Chapter

DESIGN AND DEVELOPMENT OF APPROVED NANOPHARMACEUTICAL PRODUCTS

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1.1 INTRODUCTION

1.1.1 *Nanotechnology and Nanomedicine*

Nanotechnology and nanomedicine, the high risk, high payoff global phenomenon is in full swing. Advances in nanotechnology are being driven by collaborative research, patenting, commercialization, business development and technology transfer within diverse areas such as chemical engineering, biotechnology, the medical sciences, physical sciences and information technology [1-3].

The confusion and ambiguity surrounding the definition of nanotechnology continues to be one of the most significant problems shared by regulators, policy-makers, researchers and legal professionals alike. Different definitions of

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nanotechnology have sprung up over the years. Nanotechnology has been described as the manipulation, precision placement, measurement, modeling or manufacture of matter in the sub-100 nm range [4], or in the 1 to 200 nm range [5, 6]. However, there are a number of reports in the scientific literature that mention a size ranging from 1 to 1000 nm in both nanotechnology and pharmaceutical science [7-10].

Although the term "nanotechnology" is widely used, there is no internationally accepted definition or nomenclature associated with it [3]. In fact, the term nanotechnology is a bit misleading since it is not one technology but encompasses several technical and scientific fields such as medicine, materials science, chemistry, physics, engineering and biology. One can view it as an umbrella term used to define the products, processes and properties at the nano/micro scale [3]. To reduce ambiguity, the following practical definition of nanotechnology has been proposed by Dr. Raj Bawa, which is unconstrained by an arbitrary size limitation [3]:

> *"The design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property."*

Submicron materials are essential for biological distribution of biopharmaceuticals for safety reasons [11]. Particles greater than >5μm can cause pulmonary embolism following intravenous injection with fatal results [12-15]. Therefore, submicron particle size is required for all parenteral formulations. In ophthalmic applications, the optimal particle size is less than 1,000 nm because microparticles around 5μm can cause a scratchy feeling in the eyes [16, 17]. In the pharmaceutical sciences, nanotechnology has several advantages, including [18]:

- increasing the apparent solubility and dissolution rate of a drug in relation to *in vivo* bioavailability enhancement;
- protection of encapsulated or absorbed therapeutic agents from the external environment;
- controlled release of properties; and
- ability to act as adjuvants in vaccine delivery.

Nanotechnology, due to its inherent advantages over traditional therapies with regard to size and surface modification, can achieve improved therapeutic efficacy through prolonged blood circulation time, stimuli sensitivity and intracellular delivery capacity [18]. These are some trends that pharmaceutical companies are utilizing with respect to nanotechnology in order to enhance or supplement drug target discovery and drug formulation.

Just like nanotechnology, there is no universally accepted definition of nanomedicine. The European Science Foundation [19] defines nanomedicine as:

> *"[T]he science and technology of diagnosing, treating, and preventing disease*

> *and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body."*

In addition, according to Dr. Thomas Webster, nanomedicine may be divided into five main disciplines [20]:

- analytical tools;
- nano-imaging;
- nano-materials and nanodevices;
- novel therapeutics and drug delivery systems; and
- clinical, regulator, and toxicological issues.

The National Institutes of Health (NIH) Roadmap for Medical Research in Nanomedicine [21] defines nanomedicine as:

> *"[A]n offshoot of nanotechnology, refers to highly specific medical interventions at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve."*

Accordingly, nanomedicine could be summarized as, *"emerged medicinal approaches from nanotechnology at the level of molecules and atoms"* [20]. In other words, the treatment, diagnosis, monitoring and control of biological systems may be referred to as nanomedicine [22]. In this regard, diagnostic trials and drug delivery devices are receiving the most intensive focus [23]. There also has been extensive research on the development of nanomedicines such as nanoparticles, liposomes, nano-emulsions and dendrimers for the specific delivery of drugs to target tissues [3, 24].

1.1.2 *Nanopharmaceuticals: Nanomedicine Delivery Systems*

Nanopharmaceuticals (Figure 1) have received a lot of attention due to their potential to revolutionize drug delivery systems [25]. The most critical aspect in drug delivery systems is to deliver the correct dose of a particular active agent to a specific disease site in order to reduce toxic side effects as well as to optimize the therapeutic effect of the active agent as compared to the classic drawbacks of traditional therapeutics [25-27]. In other words, nanopharmaceuticals can be used for targeted drug delivery to the site of diseased tissue or lesion to improve the uptake of poorly soluble drugs and/or the improvement of drug bioavailability [28-30].

