Journal of Controlled Release 344 (2022) 157–159

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Perspective on drug delivery in 2050☆

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1. Pictures of the past and present

The first comprehensive book on controlled drug delivery systems was edited by the late Professor Joseph R. Robinson published in 1978 [1]. It was revised and expanded upon by Professors Joseph Robinson and Vincent H.L. Lee in 1987 [2]. Around this time, controlled drug delivery technologies had been established in the clinic, and their utility fueled the introduction and development of various new controlled-release formulations along with numerous research articles and books. Professor Lee played crucial roles in maturing the controlled drug delivery field through his decades-long service as Editor-in-Chief of Pharmaceutical Research and Advanced Drug Delivery Reviews. It was a distinguished privilege working with him for the journal Pharmaceutical Research and learning from him how to see the big picture and the trend of the fast-growing and evolving drug delivery field.

Fig. 1 highlights the advances of the controlled drug delivery field from 1950 through key products approved by the U.S. Food and Drug Administration (FDA) [3]. For the first 40 years (1950–1990), the fundamental technologies of drug delivery (such as dissolution, diffusion, osmosis, and ion exchange) were established to propel drug delivery for 12 h by oral administration all the way to 5 years using an implantable device. Over the last 30 years, the field has been exploring the potential of nanomedicine. Of particular important advances during this period are PEGylation for improved stability leading to longer circulation times and new lipid formulations for enhanced efficacy through endosomal escape. While most nanomedicine research has been dedicated to tumor targeting, the technologies developed during this period, unbeknownst at the time, would prove to be crucial to developing and delivering COVID-19 vaccines in record time.

As shown in Fig. 1, the introduction of new drug delivery technologies has dominated the field for a few decades. The long-term delivery of small molecules, from 12 h to 5 years, was all based on the same drug release technologies, enabling the introduction of new products for more than four decades. The nanomedicine era produced PEGylated proteins, PEGyated liposomes, drug nanocrystals, antibody-drug conjugates, and nanoformulations for delivery of siRNA and mRNA. In particular, lipid nanoparticle formulations (LNPs) for Onpattro® and Comirnaty® have been the highlight of the achievements of the drug delivery field. The successes of the LNPs will carry over for the next decade or two, and significant resources will be poured into this technology platform. Better LNP formulations need to be developed for more stable formulations and with more specific targeting properties. As the results of the decades-long nanomedicine studies have shown, if the majority of scientists are involved in the same or similar technologies, the progress is bound to be limited and narrow [4]. This, in turn, takes the resources away that otherwise can be used for other wild and ethereal ideas. Scientists and the field need to be cautious with the herd mentality. The limitations of the LNPs need to be clearly understood. For example, the success of lipid nanoparticles in the COVID-19 vaccine should be taken as a success in vaccine delivery, not drug delivery in general. Vaccine delivery is far different from delivery of therapeutic agents at specific concentrations for predetermined periods. Thus, refrain should be exercised when trying to utilize the recent success of LNPs as a vehicle for every drug or indication.

2. The big picture for the next 30 years

In only 30 years from now, the drug delivery field will have its 100th birthday. Predicting the drug delivery field in the next 30 years is mostly irrelevant, but building a vision for the future is highly relevant. It has been said many times that the best way to predict the future is to invent it, meaning that our decisions and actions today have consequences that shape our future [5]. If all drug delivery scientists are involved in building the future vision by carrying out their own ideas, it will be the engine for creating the future. It is the ensemble of the infinite variety and vastness of visions of the future that will come true. We all have to be involved in creating and shaping the future. The question facing us now is what can be done in the future and what should be done in the present to move the field to another level.

As technological advances are exponential, many exciting new

☆ For the Special Issue Dedicated to Professor Vincent H.L. Lee.

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https://doi.org/10.1016/j.jconrel.2022.02.025
Received 15 January 2022; Received in revised form 13 February 2022; Accepted 18 February 2022
Available online 21 February 2022

technologies will emerge, but many will fail or not find usefulness immediately. This should not be construed as a failure but rather an addition to the knowledge database and the current toolbox of drug delivery technologies. That technology could be the weapon needed to combat the next pandemic. However, only those demonstrating safety and efficacy will survive, and unfortunately, essential clinical studies typically require decades. Without timely clinical studies, all advances in drug delivery technologies remain "potential." Thus, developing *in vitro* and small animal models that can predict clinical outcomes will be essential. A good example is the recent approval of aducanumab (Aduhelm®), the amyloid-β-targeted monoclonal antibody to treat Alzheimer's disease. Aducanumab was approved based on the demonstration of decreased amyloid-β levels in the brain in a dose-related fashion relative to placebo, despite the absence of clear demonstration of clinical efficacy [6]. While there is a controversy in the approval process, it signals that surrogate endpoints may substitute the costly clinical trials. Whether the biomarker approach is acceptable or not will depend on the ultimate clinical outcomes of many more drugs for treating debilitating diseases. Development of the models that can predict clinical outcomes requires exploring diverse ideas by independent minds instead of me-too minds. This, in turn, requires cultivating confident scientists who are not easily swayed by the most popular trend at the time. This also necessitates revamping the current funding system to support independent minds.

