Next Steps for Pharmaceutical Nanotechnology

Cory Berkland

Published online: 16 July 2010
© Springer Science+Business Media, LLC 2010

In the pharmaceutical community, nanotechnology has become the flavor of the day for anything with a size or feature between an Angstrom and a micron. Professor Howard Rytting, an esteemed colleague who is dearly missed, specified various areas of pharmaceutical nanotechnology in an editorial in the *International Journal of Pharmaceutics* [1]. Broadly defined, pharmaceutical nanotechnology encompasses a wide range of topics including diagnostics, drug discovery, drug formulation and delivery, analytics, devices, and biomaterials, to name a few [2]. For all practical purposes, the term has engulfed much of the research effort existing between the molecular and the cellular. In the context of drug formulation and delivery, what started as a modest proposal for improving the dissolution of poorly water-soluble drugs has now been multiplied into sophisticated approaches to improve the delivery of therapeutics. Scientists and engineers are pressing hard to develop pharmaceutical products using nanotechnology while meeting regulatory guidelines and achieving large-scale production of small-scale stuff.

Pharmaceutical applications of nanotechnology were burgeoned by Elan's NanoCrystal® technology, which improved the dissolution rate of poorly water-soluble drugs. The use of live or attenuated viruses in vaccines, however, predates any of the nanotechnology plays on pharmaceutical formulations so prevalent in the literature today. In fact, emulating viruses has provided an important impetus for some of the latest nanoparticle design efforts in the pharmaceutical community. Researchers have discovered

that particles with a diameter larger than about 10 nm may persist in circulation due to exclusion from renal filtration or leakage from blood vessels. At the other end, particles below several hundred nanometers may reduce removal by the reticuloendothelial system. For example, attaching polyethylene glycol to increase the hydrodynamic radius of proteins may extend their circulation half life [3]. Similarly, transport in tissues and drainage to the lymphatic system are size dependent; polymers or small nanoparticles approaching a nanometer may tend to exchange to the circulatory system while particles several hundred nanometers in diameter may form a depot at an injection site. Nanoparticles around 100 nm are also small enough to enter cells, making them attractive vehicles for intracellular drug delivery (e.g., DNA or RNA). These transport phenomena vary depending upon the surface of the nanoparticle as well. Many researchers have endeavored to eliminate surface fouling (e.g., protein adsorption), to control surface charge, and to actively target nanoparticles to receptors [4]. The shift in emphasis towards transport phenomena of nanoparticles may explain the increasing role of engineers in the field.

Regulatory agencies have been sensitized to nanotechnology and public perception tends to wax and wane. Multiple pharmaceutical products using nanoparticle technology have navigated through clinical trials to FDA approval including Emend®, Rapamune®, TriCor®, Abraxane™, and others. By and large, these products have used drug nanoparticles to improve dissolution (e.g., TriCor®) or to facilitate injection of poorly water-soluble drugs (e.g., Abraxane™). To date, the use of drug nanoparticles as a means to increase the dissolution rate of poorly water-soluble drugs has been repeatedly proven to be safe. In fact, these formulations often boast improved safety profiles resulting from consistency in fast vs. fed pharmacokinetics and enhanced drug bioavailability, thus reducing the required drug dose. Iron oxide

C. Berkland (✉)
The Department of Pharmaceutical Chemistry and
The Department of Chemical and Petroleum Engineering,
The University of Kansas,
Lawrence, KS, USA
e-mail: Berkland@ku.edu

nanoparticles have also been approved (FeriDex® in 1996) and other inorganic materials (e.g., colloidal gold) have been in clinical trials [5]. Nanoparticle formulations will continue to advance and more complex approaches using unique surface chemistries and targeting schemes will mature into clinical studies. Continued work on acute and long-term toxicity in preclinical models and ultimately in humans will be required if companies aim to translate some of these concepts. The Nanoparticle Characterization Laboratory established in concert with the National Cancer Institute is helping to develop assays and guidelines to define some of these emerging nanoparticles.

Large scale manufacturing of drug products containing features at the nanometer scale has also progressed [6]. Elan has paved the way by scaling up media milling processes. Today, they are able to easily produce drug nanoparticles for incorporation into tablets of the blockbuster cholesterol medication TriCor®. Abraxis Biosciences has mass produced a lyophilized nanoparticle formulation of paclitaxel, Abraxane™, via a scaled precipitation process. Finished products for injection have been produced by using sterile filtration of colloids (e.g., <0.21 µm in size). The stability of nanoparticle formulations produced at this scale is also being thoroughly investigated. Colloids, especially those containing nanoparticles, can be susceptible to physical instability. Due to the extremely large available surface area, drug nanoparticle colloids can undergo Ostwald ripening and particle agglomeration. Surfactants and viscosifying agents are often employed to stabilize hydrophobic drug nanoparticles in water and excipients in solution can be used to minimize the aqueous solubility of the drug to stymie Ostwald ripening. In addition, drying of fine colloids can result in irreversible agglomeration of particles if care is not taken. Many have reported effective use of dispersing agents and other excipients as an approach to recover a stable colloid after reconstitution of a lyophilized powder or during tablet dissolution (e.g. Abraxane™). Finally, next-generation nanoparticles will face additional challenges such as surface stability of conjugated targeting ligands.

Nanotechnology has become a more mainstream approach for drug formulation and delivery in an era of increasing investment in pharmaceutical research and development that has been constrained by a falling number of FDA-approved products. In the years ahead, several additional products that incorporate nanoparticles will emerge onto the market [2]. Although some companies are adding complexity to nanomaterials through intricate surface modification, these therapies face an uphill battle. Simpler formulations should emerge on the market much more quickly. For example, Savara Pharmaceuticals has created incredibly fine dry powder aerosols by assembling drug nanoparticles into ~1–3 µm agglomerates. In this manner, aerosols that contain up to 100% drug offer improved lung deposition and more rapid dissolution than micronized dry powder aerosol formulations [7, 8]. Strides are also being made to leverage nanotechnology for improving the performance of vaccines [9] and for facilitating the delivery of RNAi therapeutics [10]. Skepticism aside, nanotechnology has secured a future in the pharmaceutical industry.

References

1. Rytting H. *Int J Pharm.* 2004;281:1.
2. Wagner V, Dullaart A, Bock AK, Zweck A. *Nat Biotechnol.* 2006;24:1211.
3. Pasut G, Veronese FM. *Adv Drug Deliv Rev.* 2009;61:1177.
4. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. *Mol Pharm.* 2008;5:505.
5. Mintorovitch J, Shamsi K. *Oncology (Williston Park).* 2000;14:37.
6. Hu J, Johnston KP, Williams 3rd RO. *Drug Dev Ind Pharm.* 2004;30:233.
7. El-Gendy N, Berkland C. *Pharm Res.* 2009;26:1752.
8. El-Gendy N, Gorman EM, Munson EJ, Berkland C. *J Pharm Sci.* 2009;98:2731.
9. Peek LJ, Middaugh CR, Berkland C. *Adv Drug Deliv Rev.* 2008;60:915.
10. Whitehead KA, Langer R, Anderson DG. *Nat Rev Drug Discov.* 2009;8:129.