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Controlled Drug Delivery: Historical perspective for the next generation

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Abstract

The modern day drug delivery technology is only 60 years old. During this period numerous drug delivery systems have been developed. The first generation (1950–1980) has been very productive in developing many oral and transdermal controlled release formulations for clinical applications. On the other hand, the second generation (1980–2010) has not been as successful in generating clinical products. This is in large part due to the nature of the problems to overcome. The first generation of drug delivery technologies dealt with physicochemical problems, while the second struggled with biological barriers. Controlled drug delivery systems can be made with controllable physicochemical properties, but they cannot overcome the biological barriers. The third generation (from 2010) drug delivery systems need to overcome both physicochemical and biological barriers. The physicochemical problems stem from poor water solubility of drugs, large molecular weight of peptide and protein drugs, and difficulty of controlling drug release kinetics. The biological barriers to overcome include distribution of drug delivery systems by the body rather than by formulation properties, limiting delivery to a specific target in the body. In addition, the body's reaction to formulations limits their functions *in vivo*. The prosperous future of drug delivery systems depends on whether new delivery systems can overcome limits set by human physiology, and the development process can be accelerated with new ways of thinking.

Graphical abstract

Year			
1950	1980	2010	2040
1st Generation	2nd Generation	3rd Generation	
Basics of Controlled Release	Smart Delivery Systems	Modulated Delivery Systems	
Successful control of physicochemical properties of delivery systems	Inability to overcome biological barriers	Need to overcome both physicochemical and biological barriers	

Keywords

drug delivery; history; physicochemical barriers; biological barriers

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1. Drugs and Drug Delivery Systems

Drug delivery systems exist to provide a more effective way to deliver drugs. The most important ingredient in any formulation is the drug. All other ingredients, collectively known as excipients, in a formulation are used to make the drug more effective. Once in a while, a newly developed drug becomes a blockbuster drug, i.e., the annual sales exceed \$1 billion. The blockbuster drugs during the last few years include those treating hypercholesterolemia (e.g., Lipitor and Crestor), acid reflux (e.g., Nexium), arthritis (e.g., Humira, Enbrel, and Remicade), depression (Seroquel, Cymbalta, and Zyprexa), and asthma (Advair and Singular). Of these, Seroquel is unique in formulation as it employs a sustained release technology for once-a-day delivery of quetiapine. Quite often, sustained release versions of drug formulations are developed for product lifecycle management[1]. Thus, the sustained release technology is important to make existing drugs more effective.

When a new drug is developed, it is usually formulated into a simplest possible dosage form that is effective in treating the intended disease. Different drugs have different physicochemical and biological properties, necessitating different formulations. This point is made here by comparing oral and parenteral routes of administration. Table 1 lists some of the drug properties that need to be considered for finding suitable delivery systems. Since oral delivery is the most convenient and widely used route of drug administration, it is the first to consider. Some drugs, however, have very poor water solubility or very poor permeability across the cells, making it difficult to develop oral formulations. In addition, a recent breed of biotech drugs, such as peptides, proteins, and nucleic acids, are much larger than the traditional small molecular drugs. They are usually delivered by parenteral routes due to their large size, limited stability, and short half-life.

2. History of drug delivery technologies

Before 1950, all drugs were made into pill or capsule formulations that released the loaded drug immediately upon contact with water without any ability to control the drug release kinetics. In 1952, Smith Klein Beecham introduced the first sustained release formulation that was able to control the drug release kinetics and achieve 12-hour efficacy[2]. The technology, known as the Spansule technology, allowed control of the drug release kinetics at a predetermined rate. In the early days when the new controlled drug delivery technology began, various terms were introduced to describe newer formulations having minor differences each other. Controlled release formulations included those with sustained release, timed release, extended release, and others. Of these, the term “sustained release” has been used more widely than any other names. These terms, however, are used interchangeably nowadays. After several decades of advances in drug delivery technologies, the small differences in the functions that different names entail have become unnecessary.

The history of controlled drug delivery field is described in Table 2. Most of the fundamental understanding on the drug release mechanisms, especially oral and transdermal dosage forms, was obtained during the first generation (1G) of development from 1950 to 1980. This period identified four drug release mechanisms that accelerated development of numerous oral and transdermal controlled release formulations. The most widely used

mechanisms were dissolution-controlled and diffusion-controlled systems. Osmosis-based formulations gained a transient popularity, but the number of products based on osmosis is orders of magnitude smaller than those with the other two. The ion-exchange mechanism distinguishes itself from the others, but it has not been useful without combining with diffusion-controlled mechanism. Even today, many oral once-a-day formulations are developed based on the dissolution- or diffusion-controlled mechanism. Since oral delivery is the most convenient mode of drug administration, oral sustained release formulations will continue to flourish.

Unlike 1G drug delivery formulations, the second generation (2G) technologies have been less successful, as measured by the number of clinical products produced. One of the reasons for this is that the 2G technologies deal with more difficult formulations. For example, injectable depot formulations made of biodegradable poly(lactic-co-glycolic acid) (PLGA) are designed to deliver peptide and protein drugs for a month or longer. Most depot formulations have a difficult time controlling the initial burst release, which often releases 50% of the total drug in the first day or two[3]. During the 2G period, pulmonary delivery systems for insulin have been also developed. Pulmonary insulin delivery system was developed, but its lower bioavailability required delivery of several times more drug than required by parenteral injection. This, in turn, resulted in unexpected side effects that, along with other factors, caused withdrawal of the product from the market[4]. In an alternative approach, various self-regulated insulin delivery systems have been developed over the years[5–8]. Self-regulated insulin delivery systems work reasonably well in the laboratory setting, but they lose the function soon after implanted *in vivo*. The last decade of the 2G period (i.e., 2000~2010) has focused on tumor-targeted drug delivery using nanoparticles. The seemingly promising nanoparticle approaches based on small animal models have not been successful in numerous clinical trials[9, 10]. The limited successes of the 2G technologies need careful analysis to make the current 3G technologies prepared for eventual clinical applications.