2.1. Overcome the body's own defense system

With the technologies already available and those to be developed, we can think of the priorities in future formulations. While each disease is devastating for those affected by it, we can start with the leading causes of death [7]. Heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer's disease, diabetes mellitus, kidney disease, chronic liver disease and cirrhosis, influenza and pneumonia, hypertension, and depression are leading causes of death in the USA and worldwide. Many of these conditions are chronic, making the treatment even more challenging. In addition, many of the leading diseases have no curative treatments. If patients can live everyday lives with the disease(s) with adequate treatments, it can be considered an acceptable answer for now. Chronic diseases require long-term treatment, demanding many more long-acting drug delivery systems that can last for months and years. In addition, some diseases, such as diabetes, require delivery of a drug only when necessary. We need to reactivate our work on modulated release formulations that began in the 1980s. Modulated insulin delivery is a (and even sometimes considered "the") holy grail of drug delivery, i.e., tremendously challenging but enormously rewarding. Higher efficacy with lower side effects can be enabled with targeted drug delivery. The nanomedicine era has explored various approaches for targeted drug delivery, but as of 2022, the delivery systems need to overcome the body's own defense system.

2.2. Precision medicine

Treatment of various diseases will increase as the specificity and potency of the drugs increase, coupled with a growing and deeper understanding of the biological nature of the disease. More exquisite drugs, such as peptides, proteins, and nucleic acids, will be developed, but small molecular weight drugs will continue to dominate the market overall. This is simply due to the enormous benefits of small molecules over other types of drugs in terms of easy preparation, higher stability, long-term delivery, and, most importantly, lower cost. Thus, small molecular weight drugs mimicking the efficacy of large molecule drugs will be actively pursued. All FDA-approved drugs are safe and effective. However, it does not mean that a drug is effective for all patients who use it. The efficacy in clinical studies is measured by whether a drug shows a statistically higher efficacy than a placebo, i.e., not all patients may realize the drug's benefit. This is where precision medicine comes into play. "Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our

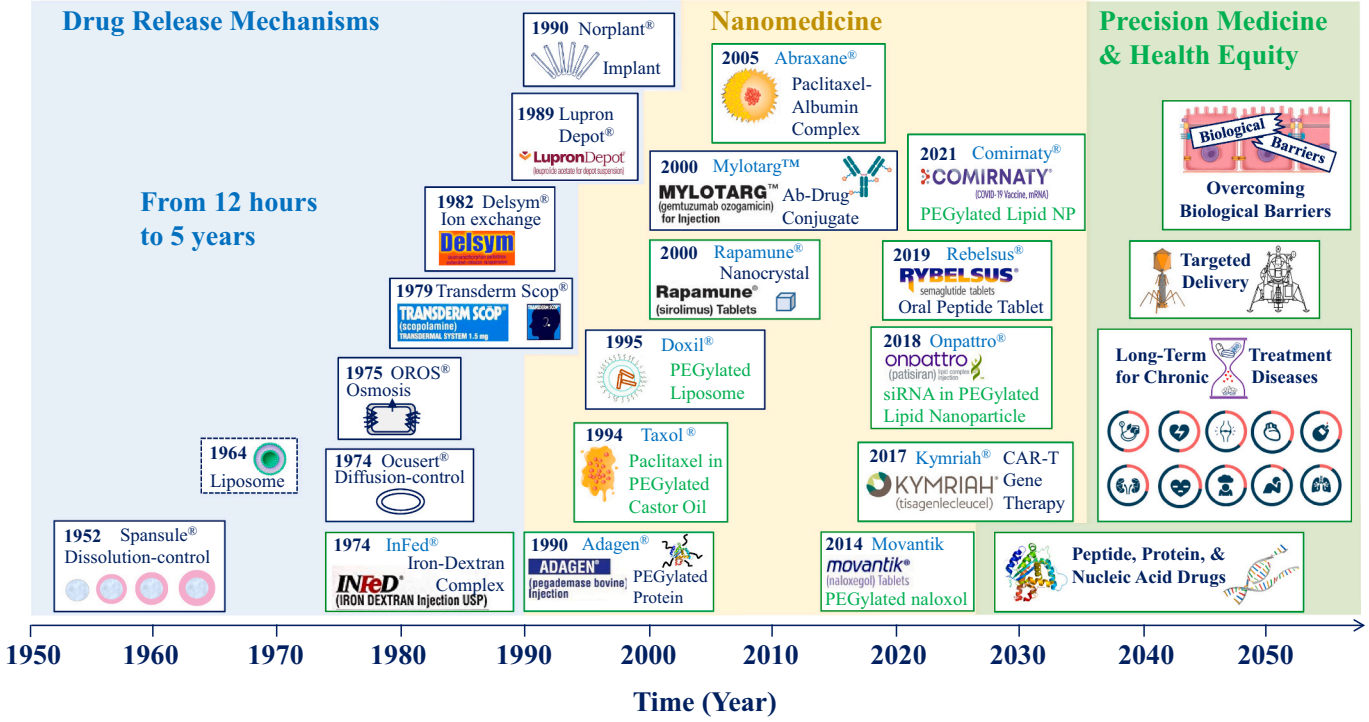

Fig. 1. Evolution of drug delivery systems during the last seven decades in two distinct stages: Development of controlled drug delivery technologies from 12 h to 5 years during 1950–1990 and the advent of nanomedicine (1990–2020). The key technologies are described by the formulations approved by the FDA. (Modified from [3]).

genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?" [8].

