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Perspective

Nanotechnology: What it can do for drug delivery

1. Nano and micro systems

Every so often, a new term comes along that represents an emerging scientific trend. Biotechnology, genetic engineering, tissue engineering, gene therapy, combinatorial chemistry, high throughput screening, and stem cells are some examples of past terms. Recently, nanotechnology has become a popular term representing the main efforts of the current science and technology. Nanotechnology, which is still not a mature technology and thus, more appropriately called nanoscience, usually refers to research at the scale of 100 nm or less. Nanotechnology is unique in that it represents not just one specific area, but a vast variety of disciplines ranging from basic material science to personal care applications. One of the important areas of nanotechnology is "nanomedicine," which, according to the National Institute of Health (NIH) Nanomedicine Roadmap Initiative, refers to highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of diseases [1].

Nanomedicine, like other technologies that have come before it, has incredible potential for revolutionizing the therapeutics and diagnostics under the premise of developing ingenious nanodevices. Drug delivery nanosystems constitute a significant portion of nanomedicine. In drug delivery, however, describing nanotechnology based on a size limit is pointless because the efficiency and usefulness of drug delivery systems are not based only on their sizes. Useful drug delivery systems range from truly nanosystems (e.g., drug–polymer conjugates and polymer micelles) to micro particles in the range of 100 μm. Both nano- and micro scale systems have been extremely important in developing various clinically useful drug delivery systems. For practical reasons, in this perspective, "nanotechnology" includes "micro technology," and "nanofabrication" or "nanomanufacturing" and its micro counterparts.

2. Nanotechnology in drug delivery

Nanotechnology received a lot of attention with the never-seen-before enthusiasm because of its future potential that can literally revolutionize each field in which it is being exploited. In drug delivery, nanotechnology is just beginning to make an impact. Many of the current "nano" drug delivery systems, however, are remnants of conventional drug delivery systems that happen to be in the nanometer range, such as liposomes, polymeric micelles, nanoparticles, dendrimers, and nanocrystals. Liposomes and polymer micelles were first prepared in 1960's, and nanoparticles and dendrimers in 1970's. Colloidal gold particles in nanometer sizes were first prepared by Michael Faraday more than 150 years ago, but were never referred to or associated with nanoparticles or nanotechnology until recently. About three decades ago, colloidal gold particles were conjugated with antibody for target specific staining, known as immunogold staining [2]. Such an application may be considered as a precursor of recent explosive applications of gold particles in nanotechnology. The importance of nanotechnology in drug delivery is in the concept and ability to manipulate molecules and supramolecular structures for producing devices with programmed functions. Conventional liposomes, polymeric micelles, and nanoparticles are now called "nanovehicles," and this, strictly speaking, is correct only in the size scale. Those conventional drug delivery systems would have evolved to the present state regardless of the current nanotechnology revolution. To appreciate the true meaning of nanotechnology in drug delivery, it may be beneficial to classify drug delivery systems based on the time period representing before and after the nanotechnology revolution.

3. Before and after nanotechnology revolution

As shown in Table 1, the drug delivery technologies in relation to the current nanotechnology revolution can be classified into three categories: before nanotechnology revolution (past); current transition period (present); and mature nanotechnology (future). The examples of drug delivery systems of the past (prior to the current nanotechnology revolution) are liposomes, polymeric micelles, nanoparticles, dendrimers, and nanocrystals, as mentioned above. The current drug delivery systems include microchips, micro needle-based transdermal therapeutic systems, layer-by-layer assembled systems, and various micro particles produced by ink-jet technology. These efforts are just beginning and many fabrication methods have been developed. The future of drug delivery systems, as far as

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Table 1. Examples of drug delivery technologies in relation to the current nanotechnology revolution

Period	Before nanotechnology (past)	Transition period (present)	Mature nanotechnology (future)
Technology	Emulsion-based preparation of nano/micro particles	Nano/micro fabrication	Nano/micro manufacturing
Examples	–Liposomes –Polymer micelles –Dendrimers –Nanoparticles –Nanocrystals –Micro particles	–Microchip systems –Micro needle transdermal delivery systems –Layer-by-layer assembled systems –Micro dispensed particles	–Nano/micro machines for scale-up production

nanotechnology is concerned, is to develop nano/micro manufacturing processes that can churn out nano/micro drug delivery systems. The current technology of fabrication and manufacturing of engineering materials at the nano/micro scale is advanced enough to develop nano/micro scale processes for producing products other than semiconductors [3]. Imagine that the current soft gelatin capsules, which are in the centimeter scale, are manufactured at the nano/micro scale.