3. Differences between 1G and 2G Drug Delivery Technologies

Development of more clinical products based on the 3G technologies, which are still under development, requires understanding why most of the 2G technologies have not been translated into clinical products. Huge successes of the 1G technology are mainly based on the oral and transdermal drug delivery systems. In these formulations, adjusting *in vitro* drug release kinetics has a direct effect on the *in vivo* pharmacokinetics. For oral and transdermal systems, the relationships between *in vitro* drug release kinetics and *in vivo* bioavailability are fairly well understood. Once the *in vitro-in vivo* correlation (IVIVC) of a formulation is established, other formulations using different mechanisms can be easily produced with an expectation that the new systems will be as effective as the reference formulation [11, 12]. For most drug delivery systems developed in the 1G period, mainly for oral and transdermal delivery, understanding the physicochemical properties (e.g., *in vitro* drug release kinetics) was enough for developing clinically useful formulations. No particular biological barriers were identified for those formulations, except for the inability to overcome the limited gastrointestinal (GI) transit time and the different absorption properties by different segments in the GI tract (i.e., absorption window) of oral formulations.

The drug delivery systems developed during the 2G period dealt with more difficult problems. The technologies developed during the 2G period are listed in Table 2. Various oral controlled release formulations were developed to achieve zero-order release, but the zero-order release achieved in various *in vitro* dissolution systems did not result in maintenance of the constant drug concentration *in vivo*, mainly due to the variations in the drug absorption properties along the GI tract. Drug absorption is controlled by the biological barrier, in addition to the drug release kinetics from oral formulations. More importantly, maintaining the constant drug concentration in the blood is not necessary, as long as the drug concentration is above the minimal therapeutically effective concentration [13]. The 2G period also introduced sustained release formulations of peptide/protein drugs after implantation in the body[14, 15]. The drug release from a formulation *in vivo* depends not only on the formulation properties, but also on the biological environment surrounding the implanted formulation. This makes prediction of the drug release kinetics *in vivo*, and thus, bioavailability, more difficult. Simply put, IVIVC has not been found for most parenteral formulations of biotech drugs, making it difficult to predict the *in vivo* bioavailability from the *in vitro* release profiles, especially for long-term depot formulations [16]. Furthermore, there are no standard *in vitro* drug release test methods that can reliably predict *in vivo* pharmacokinetic profiles[17]. The difficulty of predicting *in vivo* behavior of drug delivery systems is aggravated for self-regulated insulin delivery systems. Upon introduction to the body, modulated insulin delivery systems fail to function after a day or two due to the interference with proteins and cells present in the body[18]. Recent uses of nanotechnology for tumor-targeted drug delivery is another casualty of inadequate understanding of the effects of the body on drug delivery systems[13]. In short, the difficulty faced by the 2G drug delivery systems is mainly due to the inability of the drug delivery systems to overcome biological barriers.

4. The 3G Drug Delivery Technologies

The limited success of the 2G drug delivery technologies is, in large part, due to their inability to overcome the body responses after drug delivery systems are administered by parenteral route. The current drug delivery systems, however smart they may have been constructed, are not able to deal with challenges posed by the biological environment which is not-well understood and unpredictable. For the 1G formulations, controlling physicochemical properties, such as water solubility and cell permeability, were adequate enough to establish IVIVC. The 3G drug delivery technologies will have to be advanced much beyond the 2G technologies to overcome both physicochemical and biological barriers. As a brief review of the 2G technologies above indicates, understanding and overcoming the biological barriers, in addition to physicochemical barriers, is the key for success. Some of the barriers to overcome for developing successful 3G drug delivery systems are listed in Table 3. There are many other drug delivery systems that need to be developed during the 3G period. The four areas in Table 3 are discussed here solely to emphasize the importance of understanding and overcoming biological barriers.

4.1. Delivery of poorly water-soluble drugs

Poor water solubility of drugs was one of the most important problems in drug development, and it still remains to be true today. Discussion on poorly soluble drugs requires understanding of the meaning of drug solubility. Table 4 shows the descriptive terms used in U.S. Pharmacopeial and National Formulary to indicate approximate drug solubilities in water. The term “poorly soluble” is commonly used to describe drugs that belong to the “practically insoluble” category. For these drugs the aqueous solubility is 0.1 mg/mL or less, i.e., 100 µg/mL or less. Many new drug candidates are poorly water soluble, and thus, a large portion of the candidate drugs are not translated into clinically useful formulations. Analysis of 200 orally administered drug products showed that practically insoluble drugs account for almost 40% of the total drugs [19]. Delivering these drugs effectively through the GI tract for therapeutically effective bioavailability remains an important issue. The dissolution rate of practically insoluble drugs may be so slow that dissolution takes longer than the GI transit time resulting in therapeutically unacceptable bioavailability [20].

