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Smart nanoparticles for drug delivery: Boundaries and opportunities

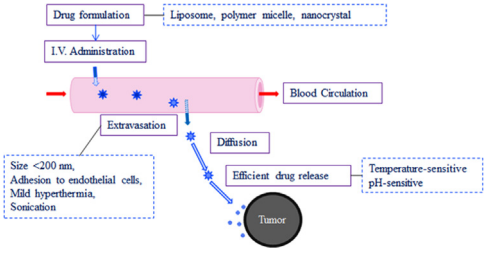
Byung Kook Lee [a], Yeon Hee Yun [a], Kinam Park [a,b,*]

[a] Purdue University, Weldon School of Biomedical Engineering, West Lafayette, IN 47907, USA
[b] Purdue University, Department of Industrial and Physical Pharmacy, West Lafayette, IN 47907, USA

HIGHLIGHTS

- Provide correct information on nanoparticle-based targeted drug delivery to tumors.
- Nanoparticles are not magic bullets and have various limitations in drug delivery.
- New smart nanoparticles require overcoming physiological barriers.
- Need to exploit reduced side effects by nanoparticles via altered bio-distribution.

GRAPHICAL ABSTRACT



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ABSTRACT

Various pharmaceutical particles have been used in developing different drug delivery systems ranging from traditional tablets to state-of-the-art nanoparticle formulations. Nanoparticle formulations are unique in that the small size with huge surface area sometimes provides unique properties that larger particles and bulk materials do not have. Nanoparticle formulations have been used in improving the bioavailability of various drugs, in particular, poorly soluble drugs. Nanoparticle drug delivery systems have found their unique applications in targeted drug delivery to tumors. While nanoparticle formulations have been successful in small animal xenograft models, their translation to clinical applications has been very rare. Developing nanoparticle systems designed for targeted drug delivery, e.g., treating tumors in humans, requires clear understanding of the uniqueness of nanoparticles, as well as limitations and causes of failures in clinical applications. It also requires designing novel smart nanoparticle delivery systems that can increase the drug bioavailability and at the same time reduce the drug's side effects.

1. Introduction

Pharmaceutical particles include a variety of sizes and shapes, ranging from traditional tablets and granules to microparticles and nanoparticles. The relative sizes of commonly used pharmaceutical particles are shown in Fig. 1. Tablets are most well-known and accepted formulations with a long history. Powders are processed and granules are made to make tablet formulations. Quite frequently, however, granules are used to make formulations different from traditional immediate release tablets. Drug-containing granules can be mixed or coated with pharmaceutical polymers to render them with delayed release or sustained release properties. In fact, the first sustained release drug delivery systems were made in 1952 by coating drug-containing cores with a polymer of varying thicknesses (Dokoumetzidis and Macheras, 2006). Microparticle and nanoparticle formulations are a more recent development in drug delivery. Microparticles are used to make long-term (i.e., weeks to months) depot formulations that can be injected by subcutaneous or intramuscular routes. The polymers

* 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 (K. Park).

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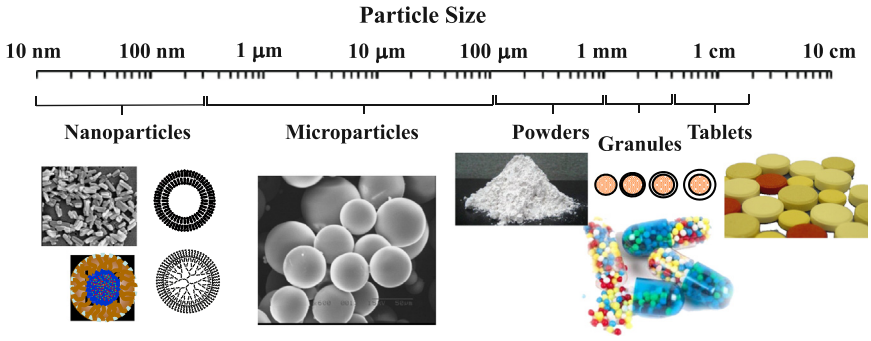

Fig. 1. Relative sizes of various pharmaceutical particles ranging from nanoparticles to tablets.

used for long-term microparticle formulations are biodegradable so that the microparticles do not have to be removed after its lifetime is over, i.e., once all loaded drug is released. The most widely used biodegradable polymer is poly(lactic-*co*-glycolic acid) (PLGA). For more than a decade, nanoparticles have been used for developing formulations with special features, and the research on the nanoparticle-based drug delivery systems has dominated the literature. While significant advances have been made, the current nanoparticle-based formulations require drastic improvements to achieve their intended goals of developing unique delivery systems that others could not have achieved.