Colloidal drug delivery carriers such as liposomes, micelles or nanoparticles, have been intensively investigated for their use in the pharmaceutical field. Nanopharmaceuticals are described as colloidal drug delivery carriers of 10 to 1,000nm [31]. Nanopharmaceuticals are synthesized by various methods (self-assembly, vapor or electrostatic deposition, aggregation, nano-manipulation, imprinting, etc.) where the protocol is dictated by factors such as the specific therapeutic used and the desired delivery route [32].

The functional complexity and application potential of nanopharmaceuticals is related to factors such as their [3]:

- nano-scale dimensions/small size (surface area-to-volume ratio);
- reduced drug toxicity;
- controlled-release property of the drugs associated therewith;
- altered/modified drug pharmacokinetics;
- enormous compositional range and variety of active agents involved;
- biological distribution and targeting capabilities due to specific targeting moieties attached;
- various delivery routes (oral, topical, and intravenous);
- variety of shapes/geometries; and
- surface charge.

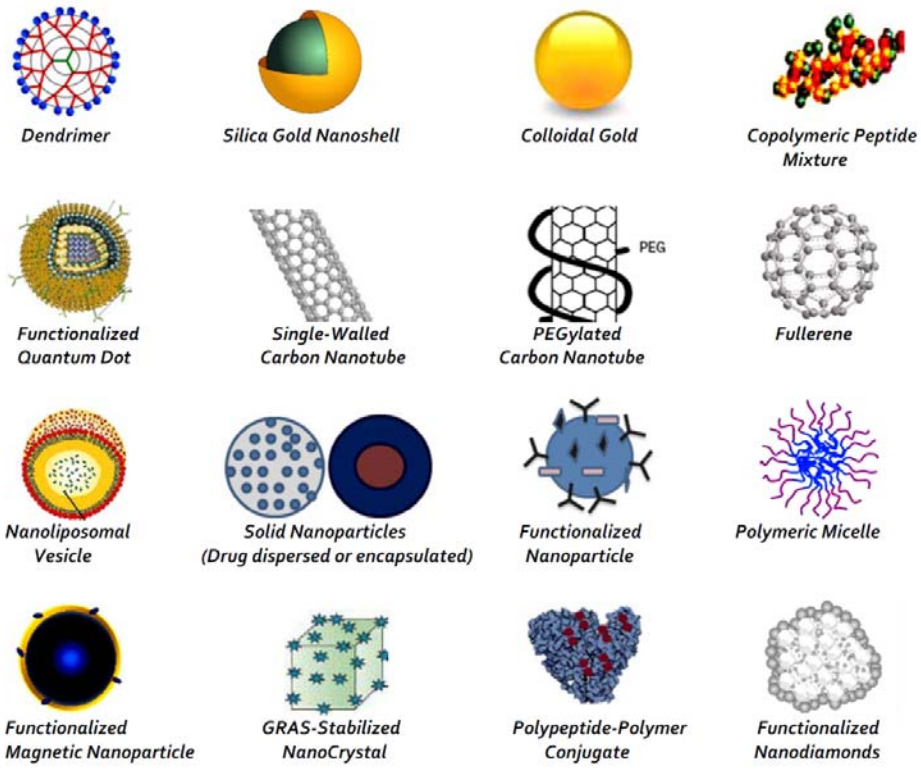

Figure 1. Main Classes of First Generation Nanopharmaceuticals (Approved or in Development) [Copyright © 2014 by Raj Bawa, reproduced with permission]

From a material science perspective, nanopharmaceuticals can be divided into two types – "hard" and "soft" – although there are obvious intermediate versions (Table 1) [33]. Hard-type nanopharmaceuticals, such as polymeric nanoparticles [34-37] and lipid nanoparticles [15, 38-40], have less flexibility and are less elastic. In contrast, soft type systems including liposomes [41-45], nano-emulsions [46-48], submicron lipid emulsions [49-54], nano-gels [55-57] and polymeric micelles [58-60], can be deformed and reformed to varying degrees by external or internal stress [24]. Hard systems can block capillaries and fenestrae that have dimensions similar to the particles, but soft systems are better able to navigate capillary beds and tissue extracellular spaces [33].

Table 1. Various types of nanopharmaceutical delivery systems based on hard and soft nanomaterials.