4. Ask what nanotechnology can do for drug delivery

It is a fair and important question to ask whether nanotechnology will realistically bring clinically useful drug delivery systems. The answer is yes; making the more appropriate question when. Theoretically, it should have happened already, as scientists fabricating nanodevices could have teamed up with those heavily engaged in drug delivery systems to manufacture clinically useful nano/micro drug formulations. However, it has not happened yet. One of the reasons for this is the overwhelming obsession with nano scale, which caused the scientists to pass over the micro scale drug delivery systems. Clinically useful drug delivery systems need to deliver a certain amount of a drug that can be therapeutically effective, and often over an extended period of time. Such requirements can be met by the micro scale drug delivery systems manufactured by nanotechnology. In addition, little attention has been paid to the fact that the systems have to be introduced into the human body, requiring approval from the Food and Drug Administration (FDA).

To describe what nanotechnology can do to manufacture nano/micro drug delivery systems, one can use manufacturing of nano/micro particles (or capsules) as an example. The current methods of preparing nano/micro particles are mainly based on double emulsion methods or solvent exchange technique [4]. The main problems with the current methods are the low drug loading capacity, low loading efficiency, and poor ability to control the size distribution. Utilizing nanotechnologies, such as nanopatterning, could allow manufacturing of nano/micro particles with high loading efficiency and highly homogeneous particle sizes.

5. Nanotechnology for acceptance by the pharmaceutical industry

One of the themes of the NIH Nanomedicine Roadmap Initiative is re-engineering of the clinical research enterprise through translational research facilitating translation of basic discoveries to clinical studies [1]. The ultimate application goal of nano drug delivery systems is to develop clinically useful formulations for treating diseases in patients. Clinical applications require approval from FDA. The pharmaceutical industry has been slow to utilize the new drug delivery systems if they include components (also called excipients) that are not generally regarded as safe. Going through clinical studies for FDA approval of a new chemical entity is a long and costly process; there is resistance in the industry to adding any untested materials that may require seeking approval. To overcome this reluctant attitude by the industry, scientists need to develop new delivery systems that are substantially better than the existing delivery systems. Only marginal increase in functions will not make seeking the required approval worthwhile. Nanotechnology has a potential just to do that: increase in efficacy by orders of magnitude. For instance, nano/micro devices can be developed for both diagnosis and therapy (theragnosis) using the same device, and such theragnosis devices hold great promises in personalized medicine [5].

6. Mature nanotechnology for drug delivery

Nanotechnology has a great potential in revolutionizing the drug delivery field, but realizing such a potential requires harmonized efforts among scientists in different disciplines and continued support by funding agencies. As shown in Table 1, the future of nanotechnology-based drug delivery systems depends on the ability of scale-up production by nano/micro manufacturing. This requires design of the simplest possible delivery systems, and this will be possible only through intimate communication between nanofabrication engineers and drug delivery scientists. Nanotechnology for drug delivery will mature faster and become more useful if we appreciate that the real potential of nanotechnology in drug delivery is based on utilization of nano/micro fabrication and manufacturing, rather than on dealing with delivery systems in the nano/micro scale.

References

[1] NIH Roadmap Initiatives. http://nihroadmap.nih.gov/initiatives.asp.

[2] L.I. Larsson, Simultaneous ultrastructural demonstration of multiple peptides in endocrine cells by a novel immunocytochemical method, Nature 282 (1979) 743–746.

[3] M.J. Jackson, Microfabrication and Nanomanufacturing, Taylor & Francis, Boca Raton, 2006.
[4] S. Freitas, H.P. Merkle, B. Gander, Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation process technology, J. Control. Release 102 (2005) 313–332.
[5] V. Ozdemir, B. Williams-Jones, S.J. Glatt, M.T. Tsuang, J.B. Lohr, C. Reist, Shifting emphasis from pharmacogenomics to theragnostics, Nat. Biotechnol. 24 (2006) 942–946.

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