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Perspective Review

Controlled drug delivery systems: Past forward and future back

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ABSTRACT

Controlled drug delivery technology has progressed over the last six decades. This progression began in 1952 with the introduction of the first sustained release formulation. The 1st generation of drug delivery (1950–1980) focused on developing oral and transdermal sustained release systems and establishing controlled drug release mechanisms. The 2nd generation (1980–2010) was dedicated to the development of zero-order release systems, self-regulated drug delivery systems, long-term depot formulations, and nanotechnology-based delivery systems. The latter part of the 2nd generation was largely focused on studying nanoparticle formulations. The Journal of Controlled Release (JCR) has played a pivotal role in the 2nd generation of drug delivery technologies, and it will continue playing a leading role in the next generation. The best path towards a productive 3rd generation of drug delivery technology requires an honest, open dialog without any preconceived ideas of the past. The drug delivery field needs to take a bold approach to designing future drug delivery formulations primarily based on today's necessities, to produce the necessary innovations. The JCR provides a forum for sharing the new ideas that will shape the 3rd generation of drug delivery technology.

1. Historical perspective

The first issue of the Journal of Controlled Release (JCR) was published in 1984. As clearly stated in the first editorial by Jorge Heller and Jan Feijen, the two founding editors, JCR was designed to serve as the leading forum for drug delivery scientists to exchange ideas through high quality manuscripts [1]. Since then, the JCR has grown to be one of the most influential journals in the pharmaceutics and drug delivery fields. The key to the success of the JCR has been its emphasis on high quality research, and this tradition continued with Colin G. Pitt, who succeeded the Founding Editors in 1996 and served as the Editor-in-Chief until 2005. The passion and dedication of these three editors during the first two decades have been essential in establishing the foundation for the journal to grow as a forum to publish new information in drug delivery.

The number of publications has gradually increased over the years, as shown in Fig. 1. The JCR receives substantially more manuscripts than it publishes. The primary criteria for publication in the JCR are the quality and novelty of the research presented in the submitted manuscripts. One parameter in measuring a journal's influence on the field is the impact factor, and the JCR impact factor has increased over the years. In 2013, the impact factor reached above 7, placing the JCR at the top of the research journals in the pharmaceutics and drug delivery fields. The success of the JCR would not have been possible without the loyalty of the authors, the dedication of the reviewers, and the diligence of all editors over the past 30 years.

The contribution of the JCR to the drug delivery field is best understood by examining the history of controlled drug delivery technologies. Table 1 describes the three generations of drug delivery. The first controlled release formulation was introduced by Smith Kline & French in 1952 for 12-hour delivery of dextroamphetamine (Dexedrine) [2,3]. From that point until the end of the 1970s, the basic understanding of controlled drug delivery was established, such as different drug release mechanisms including dissolution-, diffusion-, osmosis-, and ion exchange-based mechanisms. The technologies developed during the 1st generation were used to develop numerous twice-a-day and once-a-day oral delivery systems. The same drug release mechanisms were also used to develop once-a-day and once-a-week transdermal patches. The JCR was launched at the beginning of the 2nd generation of controlled drug delivery technologies. At the time, the research efforts were focused on developing zero-order delivery systems. It was thought that delivery systems with zero-order release kinetics would be superior because they maintain a steady drug concentration in the blood (as illustrated in Fig. 2), and the common thinking was “the flatter the better”. After a decade of extensive efforts, it was realized that zero-order delivery was not completely necessary to develop sustained drug delivery systems. First, zero-order release does not result in maintenance of a constant drug concentration in the blood. This is particularly obvious for oral delivery systems. Because of the ever decreasing drug absorption properties as the formulation moves down from the upper small intestine to the large intestine, the drug concentration reaches a peak and then slowly decreases. Second, maintaining a constant drug concentration in the blood is not necessarily required for most drugs because the drug efficacy remains