Category		Nanopharmaceutical Delivery Systems	Reference
Soft types	Polymer-base	Polymeric nanoparticles	[34-37]
	Lipid-base	Lipid nanoparticles	[15, 38-40]
Hard types	Lipid-base	Liposomes	[41-45]
	Lipid-base	Lipid emulsions	[49-54]
	Lipid-base	Microemulsions	[46-48]
	Polymer-base	Polymeric micelles	[58-60]
	Polymer-base	Nanogels	[55-57]

Liposomes were initially reported to serve as a model for cell membranes in biophysical studies [61]. Liposomes are phospholipid vesicles of varying sizes, ranging from 50 to above 1000 nm, formed by one or several lipid bilayers with an aqueous phase both inside and between the bilayers [62]. Liposome formulations have the potential (due to targeting) to reduce toxicity and increase accumulation at the target site with or without expression of target recognition molecules on lipid membranes [42]. Liposomes have advantages such as [63, 64]:

- drug encapsulation versatility in their aqueous compartments (hydrophilic drugs), in their bilayers (lipophilic drugs) or both (amphiphilic drugs); and
- potential to offer a high level of safety due to their inherent nontoxic, non-immunogenic and biodegradable property.

Polymeric nanoparticles are defined as solid colloidal particles composed of polymeric materials ranging in size from 1–1000nm. They are classified as nano-capsules, which are vesicular systems with a polymeric shell plus an inner core and nano-spheres, which are a polymeric matrix [8]. Polymeric micelles are defined as self-assembled nano-materials of amphiphilic block copolymers containing hydrophobic and hydrophilic blocks. Polymeric micelles are nano-

scopic therapeutic systems that incorporate therapeutic agents, molecular targeting, and diagnostic imaging capabilities that are emerging as the next generation of multifunctional nanomedicine intended to improve the therapeutic outcome of drug therapy [59].

For lipid nanoparticles, three different types of lipid nanoparticles exist [15, 65-67]:

- Solid Lipid Nanoparticles (SLN): colloidal particles of a lipid matrix that is solid at body temperature;
- Nanostructured Lipid Carriers (NLC): composition of solid lipid and a spatially different liquid lipid as the carrier; and
- Lipid Drug Conjugates (LDC): salt formation or covalent linkage of insoluble drug–lipid conjugate bulk with a solid matrix.

Nano-gels are aqueous dispersions of hydrogel particles formed by physically or chemically cross-linked polymer networks of nano-scale size. They can be prepared by different methods such as self-assembled polymers, polymerization of monomers, cross-linking of preformed polymers, or template-assisted nanofabrication. They can be stored in a dried form at ambient temperature to easily be re-suspended in aqueous media, forming particulate dispersions with a nano-sized hydrodynamic diameter [55, 56, 68].

The ideal features of nanopharmaceuticals include [69]:

- enhancing drug accumulation in the target site;
- providing protection of drugs against potential enzymatic or hydrolytic degradation in the body;
- providing biocompatibility and biodegradability;
- offering a high drug-loading capacity;
- extended circulation or residence time;
- controlled drug release profiles;
- providing long-term physical and chemical stability; and
- the ability to efficiently carry poorly soluble pharmaceuticals.

These features can be engineered into the delivery system along with effective delivery to target sites; hence, this area is gaining traction [70].

There are a number of FDA-approved, marketed nanopharmaceuticals [3] for the intravenous administration route (Table 2) as well as the non-intravenous route (Table 3 and Table 4). However, numerous nanopharmaceuticals are still at the development or clinical trial phase due to the extremely complex nature of human medicinal applications. This chapter will discuss approved nanopharmaceuticals for nanomedicine delivery (from a design and development perspective) by various administration routes including parenteral, oral, transdermal and pulmonary. In this chapter, the following terms are used interchangeably: nanodrugs, nanomedicines and nanopharmaceuticals.

Table 2. Select list of FDA-approved and marketed nanopharmaceutical products for the intravenous (I.V.) route of administration.