Technologies to dissolve poorly soluble drugs in water have been studied for decades, and some of the methods are listed in Table 5. Poorly soluble drugs have inherently low water solubility, and thus, suitable excipients are added to increase the solubility by using surfactants, polymer micelles, hydrotropic agents, complexing agents (e.g., cyclodextrins and proteins), cosolvents, and lipid formulations (e.g., self-emulsifying systems)[21–23]. For weakly acidic or basic drugs, pH can be controlled to increase the drug solubility. Alternative to increasing the drug solubility, drug dissolution kinetics can be enhanced through selecting appropriate polymorph, making solid dispersions (i.e., maintaining amorphous structure of the drug using polymers), reducing drug particle size, and increasing wetting with surfactants. Of these, the solid dispersion approach has been widely used for its ease of preparation and efficacy [24–26]. Making drug nanocrystals has also been frequently used, as the increase in bioavailability by increasing the drug crystal surface resulted in improved bioavailability [23]. The surface area increases proportionally as the decrease in the size of drug particles. The drug solubility is an inherent property and so it should not change as the dissolution kinetics increases. But increasing the dissolution kinetics can result in improved bioavailability of oral formulations. Enhanced dissolution of the drug can produce the dissolved drug in sufficient quantity fast enough to replace those drugs that have been absorbed from the GI tract, thereby improving bioavailability.

The problem of poor water solubility becomes even more serious for intravenous formulations. For example, many anticancer drugs are extremely poorly water soluble, e.g., <1 µg/mL, and thus they are usually dissolved in organic solvents. Paclitaxel and docetaxel are good examples of poorly soluble drugs making injectable formulations difficult. There are various injectable formulations of paclitaxel: Taxol utilizing Cremophor® EL [27], Abraxane® based on paclitaxel-albumin complex[23, 28, 29], and Genexol® utilizing PEG-PLA polymer micelle [30]. Taxotere, delivering docetaxel, a derivative of paclitaxel, is dissolved in polysorbate 80 which is suspected to cause hypersensitivity [31, 32]. Cremophor EL, an excipient used to increase the solubility of paclitaxel, can cause serious hypersensitivity reactions and kill patients if the patient is not properly preconditioned[27]. Development of new drug delivery systems for poorly soluble drugs without using organic

solvent is important for bringing promising new drug candidates to clinical applications and more effective use of existing drugs.

4.2. Peptide/protein/nucleic acid delivery

Macromolecular drugs, such as peptides, proteins, and nucleic acids, are usually delivered by parenteral administration. They are too big to cross the intestinal epithelium, i.e., to be absorbed from the GI tract[33]. A number of attempts have been made to protect them from the harsh acidic condition of the stomach by enteric coating, and from enzymatic degradation by adding enzyme inhibitors. These attempts, however, do not address the real issue that proteins cannot be absorbed without enzymatic degradation into small molecules[34, 35]. It has been suggested that nanoparticles can be translocated across M cells in Peyer's patches and enterocytes in the villus part of the intestine, but the extent of particle absorption has been controversial [36]. The absorbed amount is too low and too irreproducible to have therapeutic significance. Thus, these macromolecular drugs are mainly delivered by parenteral routes. Recently, new approaches have been attempted to deliver them by non-invasive, or minimally-invasive means, such as pulmonary, nasal, and transdermal delivery [37].

Macromolecular drugs usually have very short half-lives, ranging from minutes to hours, and thus, sustained release for months requires depot formulations. There are more than a dozen depot formulations that are administered by parenteral routes. They include Zoladex[®] Depot (goserelin acetate), Lupron Depot[®] (leuprolide acetate), Sandostatin LAR[®] Depot (octreotide acetate), Nutropin Depot[®] (somatropin), Trelstar[®] (triptorelin pamoate), Suprefact[®] Depot (Buserelin acetate), Somatuline[®] Depot (lanreotide), Arestin[®] (minocycline HCl), Eliaard (leuprolide acetate), Risperdal[®] CONSTA[®] (risperidone), Vivitrol[®] (naltrexone), Ozurdex[®] (dexamethasone), and Bydureon[®] (exenatide). The fact that there are only a handful of depot formulations, as compared with thousands of oral sustained release formulations, indicates the difficulty associated with developing parenteral depot formulations. The majority of these formulations have the initial burst release, resulting in the initial peak blood concentration much larger (up to 100 times) than the therapeutically effective concentration at the steady state (i.e., after drug concentration at the steady state after the initial peak). Thus, it is urgently required to improve the technology of controlling the drug release profiles. The ability of controlling drug release kinetics becomes even more important as the drug loading increases. Depot formulations designed to have longer duration need higher drug loading. Thus, patient-friendly depot formulations must have higher drug loading with controllable drug release kinetics for a long-period of time, up to 1 year, or even longer.

4.2.1. The Initial Burst Release from PLGA Depot Formulations—Examples of pharmacokinetic profiles of two clinically used depot products are shown in Figure 1. Each PK profile can be divided into two regions: the initial burst release region (red arrows in Figure 1) and therapeutically effective region (green arrows in Figure 1). The Y axis in Figure 1 is in the log scale, and the peak concentration in the initial burst region is about 100 times larger than the concentrations that are in the therapeutically effective range. This observation brings a few questions. First, is it really necessary to have 100 times higher drug

concentration in the first day or two than the known therapeutically effective drug concentration? Second, does the initial burst release play any role in the efficacy of the drug at the steady state? There is no scientific reason to justify that the initial burst release is necessary for the therapeutic effect. The initial burst release is simply an outcome of the emulsion methods for microparticle production available a few decades ago. Some may argue that the initial peak concentration in blood may be necessary for therapeutic efficacy. This, however, cannot be true, because it implies that daily injection of the same drug without the peak concentration should not work. This, of course, is not the case. It is the drug concentrations in the therapeutically effective region that is important. Controlling the initial burst release is still not easy, but improved understanding on the emulsion methods and recent development of new microfabrication processes have made it possible to reduce or eliminate the initial burst release.

