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REVIEW ARTICLE

Controlled drug delivery systems: the next 30 years

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Abstract The drug delivery scientists need to reexamine the advances made during the past 60 years, analyze our current abilities, and design the future technologies that will propel us to achieve the next level of drug delivery technologies. History shows that the first generation (1G) of drug delivery research during 1950–1980 was quite productive, while the second generation (2G) technologies developed during 1980–2010 were not as prolific. The ultimate goal of drug delivery research is to develop clinically useful formulations to treat various diseases. Effective drug delivery systems can be developed by overcoming formulation barriers and/or biological barriers. The engineering approach has a limit in solving the problem, if biological difficulties are not clearly identified and understood. The third generation (3G) drug delivery systems will have to focus on understanding the biological barriers so that they can be overcome by engineering manipulation of the drug delivery systems. Advances in the next 30 years will be most accelerated by starting open dialogues without any preconceived ideas on drug delivery technologies. The new generation of drug delivery scientists needs to be aware of the successes and limitations of the existing technologies to design the new technologies for meaningful advances in the future.

Keywords drug delivery, history, formulation barriers, nanotechnology, clinical product

1 Introduction

The drug delivery field has advanced for more than 60 years. Two generations have passed since the introduction of the first controlled drug delivery system (the Spansule® technology) in the early 1950s [1]. Controlled release formulations were developed to increase patient compliance and convenience. Decades ago it was common to take a drug 3–4 times a day by oral administration. Taking a medicine 3 or 4 times a day requires very inconvenient dosing schedules. Making the same drug twice-a-day or once-a-day resulted in drastic improvement in patient compliance and convenience. It was this immediate benefit that made the controlled drug delivery formulations so popular. Controlled release formulations were often called "extended release (ER)" or "sustained release (SR)" formulations, and nowadays those terms are used interchangeably. Numerous oral sustained release formulations have been developed and marketed, making the treatment more effective. The controlled release formulations also received a lot of attention because they can be used to make old drugs more effective and useful. The controlled release technology was also used for life cycle management of various drugs whose patent protection had expired. Furthermore, controlled release systems were in great need for delivery of new types of drugs, such as protein drugs, also known as biologics, and genes.

While significant advances have been made in the controlled drug delivery field, the field is still in its teenager stage and it needs to mature. Advances made in the last two generations will be the stepping stones for further development in the next generation of drug delivery systems. It is always difficult to predict the future, as the future is not going to be a linear extrapolation of the present. The future, however, is based on our current understanding and technologies. In this sense, it will be beneficial to review the past of the drug delivery technologies and the current status to predict the future, in particular, what technologies need to be developed. Table 1 describes the technologies developed since the early 1950s until 2010, and the technologies necessary for treating various diseases in the next 30 years.

In Table 1, the progresses made during the last 60 years are divided into two generations: the first generation (1G) and the second generation (2G). During the 1G drug delivery, the main focus was to develop oral and transdermal formulations. During this time, the four main controlled release technologies were established: dissolution, diffusion, osmosis, and ion-exchange [2]. There are literally thousands of oral and transdermal products that are

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Table 1 Evolution of controlled drug delivery systems since 1950

1st Generation (1G)			2nd Generation (2G)			3rd Generation (3G)		
1950s	1960s	1970s	1980s	1990s	2000s	2010s	2020s	2030s
Basics of controlled release			Smart delivery systems			Modulated delivery systems		
Oral delivery:			Zero-order release:			On-off Insulin release:		
Twice-a-day, once-a-day			Zero- vs. first-order release			Glucose-sensitive release		
Transdermal delivery:			Smart polymers & hydrogels:			Targeted delivery:		
Once-a-day, once-a-week			Environment-sensitive,			Anticancer drugs, siRNA		
Drug delivery mechanisms:			Self-regulated release			Long-term delivery systems:		
Dissolution, diffusion, osmosis, & ion-exchange			Peptide & protein delivery:			6–12 months delivery with minimal initial burst effect		
			Biodegradable depot					
			Nanoparticles:			*In vitro-in vivo* correlation:		
			Tumor-targeted delivery			Prediction of PK profiles from *in vitro* release study		
			Gene delivery					

clinically available, but they are all based on the four mechanisms, either individually or in combination. With the technologies firmly established during the 1G, attention during the 2G was focused on development of more advanced drug delivery systems, such as zero-order drug release systems and environment-sensitive delivery systems using smart polymers and hydrogels. Development of self-regulated insulin has been one of the active research areas, but it turns out to be much more difficult than simply responding to the changes in the blood glucose concentration. Insulin delivery with on-off capability has to be precise in quantity and time. This is very difficult to achieve with the technologies available today. Part of the 2G drug delivery was focused on developing injectable depot formulations for peptide delivery for weeks and months. To date, only about a dozen of such products are available, and this number is miniscule when compared with thousands of successful oral formulations. The last 10 years of the 2G was consumed by developing nanotechnology-based formulations.

