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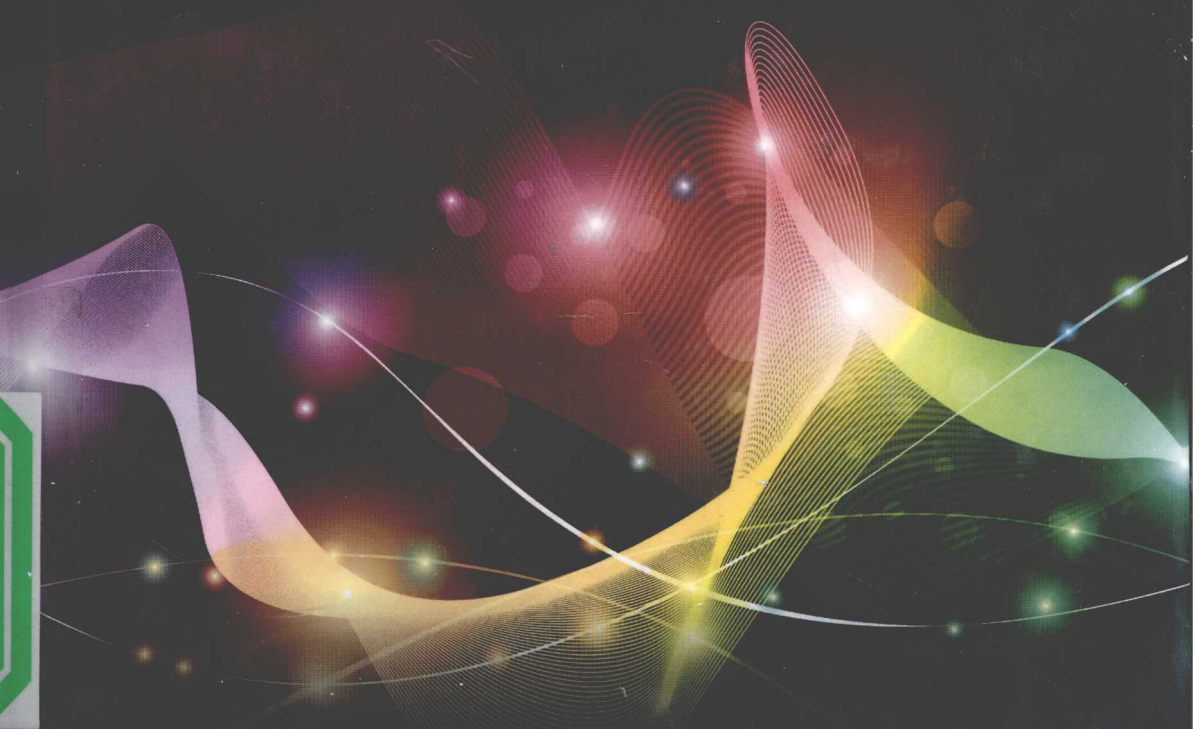
NANOPARTICULATE DRUG DELIVERY

PERSPECTIVES ON THE TRANSITION FROM LABORATORY TO MARKET

VANDANA PATRAVALE, PRAJAKTA DANDEKAR AND RATNESH JAIN



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Foreword

The topic of Nanoparticulate Drug Delivery has fascinated me for over two decades now and the one that I have enjoyed exploring in my research at the University of California, Santa Barbara over the last decade. So it is with true pleasure that I write this foreword to the book by Patravale, Dandekar and Jain on "Nanoparticulate Drug Delivery". This book provides a very timely overview of this fascinating area at the interface of nanotechnology and medicine. It includes a very comprehensive description of the key scientific and technological issues that must be addressed before bringing nanoscale drug carriers to the market. The area of nanoparticle-based drug delivery is truly fascinating; it's scientifically exciting, it thrives on technological innovation and holds tremendous promise for the future. Nanoparticles offer distinct advantages in pharmaceutical products by protecting the drug, targeting it to the diseased tissue and providing release at the desired rate. Implementation of this strategy in actual products, however, has proved challenging. Nanoparticles must perform several specific tasks in the body. They need to exhibit sufficient encapsulation of drugs and possess requisite material characteristics to release them at the required rate. Upon injection into the body, they must exhibit sufficiently long circulation so that they are able to accumulate at the target in necessary quantities. In order to accomplish this, they must escape clearance by the liver and other clearing organs. Upon accumulating at the target, they must be able to penetrate sufficiently deep into the tissue to fulfill their therapeutic objective. This delivery challenge is particularly significant for delicate drugs such as nucleic acids and proteins.

The challenges in designing nanoparticles have given rise to the field of nanomedicine, where researchers from a wide range of disciplines have gathered to formulate nanoparticles to meet the therapeutic objective. The book by Patravale, Dandekar and Jain does an outstanding job in providing a summary of the past efforts, current status and future directions on this field. I very much like the thoroughness, diversity and organization of the topics covered in the book. The book starts with the

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design goals of nanoparticles to improve drug solubility and targeting and goes on to discuss different types of nanoparticles including polymeric systems, suspensions and dendrimers that have been designed. Subsequent chapters include a thorough discussion of various routes of administration including oral, transdermal, pulmonary and intravenous. The book also outlines methods for detailed characterization and toxicity issues. In the final chapters, the book provides key challenges associated with clinical trials and perspective from various regulatory authorities.