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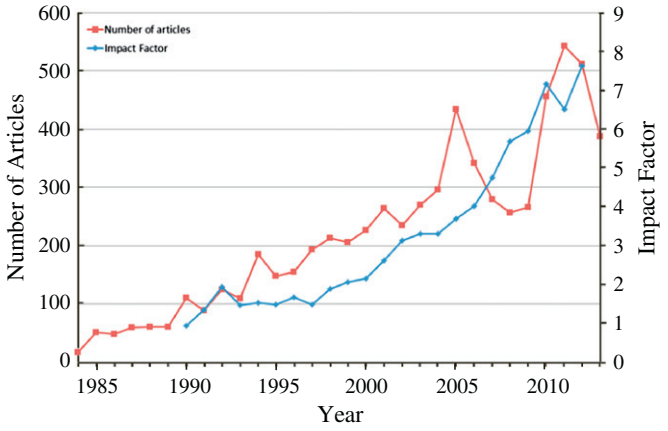

Fig. 1. The number of articles published annually in the JCR since 1984.

Table 1
Evolution of controlled drug delivery systems since 1950.

Year	1950	1980	2010	2040
	1st Generation	2nd Generation	3rd Generation	
	Basics of controlled release	Smart delivery systems	Modulated delivery systems	
	Oral delivery Twice-a-day or once-a-day	Zero-order release Zero vs first-order release	On-off insulin release Glucose-sensitive release	
	Transdermal delivery Once-a-day, once-a-week	Smart polymers & hydrogels Environment-sensitive Self-regulated release	Targeted delivery Anticancer drugs, siRNA	
	Drug release mechanisms Dissolution, diffusion, osmosis, and ion-exchange	Peptide & protein delivery Biodegradable depot	Long-term delivery systems 6–12 months with the minimal initial burst effect	
		Nanoparticles Tumor-targeted delivery Gene delivery	In vitro-In vivo correlation Prediction of PK profiles from in vitro release study	

the same as long as the drug concentration is above the minimum effective level and below the maximum safe concentration (Fig. 2). For some drugs, such as nitroglycerin, pituitary gland hormones, and insulin, a constant blood level may not even be desired. It took a decade to understand this simple and intuitive fact, but it allowed increased flexibility in the design of future drug delivery systems.

During the 2nd generation, many other drug delivery technologies were developed. The so-called "smart" polymers and hydrogels were developed to make delivery systems that are triggered by changes in environmental factors, such as pH, temperature, or glucose levels. Biodegradable microparticles, solid implants, and *in situ* gel-forming implants were used to deliver peptides and proteins over month-long periods. Zoladex® Depot was the first implant that was introduced in 1989 to deliver goserelin acetate over a 1 to 3 month period. Since then, fewer than 10 clinical products were introduced that deliver other peptides and proteins, indicating the difficulties associated with product development. The last decade of the 2nd generation was dedicated to the development of nanotechnology-based drug delivery systems. The JCR has been at the center of shaping the 2nd generation of drug delivery technologies. The 3rd generation of drug delivery is yet to be established, and thus, the technologies listed in Table 1 are predictions. For the 3rd generation of drug delivery to be beneficial, however, it should address and overcome the hurdles associated with the current drug delivery systems listed in Table 1.

2. The 2nd generation of drug delivery research

During the last 30 years, numerous articles on various topics relating to all aspects of drug delivery science have been published. Because of the complexity and interdependence of the topics, it is difficult to categorize the published articles, e.g., based on the drug release mechanisms, drug types, polymers, or drug delivery routes. Such classification may be useful in understanding the trend in drug delivery research over time, but a large number of articles with numerous variations in formulations and applications make this task difficult. The ultimate goal of drug delivery research is to develop formulations that can be used in clinical applications to treat various diseases; therefore, drug delivery research can be cataloged as shown in Fig. 3.

