



The drug delivery field at the inflection point: Time to fight its way out of the egg

Kinam Park^{a,b,*}

^a Purdue University, Department of Biomedical Engineering, West Lafayette, IN 47907, USA

^b Purdue University, Department of Pharmaceutics, West Lafayette, IN 47907, USA



ARTICLE INFO

Keywords:

Nano-sized drug delivery systems
 Nanoformulations
 Clinical trials
 Inflection point
 Inconvenient truth
 Advantage of nanoformulations
 Limitations of nanoformulations
 Future of drug delivery

ABSTRACT

The world is becoming a better place, in part, by breakthrough findings by scientists. In the drug delivery field, many breakthrough formulations have been achieved helping patients deal with various diseases effectively. The recent progress, however, has been slowing down, and many important drug delivery problems have not been resolved. They can be overcome by understanding the causes and finding the remedies. For the last three decades, the field has been overwhelmed by nanotechnology, nanomedicine, and many nano-sized drug delivery systems. Disappointing outcomes of nano-sized formulations (nanoformulations) in clinical studies indicate that our overall approach of nanomedicine needs serious reevaluation. The limited advantages of nanoformulations were drastically exaggerated, and the assumptions used in nanomedicine and nanoformulations turned out to be inapplicable to clinical applications. The drug delivery field is at the strategic inflection point, and we all have to face the reality by absorbing the inconvenient truth and fight our way out of the egg to break the ill-conceived illusion of nanomedicine. Scientists are proud of their independent thinking and their work that can change the world, but the current climate does not allow them to be true scientists. The future of the drug delivery field depends on how effectively we can find talented young scientists with motivation, cultivate them with resources, provide them with an environment for the free exchange of ideas, and nurture them with purpose, passion, and the conviction of doing meaningful science.

1. A very brief history of science and drug delivery

When we look back at the history of scientific advances, we are always marveled by those who came up with ideas against the majority or with ideas that did not before exist. Nicolaus Copernicus, Johannes Kepler, and Galileo Galilei suggested that the Earth revolves around the Sun, based on the data, against the common belief by the majority at the time. Charles Darwin framed the theory of evolution from the data he collected at Galapagos. Sir Isaac Newton and Albert Einstein came up with theories of gravity and the fabric of time, respectively, that were not known to humans before their times. One question to ask is what unique characteristics allow them to come up with such earth-shattering ideas? There are no easy answers, as there are too many traits to be analyzed and simplified into a few parameters [1]. All those great scientists, however, were able to see problems where nobody else realized that they even existed [2,3], and had “passionately curious minds” [4] to learn what they did not know based on scientific data and reasoning. The data-based deduction is what great scientists do. Fast forward to the Year 2017. Do we have such passionately curious minds

around us now in the drug delivery field? The passionately curious minds lead to different ideas from existing dogmas, eventually leading to new findings that make real differences. The advances in science will occur fast, if different opinions are cherished. Having opposing views and discussing them leads to progress. The current political system where two opposing views fight constantly against each other appears to paralyze the government, but it is exactly the reason why the democratic society progresses, albeit slowly, without major catastrophe. The democratic society makes progress by trial-and-error, trying one idea at a time, and it works even though it seems painfully slow.

The history of the drug delivery field is less than 70 years old. The term “controlled drug delivery system” means a formulation that delivers a drug at a rate controlled by the formulation itself. Thus, a formulation that does not have a built-in mechanism of controlling the drug release rate is called an “immediate release” system. The controlled drug delivery includes “sustained release”, “timed release”, “extended release”, “modified release”, “programmed release”, and others. The drug delivery technology began in 1952 with the introduction of the Spansule technology that delivers a drug for 12 h

* Corresponding author at: Purdue University, Weldon School of Biomedical Engineering, 206 S. Martin Jischke Drive, West Lafayette, IN 47907, USA.
 E-mail address: kpark@purdue.edu.

[5,6]. Compared with taking a drug every 6 h or every 8 h, twice-a-day formulation was a game changer in enhancing the patients' convenience and compliance. The introduction of the first revolutionary idea was followed by many controlled release formulations, especially for oral and transdermal administrations, over the next 30 years [7]. The mechanisms of controlled drug delivery were largely established during that period. Since the 1980s, however, development of clinically used products became sluggish. This was partly due to the difficulties in the mission of drug delivery systems. The mission requires much more than simply releasing a drug at a certain rate. The drug has to be delivered to targets overcoming biological barriers, and in some cases, the temporal drug delivery is required. The drug delivery field needs new revolutionizing concepts to improve drug delivery for treating heart disease, cancer, diabetes, Parkinson's disease, Alzheimer's disease, and various other diseases.

2. Drug delivery research: where are we now?

Many drug delivery scientists contribute to the advances of drug delivery technologies in different ways ranging from basic study to product development. Developing a successful clinical formulation requires synthesis of a new chemical entity, preformulation characterization, formulation design, biopharmaceutical characterization, process optimization, and scale-up manufacturing [8]. For each drug delivery system approved by the U.S. Food and Drug Administration (FDA), there are hundreds of formulations tested by many scientists and engineers. In the drug delivery field, whatever research area a scientist is engaged in, the ultimate goal is to contribute to or develop formulations making clinical impacts. Reviews on the history of drug delivery systems are available [9–11]. Here, the focus is on the drug delivery field for the last 30 years.