Drug	Nanotechnology	Brand-name	Company	Therapeutic Area
Doxorubicin	PEGylated liposomes	Doxil® (US) Caelyx(others)	OrthoBiotech Schering-Plough	Metastatic ovarian cancer and AIDS-related Kaposi's sarcoma
Doxorubicin	liposomes	Myocet®	Zeneus Pharma	Late stage Metastatic breast cancer
Paclitaxel	albumin-bound nanoparticles	Abraxane®	Abraxis BioScience AstraZeneca	Various cancers
Paclitaxel	polymeric micelles	Genesol-PM®	Samyang	Various cancers
Amphotericin B	liposomes	AmBisome®	NeXstar Pharmaceuticals Inc.	Fungal infections
Amphotericin B	phospholipid complex	Abelcet®	Enzon	Invasive fungal infections
Propofol	lipid emulsion	Diprivan®	AstraZeneca	Anesthetic
Cytarabine	liposomes	DepoCyt®	SkyePharma Enzon	Lymphomatous meningitis
Daunorubicin citrate	liposomes	DaunoXome®	Gilead Sciences	Advanced HIV-related Kaposi's sarcoma
Adenosine deaminase	PEGylation	Adagen®	Enzon	Enzyme replacement therapy in immunodeficiency disease
Iron oxide	superparamagnetic iron oxide nanoparticles coated with carboxydextran	Resovist®	Bayer-Schering Pharma AG	Organ-specific MRI contrast agent used for the detection and characterization of especially small focal liver lesions
Iron oxide	iron oxide nanoparticles	Feridex I.V.®	AMAG Pharmaceuticals, Inc.	MRI contrast agent used for the detection of liver lesions

Table 3. Select list of FDA-approved and marketed nanopharmaceutical products for oral and pulmonary routes of administration.

Route	Drug	Nanotechnology	Brand-name	Company	Therapeutic Area
Oral	Sirolimus	NanoCrystal®	Rapamune®	Wyeth, Elan	transplants
	Fenofibrate	NanoCrystal®	TriCor®	Abbott	primary hypercholesteremia,
	Fenofibrate	NanoCrystal®	Triglide®	SkyePharma First Horizon	lipid disorders
	Aprepitant	NanoCrystal®	Emend®	Merck, Elan	nausea in chemotherapy
	Megestrol Acetate	NanoCrystal®	Megace ES	Par Pharma, Elan	antianorexic
	Morphine sulfate	NanoCrystal®	Avinza®	King Pharma, Elan	psycho-stimulants
	Dexmethylphenidate HCl	NanoCrystal®	Focalin® XR	Novartis, Elan	attention deficit disorder
	Methylphenidate HCl	NanoCrystal®	Ritalin® LA	Novartis, Elan	attention deficit disorder
	Tizanidine HCl	NanoCrystal®	Zanaflex® Capsules	Acorda Inc., Elan	muscle relaxant
	Cyclosporine A	SMEDDS (self-microemulsifying drug delivery systems)	Neoral®	Novartis	transplants
	Saquinavir	SMEDDS	Forovase®	Roche	antiviral
	Ritonavir	SMEDDS	Norvir®	Abbott Laboratories	antiretroviral
Pulmonary	Artificial lung surfactant Replacement	synthetic recombinant polypeptide liposomal lung surfactant	Surfaxin®	Drug Discovery Lab	respiratory distress syndrome
	Artificial lung surfactant Replacement	natural bovine lung extract	Survanta®	Abbott Labs	respiratory distress syndrome
	Artificial lung surfactant Replacement	synthetic lung surfactant (protein-free)	Exosurf®	GlaxoSmithKline	respiratory distress syndrome
	Artificial lung surfactant Replacement	natural porcine lung extract	Curosurf®	Dey	respiratory distress syndrome
	Artificial lung surfactant Replacement	natural bovine lung extract	Alveofact®	Boehringer Ingelheim	respiratory distress syndrome

Table 4. Select list of FDA-approved and marketed nanopharmaceutical products for subcutaneous, intramuscular, transdermal/dermal, ophthalmic, and intravitreal routes of administration.