2 Issues with the second generation (2G) drug delivery systems

While the 1G drug delivery systems were highly successful, the 2G systems were not as fruitful in terms of producing clinically useful products. This is largely due to the differences in the routes of drug administration. The 1G formulations were mainly for oral and transdermal drug delivery, and the *in vivo* pharmacokinetic profiles could be controlled by adjusting the drug release kinetics by the system. Thus, success of 1G formulations required only engineering manipulations. The physiochemical properties of a drug, such as water-solubility and the diffusion coefficient through a polymer, determined the drug release kinetics, and subsequent pharmacokinetic (PK) profiles followed. Although the *in vitro–in vivo* correlation (IVIVC) needs to be established for each drug and each formulation, once it is established the same drug in different formulations can be assumed to result in the same PK profiles as long as the *in vitro* release profiles are statistically the same. The 1G technologies resulted in numerous me-too formulations, symbolizing the robustness and usefulness of the drug release mechanisms.

For the formulations developed during the 2G the PK profiles are determined by the body, rather than by the drug delivery systems themselves. For example, pulmonary insulin delivery is based on the body's response for efficacy, rather than by the formulation. This resulted in unpredictable PK profiles by the formulation. Another example is nanoparticle formulations which have been frequently used for targeted drug delivery. The efficiency of nanoparticles is not determined by the drug release kinetics of the formulation but by the body that can alter biodistribution and drug absorption at the target site. The 2G formulations had to overcome the biological barriers to be effective, but it has not been easy due to the unpredictability of biological responses.

A big portion of the 2G drug delivery was attributed to the nanotechnology-based drug delivery systems. The frenzy toward applications of nanoparticles in targeted drug delivery has been unprecedented, and nanotechnology for drug delivery needs in-depth discussion to understand its impact to the drug delivery field in general [3].

3 Nanotechnology for drug delivery

For more than a decade, nanoparticle formulations have been prepared and tested for their presumed ability to provide better treatment, especially treatment of tumors. The promise of nanoparticle formulations is that nanoparticles, due to their huge surface area, may have unique properties that larger drug delivery systems do not have. The whole field of nanotechnology-based drug delivery systems began with this assumption, but this assumption still remains hypothetical even more than a decade later. If nanoparticles possess unique properties, they should be

clearly understood by now. But it is still not clear what unique properties nanoparticles possess in drug delivery. Simply speaking, what are we missing if the current nanoparticle formulations do not exist?

Nanotechnology is often labeled as an enabling technology that revolutionizes the field. In the drug delivery field, nanotechnology-based drug delivery systems, i.e., nanoparticle formulations, are supposed to enable formulation scientists to develop unique formulations that were not possible before. If nanotechnology is such an enabling technology, why have there been no advances in the field where breakthrough advances are desperately needed? For example, nanotechnology has not been able to contribute to treating diabetes, giving up smoking, managing Alzheimer's disease, or preventing a heart attack. The only area that nanoparticles have been used has been targeted drug delivery to tumors. Frequently, antibody-grafted nanoparticles are used for improved targeting ability, but the increase in drug accumulation at the target tumor has been marginal [4–6]. The drug delivery scientists have been placing blind trust in nanotechnology without any evidence or proof that nanotechnology indeed brings new approaches to disease treatment. The drug delivery scientists should break out of the nanotechnology shell. Research on nanoparticles will continue for another decade or so due to its huge inertia, but the underlying assumptions, and thus the limitations, have to be understood before further investment is made. The persistence of never giving up is a virtue resulting in ultimate success, but it may be counterproductive if the current non-productive approach is repeated.

4 Research *vs.* clinical product development

Like in any scientific discipline, research on drug delivery systems is hard. Advances in the field have been slow and incremental. Over time, however, cumulated technologies allow development of novel drug delivery systems benefiting patients. During the last six decades, many controlled release formulations have been developed with clinical realization. But most of the clinically successful formulations are oral and transdermal delivery systems of the 1G. There are literally hundreds of oral and transdermal sustained release formulations with commercial success. For other routes of drug delivery, however, only a limited number of formulations have been clinically used. The number of long-term depot formulations is still very low, and also the drug release kinetics is not desirable with high initial burst release. The intravenous formulations, especially targeted drug delivery systems, are still under the research stage. The difficulty becomes even greater if a drug to be delivered has high molecular weight and hydrophilicity, such as proteins or genes.