Many new oral and transdermal controlled release formulations have been introduced for clinical use. While each formulation may be unique, the underlying principles of controlling drug release remain the same as when they were developed several decades ago. Most of the oral formulations use either dissolution- or diffusion-controlled mechanisms, or a combination of both. Unlike oral and transdermal drug delivery systems, development of injectable long-acting depot formulations and targeted delivery intravenous formulations has been sluggish. The potential of new drug delivery technologies, especially based on nanotechnology, has not been translated into clinical formulations that benefit patients. It is necessary to understand where we are and what happened, so that we can escape from the current stalemate to expand our research horizons and to accelerate advances in drug delivery technologies for the future [12]. The following sections deal with the nature of nanomedicine and nanoformulations with critical assessments. The main intention of the analysis is to understand the situation correctly so that the correct answers can be found.

2.1. The 10 leading causes of death in U.S.A.

The Centers for Disease Control and Prevention (CDC) published leading causes of death for 2014 in the United States by age, sex, race, and Hispanic origin based on information from all death certificates filed in the 50 states and the District of Columbia in 2014 [13]. The 10 leading causes of death for males and females are shown in Fig. 1. There are slight differences in rank order between males and females, but diseases of the heart, malignant neoplasms, and chronic lower respiratory diseases occupy half of all death. Stroke, Alzheimer's disease, diabetes, and influenza and pneumonia account for 11–16% of all death. When it comes to malignant neoplasms, there are dozens of different tumors occurring in the oral cavity and pharynx, esophagus, stomach, colon, rectum and anus, liver and intrahepatic bile ducts, pancreas, larynx, trachea, bronchus and lung, skin, breast, uterus, and other parts of the CNS [13]. Each of them requires different treatment. Each tumor is unique and does not represent others, and no single

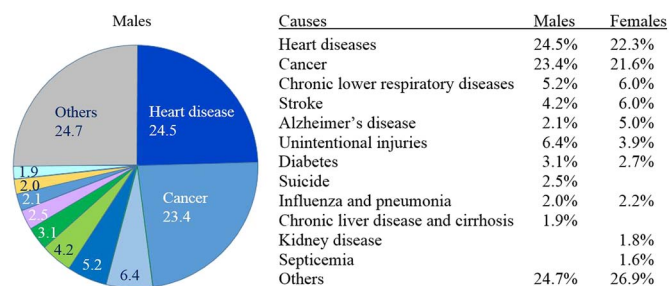


Fig. 1. Percent distribution of the 10 leading causes of death, by sex: United States, 2014. (From [13]).

anticancer drug is able to treat all tumors.

As shown in Fig. 1, there are many important diseases to treat, and even in cancer, there are many different types of tumors to conquer. Despite such diversity in diseases and tumor types, however, the majority of current research on drug delivery has been focused only on tumor-targeted drug delivery. Even in this highly focused research topic, little progress has been made after almost three decades of research. It is time to take a step back and absorb the fact and examine the current status of the drug delivery field. First, why does most of the current drug delivery research deal with only tumor-targeted drug delivery? Second, why has the progress in tumor-targeted drug delivery been so slow? Third, what are the reasons for the current stalemate in drug delivery in general? Fourth, what can we do to overcome this conundrum? Without proper analysis and understanding of the current situation, further advances in the future will be hindered.

2.2. What are the definitions of nanotechnology, nanomedicine, and nanoformulation anyway?

For the last three decades, the drug delivery field has been overwhelmed by nanomedicine, which is an offshoot of nanotechnology. The term “nanotechnology” was defined as “science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers” [14]. The term “nanomedicine” refers to “highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve” [15]. It is further explained that “It is at this size scale - about 100 nanometers or less - that biological molecules and structures operate in living cells” [15]. These definitions sound magnificent and futuristic, but closer examination of the definitions to acquire better understanding makes it confusing. First, if the matter we are dealing with is larger than 100 nm, is it not qualified to be called nanotechnology? What are the scientific criteria that set the boundary at 100 nm? Would it make a sense, if the size is limited to 200 nm, 300 nm, or larger? Second, the description of nanomedicine is so generic that the term “nanomedicine” can be easily named by others, e.g., “molecular medicine”. After all, if medical interventions are made at the molecular scale, isn't it better to call it “molecular medicine”? If engineering occurs at the molecular level, isn't it what we call chemistry, biochemistry, and molecular biology? The prefix “nano” has dominated the science throughout the world with no particular rationale; just like the prefix “i” dominated the market since the successful introduction of iPod. It is these arbitrary, generic definitions of nanotechnology and nanomedicine that set the stage of a decades-long stray from the otherwise more productive, useful, and practical path. Even nowadays, many scientists, engineers, and clinicians who are not familiar with the drug delivery field think that nanotechnology or nanomedicine, will solve their research problems regardless of the nature of the problems.

In drug delivery systems, there are not many systems that are truly less than 100 nm in size. The drug delivery systems exist to deliver a drug, and the system less than 100 nm does not have enough reservoir space for effective drug delivery. Most polymer micelles, which are one

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات