Pharmaceutical Development and Regulatory Considerations for Nanoparticles and Nanoparticulate Drug Delivery Systems

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Received 17 May 2013; revised 18 July 2013; accepted 12 July 2013

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23691

ABSTRACT: Pharmaceutical nanomaterials (NMs) encompass a wide variety of materials including drug nanoparticles (NPs), which can be amorphous or crystalline; or nanoparticulate drug delivery systems, such as micelles, microemulsions, liposomes, drug–polymer conjugates, and antibody–drug conjugates. These NMs are either transient or persistent—depending on whether the integrity of their structure and size is maintained until reaching the site of drug action. Examples of several approved drug products are included as pharmaceutical nanoparticulate systems along with a commentary on the current development issues and paradigms for various categories of NPs. This commentary discusses the preparation of nanoparticulate systems for commercial development, and the biopharmaceutical and pharmacokinetic advantages of these systems. A criterion of criticality is defined that incorporates the structure, in addition to size requirement of pharmaceutical NPs to identify systems that may require special development and regulatory considerations. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: nano milling; nanoparticles; nanotechnology; micelle; microemulsion; liposomes; polymeric drug delivery systems; polymeric drug carrier; polymeric drugs

INTRODUCTION

In 1861, Thomas Graham recognized the colloidal state; and some 50 years later, Wolfgang Osterwald described it as a "world of neglected dimensions." Even before the time of Graham, several colloidal dispersions such as sulfur, Prussian blue, sulfide, and gold colloids had been prepared by early investigators. In 1959, physicist Richard Geynman gave a provocative lecture entitled "There's plenty of room at the bottom" at an American Physical Society meeting. Eric Drexler popularized the potential of molecular nanotechnology in the 1970s and 1980s. The then emerging science of nanotechnology quickly expanded to almost every field, including pharmaceuticals and medicine. In the pharmaceutical sciences, significant research has been carried out in using liposomes, micelles, lipopolymers, and polymeric dendrimers as nanoparticulate drug delivery systems (NanoDDSs); and drug nanocrystals as nanoparticles (NPs) since 1960s. NPs and NanoDDSs are, as the name implies, particulate or biphasic DDSs, in which at least one dimension of size of the dispersed phase or particles is in the nanometer (1–100 nm) range. The term nanomaterials (NMs) is used more generally to incorporate both NPs and NanoDDSs, to reflect their intended particulate structure while acknowledging possibly different states of material presentation, such as particle agglomeration. These delivery systems are typically dispersions, where the dispersed phase may be solid or liquid, and the dispersion medium can be solid, liquid, or gas. The nanometer-size range is often defined in terms of particle diameter or dimension measured by one or more of analytical techniques used for characterization of the particle size distribution (PSD).

Approximately two dozen drug products (DPs) based on the nanotechnology platforms have been approved for commercialization in the United States. Hundreds of Investigated New Drug Applications (INDs) containing at least some form of nanosized material have been filed with the United States Food and Drug Administration (FDA, or Agency). The majority of current applications of nanotechnology to pharmaceuticals are in the drug delivery area to enhance bioavailability and to improve targeted delivery of existing molecules. The nanotechnology platforms in drug applications are expected to further expand to new nanoscale materials, with increasing complexity, functionality, and diversity.[1,2]

In this commentary, we discuss the pharmaceutical development and regulatory considerations of NPs and NanoDDSs that have influenced the use of these technology platforms for drug delivery in commercialized DPs. The technologies for commercial DP development are critically reviewed with respect to the biopharmaceutical and pharmacokinetic modification of drug properties in the dosage form, along with the developmental and regulatory challenges, and other special aspects that guide their development through commercialization. In addition, a

Abbreviation used: API, active pharmaceutical ingredient; AUC, area under the curve; BMS, Bristol-Myers Squibb, Company; C_{max}, maximum drug concentration in blood/plasma; CMC, chemistry, manufacturing, and controls; DDS, drug delivery system; DMF, drug master file; DP, drug product; $d(0.9)$, 90th percentile of drug particles by size (diameter); $d(0.5)$, 50th percentile of drug particles by size (diameter); $d(0.1)$, 10th percentile of drug particles by size (diameter); EPR, enhanced permeation and retention (effect); FDA, United States Food and Drug Administration (Agency); GI, gastrointestinal (tract); IND, investigational new drug (application); log P, log of solubility of the drug in the organic/aqueous phase at equilibrium (partition coefficient); MPS, mononuclear phagocyte system; NCE, new chemical entity; NanoDDS, nanoparticulate drug delivery system; NM, nanomaterial; NPs, nanoparticles; PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PPO, poly(propylene oxide); PSD, particle size distribution; SEDDS, self-emulsifying drug delivery system; SMEDDS, self-microemulsifying drug delivery system; SDD, solid drug dispersions; T_g, glass transition temperature; T_m, melting point; T_{max}, time of maximum drug concentration in blood/plasma.

