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Observations on Nanotechnology-based Drug Delivery Approaches: Translating Nanotechnology from Bench to Pharmaceutical Market: Barriers, Success, and Promises

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David Fairhurst, Ph.D.
Robert W. Lee, Ph.D.

Particle Sciences, Inc., 3894 Courtney Street, Bethlehem, PA 18017

Introduction

To stay competitive in today's challenging business environment, drug delivery technologies are needed that offer positive differentiation over first-generation commercial products [1, 2]. In formulations intended for oral administration, poorly water-soluble API's, classified according to the Biopharmaceutical Classification System as Class II (BCS class II), may suffer from an inadequate, or highly variable, rate and/or extent of drug absorption (sometimes as a function of food in the stomach, i.e., fed/fasted variability).

The scientific and patent literature is replete with examples of where reducing the particle size of an active pharmaceutical ingredient (API) results in increased bioavailability [3-5]. Importantly, however, particle size reduction of API's will also significantly increase the specific surface area and so further enhance the rate and extent of drug absorption such that the bioavailability requirements of the drug are met [6, 7]. Any increase in efficacy can reduce the potential toxicity (because less drug substance is needed). There is also a growing body of evidence that, specifically with nanoparticulate materials, it is the surface area and not particle size that is the defining metric that controls toxicological interaction [8-10].

The creation of API's that are "nano-size" offers additional advantages that are not attainable with typical micronized drug products. A recent article, by Morigi, *et al* [11], discusses the financial drivers responsible for the intense interest and tremendous patent activity in nanotechnology-based drug delivery and targeting. The commercial success of this approach is attributed to the improved biological performance and compliance, which in turn may give rise to patentable technologies - a key metric for investors.

In this article, we will differentiate from the typical technical reviews and give a historic perspective of nanotechnology and then discuss some of the challenges involved in translating nanotechnology from the bench to pharmaceutical market.

A Historical Perspective of Nanotechnology

Evidence dating back to the earliest records of civilization shows that mankind has observed and made use of what are termed *colloidal phenomena* for thousands of years. Stone Age paintings in the Lascaux caves of France were produced with stabilized colloidal pigments; the Bible and other early religious writings refer to strange clouds and fogs; ancient Babylonian tablets describe the preparation of inks and pigments; ancient Egyptian hieroglyphic paintings show scenes of silting of the Nile delta and Hebrew slaves made bricks of clay. Many of our earliest technological processes such as papermaking and pottery, soap and cosmetic fabrication involved manipulation of *colloids* and *colloidal systems*.

It could be argued that the origin of nanotechnology lies in the writings of Democritus (c.460-370 BC), who, in attempting to understand the material components and mechanisms of nature, created a new philosophy - *materialism* [12]; in so doing he coined the term “atom”. In 1959, Richard Feynman (the Nobel Laureate physicist) discussed the promise of miniaturization of materials down to the nanoscale [13]. The prefix “nano” was first added to the word “technology” by Nario Taniguchi in 1974 [14]; he used the composite word to signify machining with tolerances of less than one micron (□□. In 1986, the futurist writer K. Eric Drexler popularized the concept of nanotechnology in his book “*Engines of Creation”* [15] and in 2007, the FDA issued its Nanotechnology Task Force Report [16] in which nanotechnology is defined as “the ability to measure, see, manipulate and manufacture *things* usually between one and 100 nm”. Very recently, the European Commission published a recommended definition of “Nanomaterials” [17]. In addition to the size range specified by the FDA, a material is a “nanomaterial” if it has a specific surface per unit volume of >60 m^2cm^{-3}. *Natural* and *incidental* materials are included as well as manufactured particles; aggregates and agglomerates of such particles are also incorporated. The International Standards Organization has also weighed in to the debate with a concept of “nano-object” [18]. Finally, it is important to recognize that nanomaterial-specific measurement methods are still not standardized nor are they validated.

The increase in “nanotechnology” applications in the pharmaceutical and health care industries – one estimate suggests that about 80% of the 2015 market in those industries will relate to nanotechnology [19] – serves only as a reminder that nanoparticles (the *things* that underpin the technology) are but a facet of what is called the *colloidal domain*. And in the manufacture, use and analysis of nanomaterials we are dealing with *colloids* and *colloidal systems*. These names may be unfamiliar; few courses cover the subject in depth and colloid chemistry has virtually disappeared from even physical chemistry curricula. Knowledge of colloidal systems is typically acquired piecemeal without often fully comprehending the fundamental principles involved.