The book provides an excellent reference for students, professionals, researchers and educators engaged in the field of nanoparticulate drug delivery systems.

Samir Mitragotri
University of California, Santa Barbara
January 29, 2012

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Nanoparticulate systems as drug carriers: the need

Abstract: Development of nanoparticles for drug delivery has progressed by leaps and bounds over the last few decades, facilitating the possibility of an efficacious therapy for some fatal diseases. This development has stemmed from either the unsuitable physicochemical characteristics of the existing drug molecules, such as limited solubility and hence poor bioavailability, or the inadequacy of the conventional delivery systems to provide safe and efficient delivery. This chapter focuses on the precise need for the development of these novel nanoparticulate drug carriers and reasons for their popularity with the drug delivery scientists. The text also discusses the various strategies, including different formulation and targeting approaches, which have been adopted to overcome the challenges presented by the inherent properties of the drug molecules. Examples of nanoparticulate drug delivery systems which have already gained market approval have been cited in the discussion, wherever applicable.

Key words: nanoparticulate drug carriers, solubility, bioavailability, targeting, nanoemulsions, nanocrystals, nanoparticles.

1.1 Introduction: nanoparticles for drug delivery

The last decade of drug delivery research has witnessed a boom in the development of the nano-drug delivery systems. The major drivers responsible for the initiation of this new revolution were the development

of a plethora of varied nano-drug delivery systems, not only by the academic institutions but also by industrial organizations. This led to the availability of a huge database comprising several research papers and patents from all over world, describing these new dosage forms. Numerous funding agencies and industries actively promoted research into nanoparticulate drug delivery vehicles and huge investments were made to this end. All these diverse and concurrent efforts created an awareness about the immense potential of these new drug delivery systems, which were then looked upon as therapeutic regimens of the future.

There are many reasons behind the development and success of nanoparticulate drug delivery systems. A few years ago, the entire attention of pharmaceutical industry was focused on the novel developments in designing various dosage forms, primarily due to expiry of the existing patents, a surfeit of poorly soluble drug candidates and the problems of non-specificity from conventional dosage forms. Under these circumstances, the development of nanoparticulate drug delivery systems gained huge momentum due to a number of diverse factors listed in the following section of this chapter.

- The pharmaceutical industries were poised to provide quality products to the patient, at the same time increasing or maintaining their profitability. However, this process demanded extensive scientific innovation and financial support. Development of new chemical entities and their transition from the laboratory to market required the company to expend as high as 800 million US dollars [1]. Apart from a huge investment, the development of the new drug was also an extensively time consuming process with very limited success rates.
- Research progress in the drug discovery area resulted in the development of various poorly soluble drug candidates. The solubility limitations of these drug candidates, in turn, lead to poor bioavailability and lower therapeutic efficacy [2, 3]. In such situations, formulation of these therapeutic molecules into nanoparticulate delivery systems was observed to improve their bioavailability and hence elicit the desired therapeutic effects from these candidates. The nanoparticles also received a prominence due to other probable benefits like biodegradability, biocompatibility, high encapsulation characteristics and probability of surface functionalization [1–3].
- Nanoparticles were found to exhibit several advantages for parenteral drug delivery; counter to the aggregation phenomenon commonly observed with microparticles, the smaller size of nanoparticles endowed them with better distribution profiles during systemic

administration. Nanoparticles enabled an effective systemic circulation, thus leading to better therapeutic outcomes. Better systemic circulation was found to be specifically important for cancer therapies, where nanoparticles could infiltrate through the vasculature of tumor tissue and provide targeted therapeutic effects [4].

- First pass metabolism is one of the key concerns for many commercial and upcoming drugs. This phenomenon accounts for their low bioavailability and reduced efficacy at the site of action. In this regard, nanoparticulate drug delivery vehicles were particularly advantageous because of their likelihood in being modulated for site specific delivery/targeted delivery. Apart from their specificity, nanoparticles were also found to mitigate drug related side effects and dose related toxicities, resulting in enhanced bioavailability of the encapsulated agent and excellent patient compliance [1, 3, 5].
- Owing to their small size, nanoparticles were found to effectively traverse many biological barriers. Of significant importance is their ability to permeate the blood brain barrier (BBB). Although brain administration is an effective route for the treatment of various brain diseases, it is severely limited due to the highly impermeable nature of the BBB. Because of their potential to cross this barrier, numerous publications have demonstrated the effectiveness of nanoparticles for targeting various central nervous system disorders [6]. Nanospectra Bioscience, Texas, USA, has recently initiated a clinical trial of nanoparticle based 'nanoshells' for the treatment of brain tumors [7].
- The size of nanoparticles offers distinct advantages when compared with conventional dosage forms. The tunable size of these systems greatly influences the release profile of the encapsulated active component, so a formulator could thus control the drug release at the site of action [8, 9].
- Nanoparticles were found to be highly versatile systems to encapsulate and delivery not only chemical drug moieties but also nuclic acid therapeutics (DNA, siRNA), and imaging and diagnostic agents, for site-specific delivery and detection. Various ligands can be attached to the surface of nanoparticles to guide them to specific locations within the body [9, 10].

Thus nanoparticulate drug carriers found applications in several diverse quarters of drug delivery research and, due to their tunable properties, they were foreseen as the future of the pharmaceutical and biotechnology industry.