The outline presented in Fig. 3 provides an overview of drug delivery research. The most important ingredient in clinical applications is the drug. The drug, however, will not be useful without suitable delivery systems. Delivering a drug with the desired release kinetics requires an understanding of the physicochemical properties of the drug, which, in turn, determine the type of delivery material and drug release mechanism. *In vitro* drug release experimentation is followed by *in vivo* pharmacokinetic studies in animals and humans to determine the suitability of a formulation for clinical application. As shown in Fig. 3, numerous parameters need to be considered, and furthermore, their interdependence has to be taken into account to develop successful drug delivery systems for the intended applications. Because of the interconnectivity without a clear starting point, development of a new drug delivery system requires the simultaneous consideration of multiple factors. For example, after a drug is selected, a suitable delivery route, drug release mechanism, drug release kinetics, and drug delivery materials have to be taken into account simultaneously. It is important to understand the complexity associated with the development of a suitable drug delivery system that can ultimately be used in human patients.

From the first issue of the JCR in 1984 until the last issue in 2013, 6,569 articles have been published. The top cited papers in each year from 1984 to 2013 are listed in Table 2. The topics in Table 2 represent research trends in drug delivery over the last 30 years. In the 1980s, the popular topics included theoretical analysis of drug release kinetics, pH- and temperature-sensitive (i.e., smart) polymers, nasal delivery, and bioadhesive (or mucoadhesive) oral drug delivery systems. In the 1990s, research interests in smart polymers and hydrogels and mucoadhesion continued. However, a new trend emerged that dealt with nanoparticles made of biodegradable polymers, polymeric micelles, lipids, chitosan, and dendrimers. From the turn of the new century, research topics have centered on nanotechnology, in particular, targeted drug delivery to tumors and gene delivery using various nanoparticles. As the topics in Table 2 indicate, technologies in drug delivery have advanced from understanding the drug release mechanisms to manipulation of nanosized delivery vehicles for targeted drug delivery, such as pH- or temperature-sensitive nanoparticles.

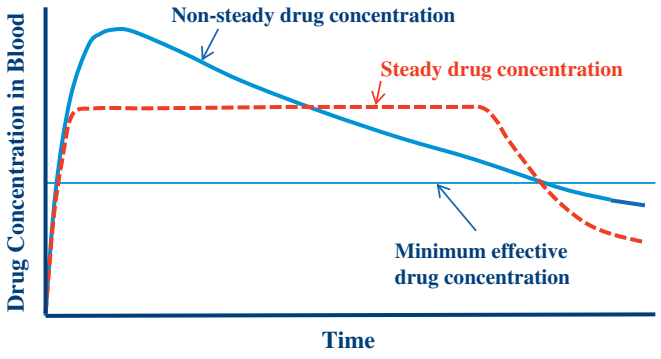

Fig. 2. The drug is effective as long as its concentration in the blood is above the minimum effective concentration regardless of the pharmacokinetic profiles. (Assuming that the maximum drug concentration is lower than the toxic level of the drug.)