4.3. Targeted drug delivery using nanoparticles

Nanoparticle-based drug delivery systems have been used extensively for the last few decades. A search in SciFinder using “drug delivery nanoparticle” resulted in 19,950 references during 1995–2014 (Figure 2). Of these, 57% are associated with the term “target” for targeted drug delivery or targeting. Clearly, the majority of the studies on nanoparticle-based drug delivery has been focused on targeted drug delivery, mainly on tumor-targeted drug delivery.

The initial excitement on nanoparticulate drug delivery systems arose from the ability of producing nanoparticles in various size and shape, and the ability to control the physicochemical and surface properties to make smart nanoparticles. Many of these systems have worked well in the laboratory where cell culture systems were used for testing drug delivery. The systems also worked reasonably well in small animal models, mostly xenograft mouse models. The nanoparticle systems showing promising results in those models have not been translated into clinical studies[38, 39]. The current nanoparticles cannot control their fate after intravenous administration. The so-called “targeting” by nanoparticles is a misleading concept, because the current nanoparticles cannot find their way to an intended target, but are simply distributed throughout the body by the blood circulation[40]. Only a very small fraction of the total administered nanoparticles end up at the target site, mostly by chance. The concept of the enhanced permeability and retention (EPR) effect is frequently cited whenever nanoparticles are used for drug delivery to tumors. However, most studies have not quantitatively measured the actual amount of drugs reaching the target tumor, and thus, there is no quantitative information on the role of the EPR effect in targeted drug delivery. The tumors grown in mice are usually 1~2 mm which are similar in size as the liver, but only a small fraction, in the range of about 1% of the total administered dose, of the so-called targeted nanoparticles end up at the tumors, while the majority ends up at the liver [41]. For nanoparticle systems to become a clinically effective tool for targeted drug delivery, they may have to be designed differently from those showing potential in small animal studies. The observations made in mice, which have only a few milliliters of blood, may not be extended to human with 5 liters of blood. Furthermore, the size ratio of a tumor in a mouse is usually much larger than that of a tumor in a human. This

massive scale differences need to be considered when experimental animal models are used and their data are analyzed.

Nanoparticles may have unexpected benefits, even though the anticipated targeting has not been observed yet. The nanoparticles, with suitable surface modification, may alter the biodistribution, which in turn, may alter the toxicity profiles of the same drug. In fact, reducing the toxicity, or the side effects, of the drug through engineering nanoparticle formulations may be a better way of utilizing the unique properties of nanoparticles. Doxil[®], the PEGylated liposome formulation, is a case in point. It was approved by the U.S. Food and Drug Administration not because of its improved drug efficacy, but because of its reduced cardiotoxicity [42]. Considering the difficulties in translating the targeting ability observed in mouse models to clinical applications, one could consider utilizing nanoparticle formulations for reducing the toxicity. This can be achieved not only by altering the biodistribution, but also by increasing the water-solubility without using toxic organic solvents. Good examples of this approach are Abraxane[®] and Genexol[®] as described above. Formulations without organic solvents, such as Cremophor EL or polysorbate, are certainly more desirable, especially when the resulting therapeutic efficacy is about the same [43].

4.4. Self-regulated drug delivery

Self-regulated drug delivery, in particular, self-regulated insulin delivery, remains one of the most important technologies to develop. Imagine that millions of diabetes patients can take care of their glucose level for months with one injection of self-regulated insulin delivery system, instead of multiple daily injections of insulin. There are several self-regulated insulin delivery systems developed over the years which work well in the laboratory setting[5–8, 44, 45]. As soon as they are introduced inside the body, however, their function decreases by hours. The glucose sensor, which is essential in detecting the varying glucose level, becomes less efficient due to protein adsorption and cell adhesion, and the insulin delivery module becomes less efficient after each cycle[18, 46, 47]. It has been several decades since the concept of self-regulated insulin delivery started, but the progress has been slow. This is also mainly due to the biological barriers that the body poses to the implanted device[48]. Unless the biological barriers are understood and the new delivery systems are designed to overcome those, development of self-regulated insulin delivery system will remain as a concept for a while. The biological barriers to overcome include maintaining glucose sensor specificity and sensitivity in the biological milieu. Another key requirement is to build an actuator that releases a right amount insulin fast with automatic turn-off function[13].

5. Perspective of the Future

Significant advances in drug development, along with better and early diagnostics for preventive medicine, have helped extend human life expectancy. This, in turn, requires development of more drugs for various diseases, such as coronary artery disease, diabetes mellitus, chronic pain, chronic lower respiratory disease, Alzheimer's disease, and Parkinson's disease. Finding drugs for these diseases is the first and most important step. The drug delivery systems can make drug candidates with poor water solubility into therapeutically effective drug formulation, and drug candidates with short half-lives into

sustained release formulations. The drug delivery technologies will have valuable contributions to the development of new drugs. Various drug delivery systems need to be developed for delivering drugs with various different properties.