Route	Drug	Nanotechnology	Brand-name	Company	Therapeutic Area
Subcutaneous	Interferon alfa-2a	PEGylation	Pegasys®	Nektar Hoffmann-La Roche	hepatitis C infection
	hGH (human growth hormone)	PEGylation	Somavert®	Nektar Pfizer	acromegaly
	recombinant methionyl human G-CSF (granulocyte colony-stimulating factor)	PEGylation	Neulasta®	Amgen	neutropenia
	Glatiramer acetate	copolymer of L-glutamic acid, L-alanine, L-tyrosine, and L-lysine	Copaxone®	Teva	multiple sclerosis
	Amphotericin B	Lipid colloidal dispersion	Amphotec®	Sequus	invasive aspergillosis
	Interferon alfa-2b	PEGylation	PEGIntron®	Enzon Schering-Plough	hepatitis C infection
	Asparginase	PEGylation	Oncaspar®	Enzon	leukemia
Intramuscular	Hepatitis A Vaccine	IRIV (immunopotentiating reconstituted influenza virosomes)	Epaxal®	Berna Biotech	hepatitis A immunization
Transdermal/ Dermal	Estradiol	micellar nanoparticles	Estrasorb®	Novavax	menopause
	Estradiol	estradiol gel (0.06%) incorporating calcium phosphate nanoparticles	Elestrin®	BioSanté	menopause
	Lidocaine	liposomes	LMX®-4	Ferndale Laboratories	topical anesthesia
Ophthalmic	Cyclosporine A	lipid emulsion	Restasis®	Allergan	dry eye
	Difluprednate	lipid emulsion	Durezol®	Siron Therapeutics	corticosteroid
Intravitreal	anti-VEGF (vascular endothelial growth factor) aptamer	PEGylation	Macugen®	OSI Pharmaceuticals Pfizer	macular degeneration

1.2 APPROVED NANOPHARMACEUTICAL PRODUCTS: PARENTERAL DRUG DELIVERY

The parenteral administration route can directly access systemic circulation with a rapid onset of drug action, achieving an advanced molecular targeting to specific organs and tissue sites [71]. However, there are certain classic disadvantages with this approach, namely, insufficient drug accumulation at target sites while large amounts are dissipated and/or undesirable drug localization at normal tissue sites [72]. Given these drawbacks, there is extensive research focussed on increasing efficiency and bioavailability of nanomedicines delivered parenterally. Current strategies under investigation include the following:

- *Creating a protective barrier around the nanomedicines:* This can be accomplished by creating steric hindrance, hydrodynamic volume effects and/or charge repulsions around the nanomedicines. For example, polyethylene glycol (PEG), an FDA-approved polymeric excipient, provides both steric hindrance and hydrodynamic volume effects for the protection of nanomedicines with an extended period of time resulting in enhanced circulation activity [45].
- *Conjugation of targeting ligands to the surface of nanocarriers:* Various target receptors such as human epidermal receptor-2, transferrin receptor, folate receptor, and vascular endothelial growth factor receptor are examples for this strategy [73-75].
- *Stimuli-triggered systems*: Examples include ultrasonic, magnetic, electric and light from external-regulated stimuli as well as thermo-sensitive, pH-sensitive and enzyme-substrate reactions following as self-regulated stimuli [76].
- *Theragnostics:* Therapeutic and diagnostic agents are merged into a single carrier to monitor real-time bio-distribution and target accumulation of nanocarriers while enhancing the pharmacological efficacy of drugs [77, 78]. For the parenteral drug delivery of nanomedicines, intravenous injection can be used for certain drugs having long half-lives. Additionally, long-acting parenteral injections are also administered through intramuscular and subcutaneous routes [79].

There have been numerous approved marketed liposome-based nanopharmaceutical products over past several years, and this proves that liposomal delivery is a viable option for nanodrug delivery. Currently marketed liposomal products are based on passive targeting such as accumulation of carriers at disease sites via extravasation through a leaky vasculature [80]. Other research is based on active targeting via conjugation of site-directing ligands [80], triggered-release systems [81], cationic delivery systems [82], and multifunctional liposome systems [76, 83]. Polymeric nanoparticles and micelles

are able to increase their potentials with the PEGylation or PEG coating of these particles to prolong the circulation time of polymeric nanoparticles [60, 84, 85]. The surface of polymeric nanoparticles can be conjugated via targeting ligands, such as antibodies, engineered antibody fragments, proteins and peptides. Polymeric micelles can incorporate hydrophobic drugs by chemical conjugation or physical entrapment. On the other hand, the hydrophilic shell of these polymeric micelles can consist of PEG moieties (i.e., PEGylated liposomal nanocarrier systems), imparting prolonged circulation time through a combination of steric hindrance and hydrodynamic volume effects, as discussed earlier [86-88].