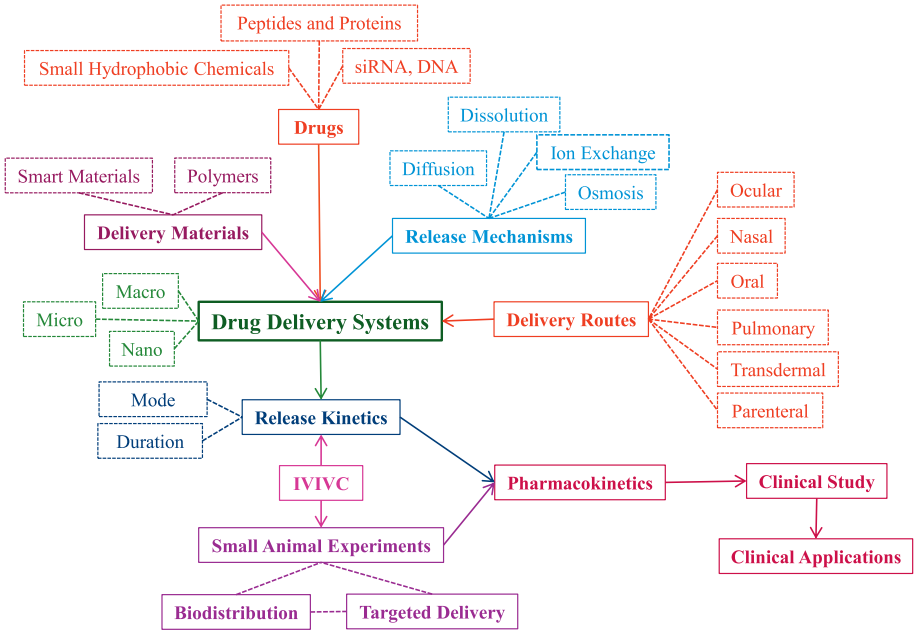

Fig. 3. Overview of drug delivery system development from basic research to clinical applications. The main components of drug delivery systems and processes are shown in a bold-face and solid box, and subsections of each component are shown in a dashed box. (IVIVC: *In vitro–in vivo* correlation).

3. The current status of drug delivery technology

For more than a decade, the most popular topic in the drug delivery field has been nanoparticles. This is a result of intensive support from governmental funding agencies on nanotechnologies since the year 2000 [34]. Significant advances have been made in manipulating properties of nanoparticles that can be administered directly to the blood with the hope of delivering the majority of the drug to the target site. After all, the success of tumor treatment and gene therapy, among others, depends entirely on the ability of drug delivery systems to reach their intended targets. As listed in Table 1, the majority of nanotechnology-based research has been focused on targeted drug delivery, such as anticancer

Table 2
Progression of the research topics as examined by the top cited papers.

Year	Title of top cited paper	Ref
1984	Powder dosage form of insulin for nasal administration	[4]
1985	Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues	[5]
1986	Thermally reversible hydrogels: II. Delivery and selective removal of substances from aqueous solutions	[6]
1987	A simple equation for description of solute release II. Fickian and anomalous release from swellable devices	[7]
1988	pH-controlled release from hydrophobic/polyelectrolyte copolymer hydrogels	[8]
1989	Solute and penetrant diffusion in swellable polymers. IX. The mechanisms of drug release from pH-sensitive swelling-controlled systems	[9]
1990	Controlled vaccine release in the gut-associated lymphoid tissues. I. Orally administered biodegradable microspheres target the Peyer's patches	[10]
1991	A novel approach for preparation of pH-sensitive hydrogels for enteric drug delivery	[11]
1992	A new class of drug carriers: Micelles of poly(oxyethylene)–poly(oxypropylene) block copolymers as microcontainers for drug targeting from blood in brain	[12]
1993	Block copolymer micelles as vehicles for drug delivery	[13]
1994	Enhanced tumor accumulation and prolonged circulation times of micelle-forming poly(ethylene oxide-aspartate) block copolymer-adriamycin conjugates	[14]
1995	*In vitro* cytotoxicity of macromolecules in different cell culture systems	[15]
1996	The potential of mucoadhesive polymers in enhancing intestinal peptide drug absorption. III: Effects of chitosan glutamate and carbomer on epithelial tight junctions *in vitro*	[16]
1997	Physicochemical characterization of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential	[17]
1998	Chitosan and depolymerized chitosan oligomers as condensing carriers for *in vivo* plasmid delivery	[18]
1999	PLGA nanoparticles prepared by nanoprecipitation: Drug loading and release studies of a water soluble drug	[19]
2000	Dendrimers: Relationship between structure and biocompatibility *in vitro*, and preliminary studies on the biodistribution of 125I-labeled polyamidoamine dendrimers *in vivo*	[20]
2001	Chitosan-DNA nanoparticles as gene carriers: Synthesis, characterization and transfection efficiency	[21]
2002	Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend	[22]
2003	Low-molecular-weight polyethylenimine as a non-viral vector for DNA delivery: Comparison of physicochemical properties, transfection efficiency and *in vivo* distribution with high molecular-weight polyethylenimine	[23]
2004	Micellar carriers based on block copolymers of poly(ε-caprolactone) and poly(ethylene glycol) for doxorubicin delivery	[24]
2005	Block copolymer micelles: Preparation, characterization and application in drug delivery	[25]
2006	PEG-modified gold nanorods with a stealth character for *in vivo* applications	[26]
2007	Coated microneedles for transdermal delivery	[27]
2008	Albumin as a drug carrier: Design of prodrugs, drug conjugates and nanoparticles	[28]
2009	Cellular uptake mechanism and intracellular fate of hydrophobically modified glycol chitosan nanoparticles	[29]
2010	Size and shape effects in the biodistribution of intravascularly injected particles	[30]
2011	Glutathione-responsive nano-vehicles as a promising platform for targeted intracellular drug and gene delivery	[31]
2012	Image-guided drug delivery with magnetic resonance guided high intensity focused ultrasound and temperature sensitive liposomes in a rabbit VX2 tumor model	[32]
2013	Nano- and microscaled particles for drug targeting to inflamed intestinal mucosa — A first *in vivo* study in human patients	[33]