It is time to review the great achievements that the controlled drug delivery field has made to date, as well as the challenges facing us. Without clear understanding of the difficulties facing the field, no solution can be found. One limitation that the drug delivery scientists are facing is the use of generally regarded as safe (GRAS) materials. If a new material is used, then its safety has to be proven by clinical studies and this is beyond the realm of the drug delivery scientists. If a new material is shown to have drastically better properties in treating diseases, it can be justified to invest a large amount of resources for clinical studies. The bottom line is that the drug delivery scientists need to work in the boundaries of materials that can be approved by FDA, i.e., safe and effective. At the same time, formulation scientists should not be afraid of using new polymers as long as they improve the drug efficacy substantially.

5 The third generation (3G) drug delivery systems

Despite remarkable advances in drug delivery technologies during the last six decades, there are many hurdles to overcome to develop better drug delivery systems. It is time to examine those hurdles to find solutions and to develop newer technologies. Table 1 lists some of the technologies to be developed during the 3G. The drug delivery systems listed in Table 1 can be further divided into two categories depending on the barriers to overcome, i.e., formulation or biological barriers (Table 2).

There are at least two formulation barriers that need to be overcome: formulation of poorly soluble drugs and elimination of initial burst release. The necessities for these systems have been around for several decades. Developing clinically useful formulations of various poorly soluble drugs has been a major issue since the formulation science began. About 70%–90% of the new drug candidates are poorly water-soluble, and new, innovative formulations are urgently needed so that the poorly soluble drugs can be administered without using

Table 2 The barriers to overcome in the 3G drug delivery systems

Formulation barriers	Biological barriers
1. Oral delivery of poorly soluble drugs	1. Gastric retention in the fast condition
2. Injectable depot formulations with no initial burst release	2. Self-regulated drug delivery systems
	3. Injectable depot formulations for peptides and proteins
	4. Targeted drug delivery (systemic and intracellular targeting)

patient-unfriendly excipients. Almost all injectable depot formulations have huge initial burst release, resulting in orders of magnitude higher drug concentration in blood in the first few days as compared with the steady state concentration. These formulations are approved for clinical use because the initial burst release can be tolerated by patients. Eliminating, or minimizing, the initial burst release will substantially make the injectable depot formulations even more patient friendly.

Overcoming biological barriers is much more difficult, as compared with formulation barriers, because they are hard to define and predict. Effective gastric retention devices, which work even in the fast conditions, will substantially enhance the usefulness of oral controlled release formulations. Many drugs have a window for absorption from the gastrointestinal tract, and delivery of those drugs using a gastric retention device will increase bioavailability as well as make it possible to develop once-a-day formulations. Many self-regulated insulin delivery systems have been prepared and they work well under *in vitro* conditions. The systems respond to the fluctuating glucose concentrations in the environment, and can release the proper amount of insulin. But when such a system is introduced in the body, the glucose sensor does not work as well as *in vitro*, and the release of the exact amount of insulin has been difficult to achieve. The body tends to respond to foreign materials, making the control of insulin release even more difficult. In another example, nanoparticles covered with antibodies are expected to zoom in to the target site, but such targeting relies on blood circulation which does not discriminate nanoparticles with grafted antibodies from control nanoparticles. Finding new approaches or ways to overcoming such biological barriers will be the key to the success of the 3G delivery systems.

6 Scientists in the drug delivery field

To make new, innovative drug delivery systems that can achieve the goals listed in Tables 1 and 2 during the 3G, the drug delivery scientists need to be more open minded. At the same time, scientists should question the existing dogmas, i.e., think outside the box or in new boxes [7]. It is common to accept an existing logic if the data fits the current knowledge basis. This is most prevalent in the area of nanoparticle formulations. Even though the increase in targeted drug delivery using nanoparticles is only marginal, it fits very well into the existing views of the enhanced permeation and retention effect. For drug delivery scientists to make real breakthroughs, they have to break away from the current knowledge basis, and ask why the nanoparticle efficacy cannot be improved by orders of magnitude. The ultimate goal of developing drug delivery systems is to cure diseases in humans, and the question should extend to "why the results of small animal models cannot be reproduced in humans?"

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