DOXIL® (Schering-Plough Corp., Kenilworth, NJ, USA; ALZA, Mountain View, CA, USA), a pegylated liposomal doxorubicin (PLD), is known as CAELYX® outside of the US. Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius*, var. *caesius*. The molecular formula of the drug is $C_{27}H_{29}NO_{11}\cdot HCl$ with a molecular weight of 579.99 [89]. DOXIL® is doxorubicin confined in liposomes that have been sterically stabilized by grafting polyethylene glycol onto the surface (STEALTH® Liposome) [90, 91]. Its circulation half-life is reported around 73.9 hours, whereas doxorubicin has a half-life of <10 minutes [92, 93]. Prolonged circulation facilitates greater uptake of PLD liposomes by tumor tissue. PLD accumulates selectively in metastatic breast carcinoma tissue, resulting in 10-foldhigher intracellular drug concentrations compared with adjacent normal tissue[94]. DOXIL® is provided as a sterile, translucent, red liposomal dispersion in 10-mL glass, single use vials. Each vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5[95]. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol,3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity [95]. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes, and it is indicated for: (a) ovarian cancer after failure of platinum-based chemotherapy, (b) AIDS-related Kaposi's sarcoma after failure of prior systemic chemotherapy or intolerance to such therapy, and (c) multiple myeloma in combination with bortezomib in patients who have not previously received it [95].

Taxanes are an important drug class of antitumor agents for the treatment of advanced and early-stage breast cancer. Paclitaxel (TAXOL®; Bristol-Myers Squibb Co, Princeton, NJ, USA) and Docetaxel (TAXOTERE®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA), are FDA-approved for the marketed products [96]. Furthermore, these drugs have shown remarkable anti-tumor activity against malignancies including non-small-cell lung cancer and ovarian cancer [97, 98]. Due to their high hydrophobicity, taxanes have a disadvantage in that they cannot be easily compounded into pharmaceutical formulations. Hence, to overcome poor water solubility of these drugs,

paclitaxel lipid-based formulations are used with a mixture of 50:50 Cremophor EL® (a non-ionic surfactant polyoxyethylated castor oil; BASF, Florham Park, NJ, USA) and ethanol [99]. Similarly, docetaxel is formulated in polysorbate 80 and ethanol diluents [100]. However, it should be emphasized that these conventional solvent-based formulations can cause serious and dose-limiting toxicities [97, 101-103].

Novel albumin-based formulations have been recently developed for paclitaxel. These formulations are highly soluble, Cremophor-free and increase the circulation time of the drug. Albumin is a natural carrier of endogenous hydrophobic molecules that are bound via a reversible non-covalent interaction [104]. Albumin-bound paclitaxel (ABRAXANE®; Celgene Corporation, Summit, NJ, USA) is a strategy to the solvent-related problems of paclitaxel and it has been recently approved by the US Food and Drug Administration for pretreated, metastatic breast cancer patients [105]. ABRAXANE® is an albumin-bound colloidal suspension of paclitaxel with a mean particle size of around 130nm. It is also free from any kind of solvent. This product is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% sodium chloride injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter of reconstituted suspension contains 5 mg paclitaxel [105]. Furthermore, in preclinical studies of athymic mice with human breast cancer, ABRAXANE® has a higher penetration into tumor cells with an increased antitumor activity compared to an equal dose of standard paclitaxel [106].

Although the incidence is decreasing, cryptococcal meningitis is still the most common manifestation of systemic fungal infection in HIV-infected patients and it remains associated with significant morbidity and mortality [107]. Amphotericin B deoxycholate has been considered for the initial treatment of cryptococcal meningitis in patients with HIV infection because initial treatment with the triazoles, fluconazole and itraconazole, is probably less effective [108]. Unfortunately, despite therapeutic advantages, amphotericin B deoxycholate may be associated with significant nephrotoxicity and acute infusion-related adverse effects. In order to reduce the risk of nephrotoxicity, a liposomal nanopharmaceutical product has been launched as AmBisome® (NeXstar Pharmaceuticals, Inc., San Dimas, CA, USA). This nanopharmaceutical product has received FDA approval for the treatment of patients with: (i) cryptococcal meningitis-HIV infection; (ii) mycosis as an empiric therapy for a presumed fungal infection in patients with febrile neutropenia; (iii) systemic mycosis due to aspergillus, candida and cryptococcus in patients refractory to amphotericin B deoxycholate or where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate; and (iv) visceral leishmaniasis [109, 110].