Advances in drug delivery systems are the results of numerous trials and errors, i.e., results of an evolutionary process. Many different drug delivery systems need to be tried, and variations of the systems with most potential need to be repeated. This process will have to continue until a proper solution is found for a disease. Trying many different approaches requires diverse ideas, instead of the same approach that others have tried for a decade or longer. For example, a large number of nanoparticle-based drug delivery systems have been developed, but they are pretty much the same approach with only minute differences. Thus, it is not surprising to see the absence of any progress by this approach. If nanoparticles are such a great tool for delivering drugs to target sites, why is it that almost all nanoparticle systems are developed for targeted delivery to tumors? There are so many other important diseases, but only a few of them were dealt with nanoparticle formulations. This is why we have to expand our imagination outside the box. If the next generation of scientists are all bound inside the current box of nanotechnology, creating new drug delivery systems will take longer. It is time to try different ideas and approaches for various diseases.

It is emphasized again that the goal of studying drug delivery systems is to develop clinically useful formulations for patients. Development of effective drug delivery systems requires clear goals. Making a new delivery system alone is not enough. It has to work in the human body, i.e., safe and effective. The goal of clinical applications poses certain restrictions, and overcoming those from the early stage of the development is critical. Developing clinically useful drug delivery systems, which many incorrectly call solving practical problems, is based on understanding properties of the drug delivery systems as well as biological barriers. There is no so-called basic study versus practical study in drug delivery. There is only the study of developing clinical formulations treating various diseases.

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References

1. Davar, N.; Ghosh, S. Oral controlled release-based products for life cycle management. In: Wen, H.; Park, K., editors. *Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice*. New York, NY: John Wiley & Sons; 2010. p. 305-320.
2. Lee, PI.; Li, J-X. Evolution of oral controlled release dosage forms. In: Wen, H.; Park, K., editors. *Oral Controlled Release Formulation Design and Drug Delivery*. Hoboken, NJ: John Wiley & Sons, Inc.; 2010. p. 21-31.
3. Ye M, Kim SW, Park K. Issues in long-term protein delivery using biodegradable microparticles. *J. Control. Release*. 2010; 156:241–260. [PubMed: 20493221]
4. Heinemann L. The failure of Exubera: Are we beating a dead horse? *Journal of Diabetes Science and Technology (Online)*. 2008; 2:518–529.

5. Sung Wan K, Chaul Min P, Kimiko M, Seminoff LA, Holmberg DL, Gleeson JM, Wilson DE, Mack EJ. Self-regulated glycosylated insulin delivery. *Journal of Controlled Release*. 1990; 11:193–201.
6. Klumb LA, Horbett TA. Design of insulin delivery devices based on glucose sensitive membranes. *Journal of Controlled Release*. 1992; 18:59–80.
7. Kim JJ, Park K. Modulated insulin delivery from glucose-sensitive hydrogel dosage forms. *Journal of Controlled Release*. 2001; 77:39–47. [PubMed: 11689258]
8. Siegel RA. Stimuli sensitive polymers and self regulated drug delivery systems: A very partial review. *Journal of Controlled Release*. 2014; 190:337–351. [PubMed: 24984012]
9. Park K. Facing the truth about nanotechnology in drug delivery. *ACS Nano*. 2013; 7:7442–7447. [PubMed: 24490875]
10. Lee BK, Yun YH, Park K. Smart nanoparticles for drug delivery: Boundaries and opportunities. *Chemical Engineering Science*. 2015; 125:158–164. [PubMed: 25684780]
11. Guo, MX. Dissolution testing: In vitro characterization of oral controlled release dosage forms. In: Wen, H.; Park, K., editors. *Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice*. New York, NY: John Wiley & Sons; 2010. p. 245-256.
12. Lu Y, Kim SW, Park K. In vitro-in vivo correlation: perspectives on model development. *Int. J. Pharm.* 2011; 418:142–148. [PubMed: 21237256]
13. Park K. Controlled drug delivery systems: Past forward and future back. *Journal of Controlled Release*. 2014; 190:3–8. [PubMed: 24794901]
14. Okada, H. Depot injectable microcapsules of leuprorelin acetate (Lupron Depot). In: Morishita, M.; Park, K., editors. *Biodrug Delivery Systems: Fundamentals, Applications and Clinical Development*. Boca Raton, FL: CRC Press; 2009. p. 370-383.
15. Rawat, A.; Burgess, DJ. Parenteral delivery of peptides and proteins. In: Morishita, M.; Park, K., editors. *Biodrug Delivery Systems: Fundamentals, Applications and Clinical Development*. Boca Raton, FL: CRC Press; 2009. p. 50-68.
16. Cadot, J-M. In vitro-in vivo correlation: Application to biotech product development. In: Morishita, M.; Park, K., editors. *Biodrug Delivery Systems: Fundamentals, Applications and Clinical Development*. Boca Raton, FL: CRC Press; 2009. p. 341-356.
17. Martinez M, Rathbone M, Burgess D, Huynh M. In vitro and in vivo considerations associated with parenteral sustained release products: A review based upon information presented and points expressed at the 2007 Controlled Release Society Annual Meeting. *Journal of Controlled Release*. 2008; 129:79–87. [PubMed: 18514351]
18. Koschwanez HE, Reichert WM. In vitro, in vivo and post explantation testing of glucose-detecting biosensors: Current methods and recommendations. *Biomaterials*. 2007; 28:3687–3703. [PubMed: 17524479]
19. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A Provisional Biopharmaceutical Classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. *Molecular Pharmaceutics*. 2006; 3:631–643. [PubMed: 17140251]
20. Hörter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. *Advanced Drug Delivery Reviews*. 2001; 46:75–87. [PubMed: 11259834]
21. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. *European Journal of Pharmaceutical Sciences*. 2006; 29:278–287. [PubMed: 16815001]
22. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. *International Journal of Pharmaceutics*. 2011; 420:1–10. [PubMed: 21884771]
23. Lu Y, Park K. Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. *Int. J. Pharm.* 2013; 453:198–214. [PubMed: 22944304]
24. Paudel A, Worku ZA, Meeus J, Guns S, Van den Mooter G. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: Formulation and process considerations. *International Journal of Pharmaceutics*. 2013; 453:253–284. [PubMed: 22820134]