What follows is a brief explanation of some of the key ideas and technical terms associated with the subject. For a more detailed and in-depth study the reader is referred to specialized textbooks [20, 21].

The concept and the name of “colloid” are credited to Thomas Graham (1861). He showed that colloid systems comprise moieties that range from very large molecules to small particles, i.e., systems which occupy an intermediate position with respect to particle size between true solutions of low molecular weight substances and coarse suspensions. As a very rough guide, a colloid is any particle whose size includes a linear *dimension* in the range from about 0.5 to 10 nm to about 500 - 1,000 nm, (or alternately, between 10^3 and 10^9 atoms per particle). However, these figures are arbitrary since no sharp distinction exists between colloidal and non-colloidal systems, especially at the upper size limit. Note that it is the particle *dimension* - not the chemical composition (organic or inorganic), nor source of the sample (biological or mineralogical), nor physical state (one phase or two) that consigns it to our attention.

Thus, colloid chemistry is the science of both large molecules and finely subdivided multiphase systems and is quite multidisciplinary impacting not just chemistry but biology, physics, engineering, and material science. It is this multidisciplinary facet that is of interest and importance to pharmaceutical scientists involved in drug delivery and targeting.

The characteristic feature of colloid science lies in the relative importance attached to certain physicochemical properties of the systems studied:

1. Particle size
2. Particle shape (and flexibility)
3. Surface chemical (and electrical) properties

The particles in a colloidal dispersion are sufficiently large for a well-defined surface of separation, an *interface*, to exist between the particles and the medium in which they are dispersed. The presence of an *interface* leads to effects such as capillarity and adsorption [22]. This interface also controls how nanotechnology-based pharmaceutical products interact with their biologic targets and the biological systems encountered during the journey to its final disposition. It is in understanding and controlling these interfaces where pharmaceutical scientists can potentially develop improved and differentiated products.

Considerations for Pharmaceutical Nanotechnology

As many readers may have experienced, progressing a new chemical entity into the clinic is a challenging but rewarding task. Sadly, despite years of experience and advances in pharmaceutical sciences, only one of every 5,000 to 10,000 prospective drugs achieve FDA approval and only 5% of oncology drugs entering Phase 1 clinical trials are approved [23].

In the area of oncology, nanotechnology-based drug delivery approaches have been shown to be a powerful tool in the pharmaceutical developer's toolbox since oncology agents are typically administered intravenously and are typically sparingly soluble. Furthermore, nanoparticle carriers are also capable of addressing several drug delivery problems, including overcoming multi-drug-resistance phenomenon, penetrating cellular barriers that may inhibit reaching the intended target site, and improving *in vivo* stability of the API. Rios-Doria, *et al* describe one such approach that utilizes a novel tri-block copolymer to encapsulate daunorubicin (a hydrophobic anticancer drug) for intravenous delivery [24]. The resulting construct could be cross-linked and it exhibited significantly improved *in vivo* stability, along with improved C_{Max} and AUC. Such polymer micelle drug delivery systems may be well-suited for a variety of hydrophobic APIs.

Manufacturing Process

For successful development and commercialization of any pharmaceutical product, it is critical to have a scalable and reproducible manufacturing process. This should be considered early in the formulation/manufacturing development process. Besides the typical considerations and challenges associated with the more conventional drug products, there are additional demands for nanotechnology-based products. Critical parameters in the manufacture of nanomedicines include sterility (if the route of administration is parenteral), particle size and polydispersity (especially critical for intravenous administration), zeta potential, encapsulation efficiency and removal of free drug (dependent on the formulation approach) and drug release rate.

For injectable nanotechnology-based drugs, two of the most important quality parameters for an injectable product are sterility and acceptable bacterial endotoxin levels. Achieving sterility may be very challenging since terminal heat

sterilization typically has a detrimental effect on nanoparticle size and polydispersity, which may negatively impact biodistribution and efficacy. If the mean particle size is much greater than 100 nm and polydispersity is broad, sterile filtration is probably not an option either. This leaves few options, including use of sterile API and raw materials coupled with aseptic processing, which is costly and complicated. In some cases, lyophilization followed by gamma irradiation to produce a terminally sterilized product might be feasible.