drug delivery to tumors and siRNA delivery to target cells, using nanoparticles. Although all nanoparticle drug delivery systems showed improved efficacy over the control in shrinking the tumor size in small animal models, none of the nanoparticle formulations have been successfully translated into clinical applications. As shown in Fig. 3, the ultimate goal of drug delivery research is to produce clinically useful formulations that can help patients in treating various diseases. Thus, the lack of successful translation of nanoparticle formulations to clinical applications requires careful review of the limitations associated with the current nanoparticle systems.

In the drug delivery field, Jörg Kreuter may have been the first to use the term "nanoparticle" in 1976 [35]. In the JCR, Robert Gurny published the first research article using nanoparticulate systems for ocular drug delivery in 1986 [36]. Evidently, the term "nanoparticle" was in use prior to 2000 when the current nanotechnology revolution began, which includes nanoparticle-based drug delivery systems. The properties of nanoparticles in drug delivery have not changed significantly over the years, and yet for more than a decade, nanoparticles have been hailed as a new tool that is revolutionizing drug delivery. In hindsight analysis of the progress made to date, one wonders what caused such frenzy over nanotechnology or nanoparticles in the first place. There was no evidence that nanoparticles would be better drug delivery systems than other formulations. Nanoparticles were simply assumed to have "different" properties from those of micro/macro particles simply because of their huge surface area. Nanoparticles with enormous surface area may be useful for certain applications, such as increasing the dissolution rate of poorly soluble drugs, but other than that, no substantial advantages have been observed. Thus, a question is raised as to whether nanoparticle-based drug delivery systems will truly achieve targeted drug delivery. Numerous nanoparticle systems have been shown to accumulate at the tumor site more than the control non-particulate formulations due to the so-called enhanced permeation and retention (EPR) effect [37,38]. It needs to be understood, however, that the increase in nanoparticle accumulation at the tumor is only marginal and, at best, the total drug found at the tumor site is only a small fraction of the total administered dose [34,39–41]. While more efficient targeted drug delivery systems need to be developed, drug delivery research needs to move forward to address other equally important topics.

Most 2nd generation topics listed in Table 1 still require answers to advance the field. Significant advances in smart polymers and hydrogels were achieved, but their clinical applications are yet to be realized. Despite the introduction of numerous biodegradable polymers and a better understanding of microparticle formulations, long-term delivery of drugs, whether small or large and whether hydrophobic or hydrophilic, has been limited. For the drug delivery field to make tangible impacts in improving patients' quality of life, several drug delivery technologies must be perfected.