25. Soththivirat S, McKelvey C, Moser J, Rege B, Xu W, Zhang D. Development of amorphous solid dispersion formulations of a poorly water-soluble drug, MK-0364. *International Journal of Pharmaceutics*. 2013; 452:73–81. [PubMed: 23651642]
26. Sun DD, Lee PI. Probing the mechanisms of drug release from amorphous solid dispersions in medium-soluble and medium-insoluble carriers. *Journal of Controlled Release*. 2015; 211:85–93. [PubMed: 26054795]
27. Gelderblom H, Verweij J, Nooter K, Sparreboom A. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *Eur. J. Cancer*. 2001; 37:1590–1598. [PubMed: 11527683]
28. Kratz F. Albumin as a drug carrier: Design of prodrugs, drug conjugates and nanoparticles. *Journal of Controlled Release*. 2008; 132:171–183. [PubMed: 18582981]
29. Yardley DA. nab-Paclitaxel mechanisms of action and delivery. *Journal of Controlled Release*. 2013; 170:365–372. [PubMed: 23770008]
30. Kim TY, Kim DW, Chung JY, Shin SG, Kim SC, Heo DS, Kim NK, Bang YJ. Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clin. Cancer Res*. 2004; 10:3708–3716. [PubMed: 15173077]
31. Engels FK, Mathot RA, Verweij J. Alternative drug formulations of docetaxel: a review. *Anticancer Drugs*. 2007; 18:95–103. [PubMed: 17159596]
32. Norris LB, Qureshi ZP, Bookstaver PB, Raisch DW, Oliver Sartor M, Chen H, Chen F, Bennett CL. Polysorbate 80 hypersensitivity reactions: a renewed call to action. *Community Oncology*. 2010; 7:425–428.
33. Vander, AJ.; Luciano, D.; Sherman, J. *Human Physiology: The Mechanism of Body Function*. Eighth Edition. Vol. Ch. 17. Boston, MA: McGraw–Hill; 2001. p. 803
34. Shen W-C. Oral peptide and protein delivery: unfulfilled promises? *Drug Discovery Today*. 2003; 8:607–608. [PubMed: 12867138]
35. Yun Y, Cho YW, Park K. Nanoparticles for oral delivery: Targeted nanoparticles with peptidic ligands for oral protein delivery. *Advanced Drug Delivery Reviews*. 2013; 65:822–832. [PubMed: 23123292]
36. Rieux, Ad; Fievez, V.; Garinot, M.; Schneider, Y-J.; Pr at, V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. *J. Control. Release*. 2006; 116:1–27. [PubMed: 17050027]
37. Walle, CFVD. *Peptide and Protein Delivery*. Burlington MA: Academic Press; 2011. p. 360
38. Park K. Lessons learned from thermosensitive liposomes for improved chemotherapy. *J. Control. Release*. 2014; 174:219. [PubMed: 24440028]
39. Park K. Translation from mouse to human: Time to think in new boxes. *Journal of Controlled Release*. 2014; 189:187. [PubMed: 25091393]
40. Nichols JW, Bae YH. EPR: Evidence and fallacy. *Journal of Controlled Release*. 2014; 190:451–464. [PubMed: 24794900]
41. Hollis CP, Weiss HL, Leggas M, Evers BM, Gemeinhart RA, Li T. Biodistribution and bioimaging studies of hybrid paclitaxel nanocrystals: lessons learned of the EPR effect and image-guided drug delivery. *J. Control. Release*. 2013; 172:12–21. [PubMed: 23920039]
42. Barenholz Y. Doxil® - The first FDA-approved nano-drug: Lessons learned. *J. Control. Release*. 2012; 160:117–134. [PubMed: 22484195]
43. Stirland DL, Nichols JW, Miura S, Bae YH. Mind the gap: A survey of how cancer drug carriers are susceptible to the gap between research and practice. *J. Control. Release*. 2013; 172:1045–1064. [PubMed: 24096014]
44. Kitano S, Koyama Y, Kataoka K, Okano T, Sakurai Y. A novel drug delivery system utilizing a glucose responsive polymer complex between poly (vinyl alcohol) and poly (N-vinyl-2-pyrrolidone) with a phenylboronic acid moiety. *Journal of Controlled Release*. 1992; 19:161–170.
45. Peppas NA. Is there a future in glucose-sensitive, responsive insulin delivery systems? *Journal of Drug Delivery Science and Technology*. 2004; 14:247–256.
46. Gilligan BJ, Shults MC, Rhodes RK, Updike SJ. Evaluation of a subcutaneous glucose sensor out to 3 months in a dog model. *Diabetes Care*. 1994; 17:882–887. [PubMed: 7956636]

47. Wisniewski N, Reichert M. Methods for reducing biosensor membrane biofouling. *Colloids and Surfaces B: Biointerfaces*. 2000; 18:197–219. [PubMed: 10915944]
48. Abel PU, von Woedtke T. Biosensors for in vivo glucose measurement: can we cross the experimental stage. *Biosensors and Bioelectronics*. 2002; 17:1059–1070. [PubMed: 12392956]

