competition and Patent Term Restoration Act of 1984 [5], also known as the Hatch-Waxman Amendments [6]. It authorizes applicants to submit an abbreviated new drug application (ANDA), i.e., generic versions of brand-name drugs, without repeating the extensive clinical studies to prove the safety and effectiveness of the brand-name drugs [7]. As a result, the Hatch-Waxman Act of 1984 has propelled a prosperous generic drug industry [8]. Various generic products, mostly oral formulations, were produced partly due to the improved understanding of drug release mechanisms, providing generic formulations with the drug release kinetics matching that of the brand name products. The year 1984 is also memorable for the war on illicit drugs by First Lady Nancy Regan with her “Just Say No” campaign. In 1984, it was the crack cocaine epidemic that had devastating effects by causing the increase in addiction, death, and

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Table 1
Examples of the number of articles for each topic published in the September issues of JCR from 1984 to 2018.

Topic	1984	1989	1994	1999	2004	2009	2014	2018
Pinocytosis	1							
Monoclonal antibodies		1						
Bioactive glass			1					
Emulsion				1				
Intravaginal ring				1				
Local delivery				1				
Membranes, microporous				1				
Protein, diffusion				1				
Collagen					1			
Dendrimers					1			
Diffusion					1			
Intracellular delivery					1			
Particle, porous, silica					1			
Superporous hydrogels					1			
Poorly-soluble drugs					1			
Endosomal escape						1		
Polyplexes						1		
Tissue engineering							1	
Electrochemotherapy								1
Blood-brain barrier		1						1
Injectable depot, suspension			1		1			
Vaccination, transdermal, pulmonary						2		
Oral delivery, insulin, gases							2	
Microneedle								2
Prodrugs								2
PEGylation		1		1		1		
Hydrogels, hydrophilic matrix, depot			2				1	
Smart polymers, pulsatile drug delivery						1		2
Intranasal delivery							1	2
Transdermal delivery, iontophoretic., antibodies							1	2
Polymer micelles							2	1
Transfection vectors								3
Biodegradable polymers (enzymatic, erodible)	2	1	1					
Bioadehesion / mucoadhesion			2	2				
Liposomes					1			3
Insulin, Self-regulated insulin delivery, oral	3						1	1
Microencapsulation, microspheres, micro implants			2	2	2		1	1
Polymer-drug conjugates	2	6	1		1			
Targeted drug delivery		1				1	1	9
Nanoparticles, nanocarriers, nanomaterials					1	3	6	15

drug-related crimes [9]. In 2019, it is the opioid overdose epidemic resulting in more than 50,000 deaths annually, caused by the prescription opioid drugs as well as highly potent opioids from illicit sources [10].

3. 1984 - 2019

As the above examples show, the technological advances, such as computers and the World Wide Web, have been breathtaking, but the advances in the drug delivery field have been only tantalizing. This is mostly due to an incomplete understanding of our own body, making it difficult to design drug delivery systems that can overcome the body's responses. The research topics published in JCR have changed over the years, and this may be due to a variety of reasons, such as changes in research interests, importance, or funding availability. In addition, introduction of new technologies may have enabled us to focus on certain research topics. There is no easy way of examining the changes in research topics published in JCR since 1984 until today. The changes in research topics have been reviewed by checking the topics published in JCR since September 1984 every five years. The topics in those issues are summarized in Table 1. As shown, a variety of topics in the drug delivery field have been studied, but Table 1 makes it clear that a few research topics transcend the time. Microencapsulation is still a very important topic, and the research on polymer-drug conjugates has evolved into targeted drug delivery nanomedicine formulations. The two most popular topics in drug delivery turn out to be nanocarriers and tumor-targeted drug delivery. This general trend is not limited to JCR, and many leading journals have published numerous articles on these topics.

The goal of drug delivery research is to develop formulations that treat diseases and alleviate symptoms associated with the diseases. Unfortunately, however, the large number of research publications have not been translated into clinical products. In an effort to improve the process of translating scientific discoveries into new drugs, diagnostics, and devices, the National Institute of Health (NIH) established the National Center for Advancing Translational Sciences (NCATS) [11]. NCATS has recognized that there are common barriers in translational research that can delay the development of new interventions for patients in need, and has initiated many programs designed to turn observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public [12]. The focus on translational aspect is necessary and important, as the end points of most academic research are limited to publication of research articles, falling well short of developing products for clinical use. The perception on the basic research in drug delivery needs to be modified, as the ultimate goal of the basic research is translational research. This requires changes in the promotion system in academia, the evaluation system in funding agencies, and the review system in scientific journals.

4. 2019 and beyond

"Is this the real life?
Is this just fantasy?
Caught in a landslide.

No escape from reality.
Open your eyes.
Look up to the skies and see."
(Bohemian Rhapsody by Queen).

The future is uncertain. We must train the next generation of scientists for the uncertain future to solve problems that have no easy answer, to learn failure is a part of progress, to keep learning and innovating, to diversify our efforts to limit the damage of uncertainty, and to keep an open mind and empathize with different viewpoints [13]. Scientists should be able to navigate the risks and rewards, build the ability to shift resources and focuses to a completely unexpected direction, continue relentless improvements by challenging paradigms, and mix ideas to enrich humanity [14]. History shows that people give their best when their best is required of them [15]. That day is here now. Human beings have evolved to use their natural ingenuity to create the tools they need to survive [15]. The survival of the drug delivery field requires that we accelerate translational research by building better systems. Concepts, ideas, and potentials in research articles are just the first step. It is the execution that makes the real difference. The drug delivery field needs more implementations in clinical applications.

In his book "The Four Agreements: A Practical Guide to Personal Freedom", Don Miguel Ruiz describes how we can see the world beyond our filters of our own beliefs or attachments [16]. The four agreements are: be impeccable with your word; don't take anything personally; don't make assumptions; and always do your best. Practicing these agreements in our daily life makes us stronger. They are also applicable to our professional life of doing science. Our publication is our word. Let's speak with integrity and say only what we mean based on objective data. When we take nothing personally, a huge amount of freedom comes to us. We should not make any assumptions about what others are thinking or doing, and find the courage to ask difficult questions and to express what we really think even if it is very different from the majority. We will move closer to the truth by seeking evidence to the contrary [17]. As long as we always do our best under any circumstance, what we do collectively will make amazing progress. JCR will continue to be the leading forum for all drug delivery scientists to publish their impeccable research articles, and the editors of the JCR promise to do their best in handling all manuscripts with utmost fairness.

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