4. Future back

The advances that will take place in drug delivery technologies during the next 30 years are difficult to predict. Regardless of the new technologies that are developed, the diseases to treat and the hurdles to overcome for improved drug delivery will not change significantly from our current needs. Improved drug delivery technologies will have to solve the problems listed in Table 1. The demand for developing modulated insulin delivery systems will continue to increase as the number of patients with diabetes continues to rise. The need for targeted drug delivery to tumors, which has been a main research focus for more than a decade, will not suddenly diminish. The ability of long-term drug delivery, i.e., 6 months or longer, for treating chronic diseases will be essential in improving patient compliance. Furthermore, innovative *in vitro* testing methods will have to be developed to accurately predict the *in vivo* pharmacokinetics of drugs and drug formulations in humans.

Drug delivery scientists can wait and see what new technologies are developed in the future to solve the problems at hand. This passive approach, however, will not allow us to achieve the goals in a timely manner. Instead, drug delivery scientists can take a bold new approach known as "future back". The future back approach is not about imagining the future, but is about understanding what is possible or clearly impossible and, thus, finding a way to achieve a goal [42]. If scientists rely on future innovations yet to be made, the progress will be limited to the priorities and conventions at that time, leading to limited progress. This is especially true when the innovations are incremental and quickly outdated [42]. Thus, scientists can first describe an ultimate drug delivery system with all desirable properties and work backwards to find out how to achieve the goal, i.e., to define what innovations are necessary and how to assemble those innovations to achieve the ultimate drug delivery system.

There are at least 4 modulated delivery systems to be developed during the 3rd generation. They are glucose-sensitive transient insulin delivery with on–off switching capability, targeted delivery of anticancer agents or siRNA to tumors, long-term drug delivery ranging from 6 months to 1 year, and *in vitro* testing methods that can predict *in vivo* pharmacokinetic profiles. Of these, developing a modulated insulin delivery system is, technically speaking, the most challenging. Insulin delivery is different from delivery of other drugs, in that insulin has to be delivered at the right time, i.e., when the blood glucose level increases, in an accurate amount that is just enough to reduce the blood glucose level. As shown in Fig. 4, the insulin level in the blood should not be constant, but pulsatile. The insulin concentration in the blood should be reduced after the glucose concentration decreases. Otherwise, hypoglycemia will occur. Despite significant advances, pulsatile drug release systems useful in clinical applications are yet to be achieved [43]. A compounding difficulty in developing successful modulated insulin delivery systems is the fact that the system has to be implanted in the body for extended periods of time, and the system should not cause any biocompatibility issues. This requires the use of biocompatible materials, which may be biodegradable and can respond to fluctuations in blood glucose levels within a matter of minutes, if not seconds. This is a tall order by any standard and requires multiple innovations.

Targeted drug delivery research will continue, but the methods to achieve it need to be changed. Thus far, the scientists rely solely on nanoparticle formulations for targeted delivery to tumors. As mentioned above, this has been based on a rather naïve assumption that nanoparticles have different properties than larger-sized particles. Achieving true targeted delivery requires an understanding of how foreign materials are distributed throughout the body and how to minimize the distribution of the administered nanoparticles to non-target tissues. Drug delivery scientists have shown a limited consideration of the biodistribution of nanoparticle formulations. Altering the biodistribution of administered formulations may decrease side effects, even if the drug efficacy is not

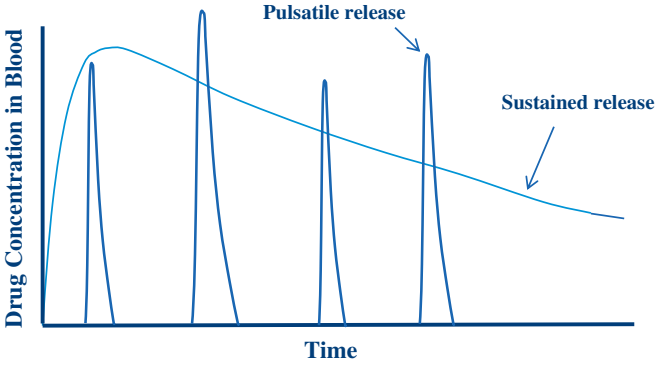

Fig. 4. Drug concentration profiles in the blood by pulsatile drug release systems compared with the sustained release systems. The pulsatile release system requires a sensor, an on–off switch and an ability to deliver an accurate amount at the right time.

increased significantly. Reducing the side effects of a drug is as important as delivering more of the drug to the target site. Development of the PEGylated liposome formulation of doxorubicin is a good example of this concept [44].