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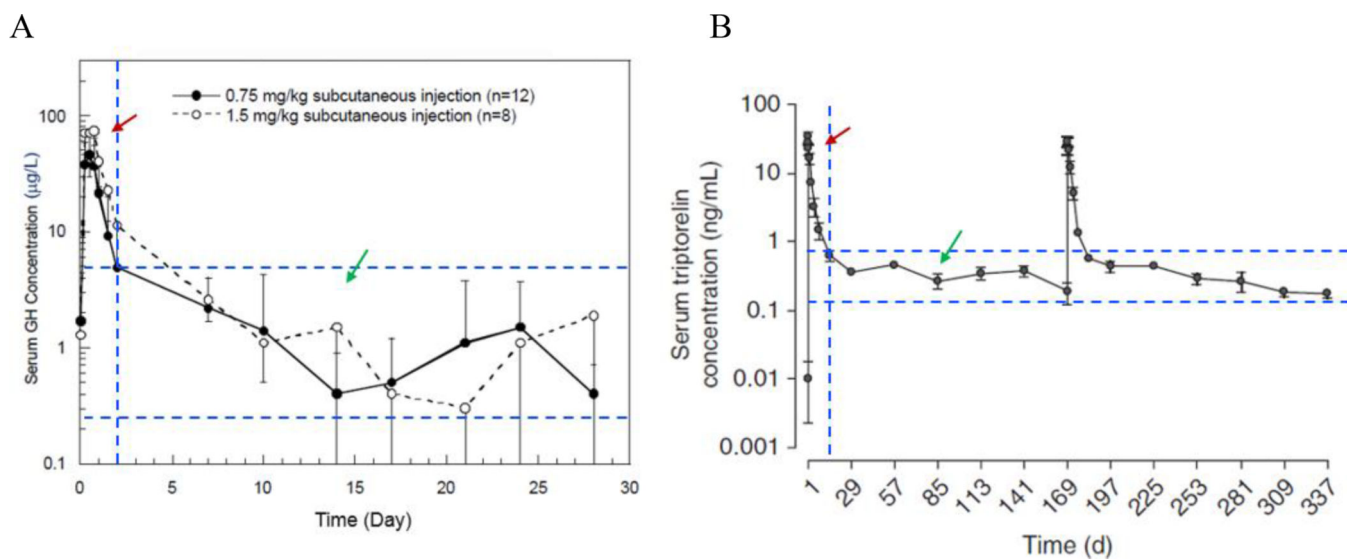


Figure 1. Examples of pharmacokinetic profiles of Nutropin Depot (A) and Trelstar (B) (obtained from the packaging inserts). The red arrow indicates the PK region resulting from the initial burst release of a drug, and the green arrow indicates the PK region of the therapeutically effective drug concentrations.