The FDA has well-defined criteria for the preclinical data that should be included in an Investigational New Drug application for a small-molecule drug, such as purity, safety, adequate physicochemical characterization, reproducible manufacturing process, and acceptable microbiological properties. However, there is no corresponding standardized characterization list for nanotechnology-based drugs. For an approvable nanotechnology-based drug, the developer needs a reproducible synthetic or manufacturing process and adequate characterization methodology to ensure batch-to-batch consistency and physicochemical data that can be correlated to *in vivo* performance. Although the basic criteria for the chemistry, manufacture, and control (CMC) section of an IND filing is the same, the methodologies and instrumentation should be appropriate to the type of nanomaterial being assessed. Additional physicochemical properties that may need to be considered include particle size, size distribution, polydispersity, surface area (wetted or dry depending upon the mode of delivery), zeta potential, surface functionality, shape and conformation (if proteins are incorporated onto the surface), composition, encapsulation efficacy, drug release rate, purity, and stability.

As with any pharmaceutical product, the stability of the formulations as a function of time, storage temperature, relative humidity, light (photostability) and primary packaging have to be assessed. Significant formulation development may be required to have a pharmaceutically acceptable and elegant product. This is typically guided by the appropriate pre-formulation studies.

While the extent of physicochemical characterization may be quite extensive, once a set of characterization assays and tools have been identified as the critical quality parameters that are predictive of what gives rise to variability in safety, efficacy and biological activity, the methodologies can be developed and validated to qualify lots for batch-to-batch consistency.

Regulatory agencies are becoming increasingly stringent regarding characterization of the particle size distribution (PSD) of nanotechnology-based products. Measurement and monitoring of this parameter in stability studies is not a trivial task. As well as the appropriate tools the developer needs to be sufficiently informed and be able to ask the right questions in order to generate meaningful and actionable data. A review of particle size analysis is beyond the scope of this article and the reader is referred to the literature [25, 26].

Neither does this article address commercial examples or the potential market; the reader is referred to the article by Morigi, *et al* [11]which covers the nanomedicine market, financial considerations, including an analysis of the venture capital funding landscape, regulatory implications and best practices in clinical research.

Nanotechnology: the Future is Now

Although it is thought that nanotechnology is still a futuristic rather than a contemporary industry, over 500 manufacture-identified, nanotechnology-based products have already been catalogued [27] and the global market in 2007 totaled $147 billion; that figure is projected to grow to $3.1 trillion by 2015 [28]. These include sunscreen products using zinc oxide and titanium dioxide in which the particle size is small enough that they are optically transparent (non-whitening on the skin) [29] but still very effectively attenuate the UVA and UVB radiation that causes sunburn and skin cancer [30, 31]. In consumer healthcare, toothpastes that contain nanoparticulate hydroxyapatite for filling minute cracks in tooth enamel are currently on the market as are many anti-aging products using nanocapsule technology to deliver actives

such as vitamins into the skin [32]. Nanosilver particle can be found in FDA-approved wound dressings. Bioactive ceramic material (based on mixtures of nanosize zirconia and hydroxyapatite) are already in the development stage for orthopedic weight-bearing implants; one major advantage of nanoparticles is a vast improvement in sintering behavior.

Thus, the new field of "nanomedicine" – the application of nanotechnology to achieve breakthroughs in healthcare – promises to impact all stages of healthcare [33]. Drug delivery is but one of four main areas in nanomedicine (the others being: molecular diagnostics, tissue engineering, and cell/gene therapy). The challenge for traditional pharmaceutical companies is to deliver the right therapeutic to the right target with no, or minimal, side effects and at reduced cost. Nanoparticles can, at least theoretically, improve all common drug administration techniques - oral, injection, transdermal, transmucosal, ocular, pulmonary and implant. Thus, they are likely to be the cornerstone of all the promising technologies. Some early successes are evident such as the proprietary NanoCrystal® technology (formerly Élan Corporation, now Alkermes; http://a.alermes.com/rd/technology.aspx) for APIs that have poor water solubility, yet the field is still in its infancy with more potential still to be fulfilled.

Colloid science is, to paraphrase Richard Smalley (Nobel Laureate in chemistry), the "*garden of nanotechnology*". It should be apparent from all the above that, by the application of colloid science principles to the problems facing drug delivery and targeting, drug developers will be more readily able to design and ultimately commercialize nanotechnology -based approaches that provide improved safety, efficacy, and value to pharmaceutical products.

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