Recent review articles describe many aspects of nanoparticles, such as history, advances, advantages, and potentials (Zhang et al., 2008, 2013; Cho et al., 2008; Irvine, 2011; Florence, 2012; Brannon-Peppas and Blanchette, 2012; Crommelin and Florence, 2013; Allen and Cullis, 2013; Thoma et al., 2014). All nanoparticle-based drug delivery systems were developed largely by trial-and-error approach in a long chain of case-by-case studies without a rational formulation design (Wacker, 2013). While promises and potentials have been the main topics of most review articles, the real progress requires a clear understanding of the current status, mainly limitations, of nanoparticle technologies. Without defining the problem, its solution will not be found. The objective of this article is to examine the promises, in the context of limitations, of nanoparticles used in the drug delivery field. In particular, the current misconceptions blocking faster progress are discussed. The majority of the articles in the literature on nanoparticles deal with targeted drug delivery to tumors, only one aspect of numerous drug delivery technologies. To realize breakthroughs in the targeted drug delivery area as well as in other equally important areas, the strength and limitations of the current nanoparticle technology need to be carefully evaluated for opening up new opportunities.

2. Nanoparticle: Definition

The term “nanoparticle” has become fashionable and almost all scientific literature deals with nanoparticles in one way or another. In the drug delivery area, the first nanoparticles of 100 nm diameter were made of poly(methyl methacrylate) as a new adjuvant in 1976 (Kreuter and Speiser, 1976). Since then, literally hundreds of thousands of articles deal with nanoparticles, and yet, the clear definition of nanoparticles is lacking. According to the National Nanotechnology Initiative (www.nano.gov), nanotechnology is utilizing the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at the nanoscale, i.e., the dimensions between approximately 1 nm and 100 nm. Both International Organization of Standardization (ISO) and American Society for Testing Materials (ASTM) have provided their definitions of nanoparticles which are practically the same (ISO/TS, 2008; ASTM). A nanoparticle is defined as a nano-object with all three dimensions in the size range from approximately 1 nm to 100 nm. Thus, nanoparticles are those within this size range. The IUPAC also defines nanoparticle as a particle of any shape with dimensions in the 1–100 nm range (Vert et al., 2012); however, there is no specific reason to use 100 nm as the size that separates nanoparticles from non-nanoparticles (Ruzer, 2013). The only guiding principle of differentiating nanoparticles is that novel properties which bulk materials typically do not have can be developed, if the size is below 100 nm. Also, included in the IUPAC definition of nanoparticle is when the objects with only two dimensions are below 100 nm, e.g., tubes and fibers (Vert et al., 2012). Thus, the definition of nanoparticle is not really based on the exact size of the particles, rather depends on whether nanoparticles have novel properties that non-nanoparticles of the same material do not have.

2.1. Novel properties of nanoparticles

The fascination on the novel properties of nanoparticles mainly stems from the fact that nanoparticles have a huge surface area as compared with microparticles or other bulk materials. The assumption that goes together with this huge surface area is that the properties of nanoparticles are very different from larger particles. The relatively significant amount of atoms and molecules on the surface of nanoparticles is expected to bring interesting new properties. But the question is whether there have been any really interesting and unexpected properties that only nanoparticles have while their bigger counterparts do not. These novel properties should not include those which are already well known through traditional colloid chemistry. For example, colloidal gold particles have been made since the days of Michael Faraday in the middle of the 19th century (Faraday, 1857), and it has been well known that the color of colloidal gold particles changes depending on the size of the gold particles. If such a well-known phenomenon is considered a representation of a novel property of nanoparticles, then current nanoparticles in general really do not provide any unique properties. Likewise, the nanoparticles that are supposed to have novel properties are not really new. Thus, the question is what novel properties do nanoparticles provide that have not been known. This question is important in applications of nanoparticles to the pharmaceutical industry, in particular, drug delivery systems where drug-loaded nanoparticles are usually larger than 100 nm. The current fever in nanoparticles is largely based on the assumed, yet unrecognized, novel properties.

2.2. Advantages of nanoparticles over small molecules

Although the nanoparticle itself may not possess any novel properties, nanoparticle formulations could provide new properties that may benefit drug delivery. Nanoparticles are distinguished from small molecules which represent free drugs that are not incorporated