The number of long-term depot formulations for peptide and protein delivery is limited to only a dozen products. This number is trivial compared to the thousands of products developed for oral sustained release products. There are clearly differences in the technical challenges. For oral drug delivery systems, the formulations do not have to be degradable or to deliver a drug for more than 24 h. Long-term depot formulations need to deliver a drug for months. The most pressing challenge to overcome in this respect is reducing the initial burst release. Almost all depot formulations are using double emulsion methods that generally result in a substantial initial burst release. The drug concentration in the blood in the first few days is orders of magnitude higher than the steady state drug concentration. Eliminating the initial burst release for depot formulations is the key to the development of these products. Recent advances in microfabrication technologies are expected to achieve this goal. Small animal models have not been a good predictor of the drug efficacy in humans. This is especially significant in targeted drug delivery. Development of *in vitro* models that allow prediction of *in vivo* pharmacokinetic profiles will revolutionize the development of new drugs and new drug delivery systems.

5. The role of the JCR in the future of drug delivery research

The JCR has played a pivotal role in advancing the drug delivery field over the last 30 years and will continue to play an essential role in the next 30 years. The role of the JCR in the 3rd generation of drug delivery is best understood by asking a simple question: what will the drug delivery field miss if the JCR no longer existed? If the JCR did not exist, then scientists would not have a primary means of publishing important findings in drug delivery. There are other journals for publication, but the significance of publishing in the JCR cannot be replaced because of its focus on drug delivery technologies and its long history. It is the first journal to publish articles strictly on drug delivery. The absence of the JCR will slow, if not jeopardize, the steady advances of the drug delivery field. The JCR is the only journal that has a cover story that is selected from the papers in each issue. Since 2008, when the first cover story was published, more than 100 cover stories have been published. The JCR is also the only journal that publishes concept papers that present innovative new ideas, however with limited data, to accelerate the publication process [45]. The JCR is the only journal that features perspective reviews that differ from traditional review articles in that the authors' opinions on a topic are reflected. It has been the only journal that has raised valuable questions against common beliefs, e.g., questions about the validity of nanoparticle approaches [40,46,47]. Furthermore, the JCR has been regularly publishing special issues based on international symposiums, including the International Symposium on Recent Advances in Drug Delivery Systems held in the U.S.A. [48], the European Symposium on Controlled Drug Delivery held in the Netherlands [49], International Nanomedicine and Drug Delivery Symposium held in the U.S.A. [50], Asian 3 Foresight Program held in Asia [51], and Innovative Polymers for Controlled Delivery held in China [52]. Special issues or thematic issues have also been published based on symposiums on specific topics, such as nanotechnology [53], liposomes [54], and tumors [55], or research by scientists in Japan [56] and Europe [57]. The JCR will continue its tradition of excellence and leadership through publishing innovative new ideas and controversial topics.

Drug delivery scientists can greatly impact the treatment of various diseases by developing new drug delivery systems. It requires relentless curiosity and experimentation, bigger thinking, and embracing a paradox [42]. It also requires the ability to escape from dogma, which lives in the results of other people's thinking [58]. The answers to solving the problems listed in Table 1 may already exist and all we need to do is simply connect the dots. Connecting the dots is not possible looking forward but is possible only looking backward [58]. This is another reason why the "future back" approach is necessary for drug delivery scientists to make "insanely good" drug delivery systems. Drug delivery scientists should keep an open mind to accept different views and allow uninterrupted communication. The JCR promises to provide a forum for the free flow of new ideas and different points of views in the years to come.

Acknowledgments

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