2.3. Health equity

The future will always be better than the present. Healthcare should be affordable for everybody. Implementing precision medicine for everybody requires lowering the health care cost dramatically. The availability of new drugs and treatments, including potential curative treatments via gene therapy, does not mean much for those who cannot afford them. Functional cures for chronic conditions, such as sickle cell disease, are on the horizon, although its treatment cost is staggering at around $100,000/year [9]. Another example is the approval of aducanumab. Its initial price for treatment was $56,000/year, which was subsequently reduced to half. The drug is only for those who can afford it, whether clinically effective or not. The health equity issue also applies to the availability of the COVID-19 vaccine throughout the world, where less than 9% of the African continent was vaccinated by the end of 2021 [10]. Economic models will rationalize that the treatment is more cost beneficial than the lifetime costs of treating the disease, which is often true. If companies and policymakers in the world cannot come together and find a means to get patients these treatments, have we as a society cured the disease?

Low-cost, affordable health care is a must for all of us to be taken care of properly and realize the benefits of medical and pharmaceutical progress. Low-cost health care is not just about the drug cost. It includes making the formulation more affordable through a series of innovations in drug delivery technologies and delivery systems that can allow better efficacy, prolonged efficacy, and reduced side effects, all of which reduce office visits and minimize wastes of packaging materials and disposable items. Low-cost health care will naturally lead to health equity. Even in the same country, health care quality varies significantly based on geographical location (related to the economy) and individual affordability.

2.4. The future is bright

Our quick responses against the COVID-19 pandemic have limited its damage, and it appears countries are moving into the endemic phase. This brings hope for still higher responses to whatever new diseases we will face in the future. Maybe COVID-19 is training us to prepare for the future. Understanding what we have done now and what we have not will allow us to focus on what we can do in the future to keep improving drug delivery technologies. Such a visceral experience of future possibilities allows our long-term view, keeping near-termism at bay [11]. Let's focus on what matters in our daily lives, not just the number of publications and patents. Let's continue our journey of making this world a bit better by visualizing that our big future is without boundaries. As we grasp the seriousness of future diseases, we can improve the world with our policies and technologies [12]. Let's make an entirely new converging world where we can deal with any challenges and everyone can access the same health care. It is our future after all, and we are all the same.

Acknowledgments

This study was supported by the Showalter Research Trust Fund and in part by UG3 DA048774 from the National Institute on Drug Abuse (NIDA).

References

[1] J.R. Robinson, Sustained and Controlled Release Drug Delivery Systems, Dekker, New York, NY, 1978, 773 pages.
[2] J.R. Robinson, V.H.L. Lee, Controlled Release Drug Delivery: Fundamentals and Applications. Second Edition, Revised and Expanded, CRC Press, New York, NY, 1987, 716 pages.
[3] H. Park, A. Otte, K. Park, Evolution of drug delivery systems: from 1950 to 2020 and beyond, J. Control. Release 342 (2022) 53–65.
[4] Y.H. Bae, K. Park, Advanced drug delivery 2020 and beyond: perspectives on the future, Adv. Drug Deliv. Rev. 158 (2020) 4–16.
[5] E. Catmull, A. Wallace, Creativity, Inc.: Overcoming the Unseen Forces That Stand in the Way of True Inspiration, Random House, 2014, 368 pages.
[6] K.Y. Liu, R. Howard, Can we learn lessons from the FDA's approval of aducanumab? Nat. Rev. Neurol. 17 (2021) 715–722.
[7] M. Heron, Deaths: leading causes for 2019, Natl. Vital Stat. Rep. 70 (2021) 1–114.
[8] B.H. Obama, The Precision Medicine Initiative. https://obamawhitehouse.archives.gov/precision-medicine, 2015.
[9] PBS, U.S. Approves New Drug to Manage Sickle Cell Disease, Costs $85,000 to $113,000. https://www.pbs.org/newshour/health/u-s-approves-new-drug-to-manage-sickle-cell-disease-costs-85000-to-113000, 2019.
[10] Editorial, Time for Africa to future-proof, starting with COVID-19, Lancet Infect. Dis. 22 (2022) 151.
[11] C. Ertel, L.K. Solomon, Moments of Impact: How to Design Strategic Conversations That Accelerate Change Simon & Schuster, 2014, 272 pages.
[12] A. Saenz, Hans Rosling Shows You 200 Years of Global Growth in 4 Minutes. https://singularityhub.com/2010/12/09/hans-rosling-shows-you-200-years-of-global-growth-in-4-minutes-video/, 2010.