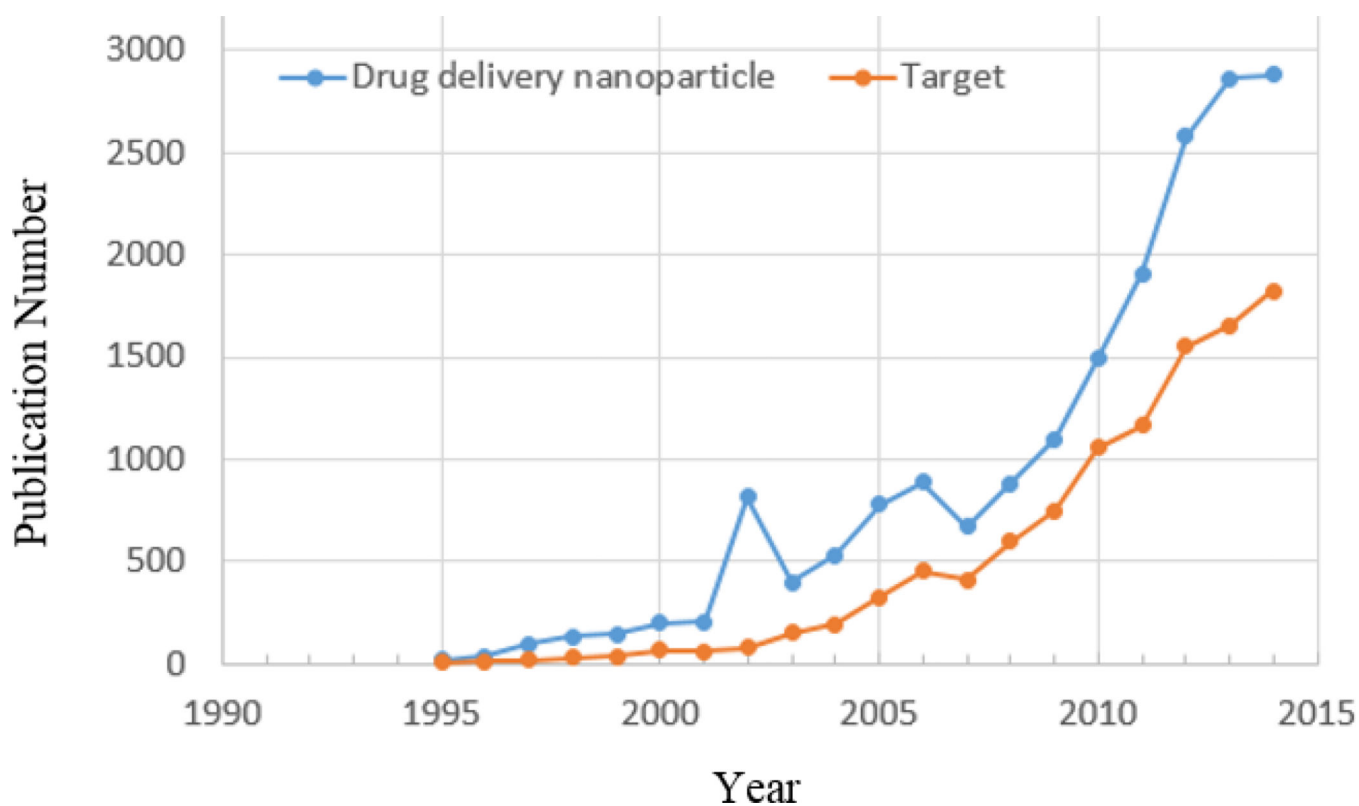


Figure 2. The number of articles on nanoparticle drug delivery systems published from 1995 to 2014. In SciFinder, the research topic of “drug delivery nanoparticle” was used for the initial search to find more than 30,000 references containing the concept. The search was further refined using the research topic of “target”.

Table 1

Drugs with different properties requiring different delivery systems.

	Drugs							
	Small Molecules				Large Molecules			
	BCS Class I	BCS Class II	BCS Class III	BCS Class IV	Peptides	Proteins	Nucleic Acids	
Molecular weight	↓	↓	↓	↓	↑	↑	↑	↑
Water solubility	↑	↓	↑	↓	↔	↔	↔	↔
Cell permeability	↑	↑	↓	↓	↓	↓	↓	↓
Half life	↔	↔	↔	↔	↓	↓	↓	↓
Main delivery route	Oral	Oral	Oral	Oral	Parenteral	Parenteral	Parenteral	Parenteral

BCS: Biopharmaceutics Classification System

↓: Low ↑: high ↔: Acceptable ↕: Individual variation from low to high

Table 2

History of drug delivery technology from 1950 to the present and the technology necessary for the future.

Year			
1950	1980	2010	2040
1st Generation		2nd Generation	
Basics of Controlled Release		Smart Delivery Systems	
Oral delivery <ul style="list-style-type: none"> • Twice-a-day, once-a-day 		Zero-order release <ul style="list-style-type: none"> • First-order vs zero-order 	
Transdermal delivery <ul style="list-style-type: none"> • Once-a-day, once-a-week 		Peptide & protein delivery <ul style="list-style-type: none"> • Long-term depot using biodegradable polymers • Pulmonary delivery 	
Drug release mechanisms <ul style="list-style-type: none"> • Dissolution • Diffusion • Osmosis • Ion-exchange 		Smart polymers & hydrogels <ul style="list-style-type: none"> • Environment-sensitive • Self-regulated release (working only <i>in vitro</i>) 	
		Nanoparticles <ul style="list-style-type: none"> • Tumor-targeted delivery • Gene delivery 	
Successful control of physicochemical properties of delivery systems		Inability to overcome biological barriers	
		Targeted drug delivery <ul style="list-style-type: none"> • Non-toxic to non-target cells • Overcoming blood-brain barrier 	
		Need to overcome both physicochemical and biological barriers	

Table 3

Barriers to overcome by the 3G drug delivery systems.

Delivery Technology	Formulation Barriers	Biological Barriers
Poorly water-soluble drug delivery	<ul style="list-style-type: none"> • New excipients for increasing drug solubility 	<ul style="list-style-type: none"> • Non-toxic to the body • No drug precipitation in the blood
Peptide/protein/nucleic acid delivery	<ul style="list-style-type: none"> • Control of drug release kinetics • Control of drug loading • Control of therapeutic period 	<ul style="list-style-type: none"> • IVIVC • Long-term delivery up to a year • Non-invasive delivery
Targeted drug delivery using nanoparticles	<ul style="list-style-type: none"> • Control of nanoparticle size, shape, surface chemistry, functionality, and flexibility. • Surface modification with ligands • Stimuli-sensitive delivery systems 	<ul style="list-style-type: none"> • Controlling biodistribution through altering vascular extravasation, renal clearance, metabolism, etc. • Navigating microenvironment of diseased tissues to reach target cells • Crossing endothelial barriers (e.g., blood-brain barrier) • Crossing mucosal barriers
Self-regulated drug delivery	<ul style="list-style-type: none"> • Signal specificity & sensitivity • Fast responsive kinetics • Ability to stop drug release 	<ul style="list-style-type: none"> • Functional inside the body • Functional over the lifetime of drug delivery

Table 4

Solubility Definitions.

Descriptive Terms	Parts of Solvent Required for 1 Part of Solute	Solubility Range	
		mg/mL	%
Very soluble	Less than 1	> 1,000	>100
Freely soluble	From 1 to 10	100 ~ 1,000	10 ~ 100
Soluble	From 10 to 30	33 ~ 100	3.3 ~ 10
Sparingly soluble	From 30 to 100	10 ~ 33	1 ~ 3.3
Slightly soluble	From 100 to 1,000	1 ~ 10	0.1 ~ 1
Very slightly soluble	From 1,000 to 10,000	0.1 ~ 1	0.01 ~ 0.1
Practically insoluble	10,000 and over	0.1	0.01

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Table 5

Methods to improve drug dissolution.

Enhancing Drug Solubility	Enhancing Dissolution Kinetics
Using surfactant micelles	Selecting appropriate polymorph
Using polymer micelles	Making amorphous forms (solid dispersions)
Using hydrotropic agents	Reducing particle size (nanocrystals)
Using complexing agents	Adding surfactant for better wetting
Using cosolvents	
Using self-emulsifying systems	
Controlling pH	

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