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Journal of Pharmaceutical Sciences

classification system is proposed to identify the nanosystems whose structure and/or size parameters are critical to performance, and may require greater rigor of development and regulation. The commentary concludes with an outlook to the future prospects of NMs in drug development.

BIOPHARMACEUTICAL MODIFICATION

The use of drug NPs is generally aimed at improving the dissolution rate and/or solubility of a drug molecule. The use of NanoDDS for altering the pharmacokinetics and/or targeted drug delivery[3,4] is discussed in the next section on *Pharmacokinetic Modification*. Many new chemical entities (NCEs) entering drug development have low aqueous solubility. Inadequate aqueous solubility reflects a less than desirable free energy of transfer of drug molecules from the solid phase to an aqueous solution. For crystalline solid drug molecules to dissolve in water, intermolecular bonds in the crystalline solid need to be broken and replaced with drug–water bonds in solution in an energetically favorable manner. Of the two thermodynamic parameters in the Gibb's free energy equation, enthalpy change and entropy change, the latter is usually favorable to drug dissolution, but the former may not be. This may result from two causes: (a) lipophilic/hydrophobic compounds are likely to exhibit low water solubility due to unfavorable free energy of solvation by water; or (b) compounds with high crystal lattice energy due to intermolecular interactions may exhibit low water solubility as a result of strong crystalline interactions.

Limited drug solubility can cause low and/or variable drug absorption. Low drug solubility might also lead to nonlinear increase in drug absorption as a function of dose (fraction of drug absorbed decreases as the dose increases), and disproportionate increase in bioavailability with increase in the dissolution rate [e.g., by reduction of active pharmaceutical ingredient (API) particle size]. Low and/or variable oral absorption of such drugs could be either solubility or dissolution rate limited, depending on the dose to solubility ratio and the relative rates of drug dissolution and permeation.[5] For example, at high dose to solubility ratio, drug solubility is low for the required dose and drug absorption is solubility rate limited. At low dose to solubility ratio, drug solubility is sufficiently high for the required dose, resulting in either the dissolution rate or the permeation rate as a limiting factor for drug absorption.[6] The challenges of dissolution rate and/or solubility limited drug absorption can be approached with a host of technologies, such as salt formation, crystal polymorphic form change, formation of amorphous drug in solid drug dispersions (SDDs), particle size reduction to micro- or nanosize range, or the use of a solution dosage form with pH modification if the drug is ionizable in the physiologically relevant pH range, addition of cosolvent(s) or solubilizer(s), or cocrystal formation. Selection of solubility improving method depends on several factors such as the biopharmaceutical properties of the drug, disease condition, patient population, dosage form of choice, dose and route of administration, and the site of drug absorption. Among these, the use of NanoDDS and NPs has recently evolved to occupy a unique position as an enabling technology.

Types of NMs

There are several commercially available DPs in the US market that utilize nanosized API (Table 1). Common types of NMs

Table 1. Examples of FDA-Approved Drug Products Containing Nanometer-Sized Drug Substance

Trade Name	Active Ingredient	Indication	Dosage Form	Sponsor	US Patent Listed in Orange Book	Nanotechnology Platform Used
Rapamune	Sirolimus	Immunosuppressant	Tablet (1 mg and 2 mg)	Wyeth	5145684, 5536729, 5989591	Ball milling
Emend	Aprepitant	Antiemetic	Capsule (40 mg and 125 mg)	Merck	5538982, 5719147, 6048859, 6096742, 6235735, 7214692, 8258132	Ball milling
Tricor	Fenofibrate	Lipid regulation	Tablet (48 mg)	Abbott	6277405, 6375986, 6652881, 7037529, 7041319, 7276249, 7320802	Ball milling
Triglide	Fenofibrate	Lipid regulation	Tablet (50 mg and 160 mg)	First Horizon	6696084	Microfluidizer
Megace ES	Megestrol	Antineoplastic	Oral suspension (125 mg/mL)	Par	6592903, 7101576	Ball milling
Invega Sustenna	Paliperidone palmitate	Schizophrenia	Injectable suspension	Johnson & Johnson	5352459, 6077843. 6555544	Ball milling
Abraxane	Paclitaxel	Metastatic breast cancer	Injectable suspension	Celgene	5439686, 5498421, 6096331, 6506405, 6537579, 6749868, 6753006, 7820788, 7923536, 8138229	High pressure homogenizer
OTC products[a]	Silver, titanium dioxide, zinc oxide	Antimicrobial, Sunscreen	Wound dressing, topical products	L'Oreal	–	–

[a]For example, Acticoat (Smith & Nephew), Silvagard (Acrymed), and many other colloidal silver preparations contain nanosized silver; Anthelio and Helioblock (L'Oreal) contain avobenzone, ecamsule, octocrylene, and nanosized titanium dioxide.

DOI 10.1002/jps.23691