Infection with hepatitis C virus is the most common blood-borne infection in the US, eclipsing even HIV infection [111]. Interferon-α acts mainly as an immunomodulator and enhances the host cell-mediated immune response in clearing the virus [112]. In the case of protein drugs, such as interferon- α, there

have been enzymatic degradation and rapid clearance, which can be lead to wide fluctuations in blood levels due to frequent administration. PEGylation is a process with the attachment of PEG to prolong *in vivo* half-life of the protein. Two kinds of nanopharmaceutical products of PEGylated interferon-α have been marketed [113]. PEGylated interferon-α2b (PEGASYS®; Hoffmann–La Roche Ltd., Basel, Switzerland) contains covalently linked recombinant interferon-α2b and a straight chain molecule of 12 kDa PEG. PEGylated interferon-α2a (PEGINTRON®; Schering-Plough, Kenilworth, NJ, USA) is made up of interferon-α2a and a 40 kDa branched PEG [112, 114].

Nanopharmaceutical products based on submicron lipid emulsions were launched for the purpose of parenteral nutrition (INTRALIPID®) in the 1960s [115], and lipid emulsion formulations have been approved for marketed products such as diazepam (DIAZUMULS®; Pfizer, USA), etomidate (ETOMIDATE® Lipuro; Braun Melsungen, Germany) and propofol (DIPRIVAN®; AstraZeneca, USA) [51].

One of the exciting areas in nanotechnology is the use of magnetic (Fe_3O_4) nanoparticles as diagnostics [116, 117]. The magnetic properties of nanoparticles can be leveraged in diagnostics for disease states such as tumors, atherosclerosis, sclerosis, rheumatoid arthritis, and gliomas [118, 119]. Magnetic resonance imaging (MRI) is working with the superparamagnetic function of iron oxide nanoparticles for biopharmaceutical imaging [120]. Moreover, Fe_3O_4 particles also have superior biocompatibility, excellent chemical stability and low toxicity. Resovist® (Bayer-Schering Pharma, Germany) is a liver-specific magnetic resonance (MR) contrast agent and its active agents are carboxydextran-coated superparamagnetic iron oxide (SPIO) particles (ferucarbotran). The coating prevents the iron-oxide particles from aggregating and makes the compound highly hydrophilic. Resovist® exhibits low viscosity, is isotonic to blood plasma, and the hydrodynamic diameters of the coated particles range between 45 and 60 nm [121, 122].

1.3 APPROVED NANOPHARMACEUTICAL PRODUCTS: ORAL DRUG DELIVERY

Oral delivery is the most common administration route. This is mainly because of its high level of patient compliance due to its non-invasive nature, simplicity and convenience. Nanomedicines based on oral drug delivery have been extensively investigated and have resulted in various approved, marketed products. However, the oral delivery of liposomes has been somewhat limited due to their unpredictable absorption profiles and the rapid degradation of liposomes in the GI tract via interaction with bile salts [123, 124]. As a result, surface-modified liposomal systems were prepared for the biological instability of liposomes, which showed some success in intestinal absorption of protein drugs [125, 126]. Proliposomes were alternatively introduced and are defined as dry, free-flowing particles that have the ability to form liposomal dispersion when dispersed in an aqueous phase [127-129].

Some advantages of polymer-based nanomedicines include the following [3, 24, 130-133]:

- increasing bioavailability with enhanced water solubility of hydrophobic drugs due to a large specific surface area;
- ability to protect biologically unstable drugs from the hostile environment of the gastrointestinal tract;
- extending drug residence time through strong mucoadhesive properties;
- controlled drug release;
- facilitating transport of the drug through the epithelial membrane via endocytosis;
- bypassing or inhibiting efflux pumps such as P- glycoprotein; and
- targeting specific carriers for receptor-mediated transport.

NanoCrystal® technology (ELAN Corporation; Ireland) [3] is: (1) an enabling technology for evaluating NCEs that exhibit poor water solubility; and (2) a valuable tool for optimizing the performance of current drugs. NanoCrystal® technology can be applied to both parenteral and oral dosage forms, and can reduce particle size to less than one micron by proprietary attrition-based wet-milling techniques [134]. This nano-sized formulation can increase the surface area resulting in an increase in solubility and surface stabilization by the surface adsorption of selected GRAS (Generally Regarded As Safe) stabilizers [135]. Based on this technology, various solid oral dosage forms of nanomedicines are marketed in products. Examples include RAPAMUNE® (sirolimus), TRICOR® (fenofibrate), EMEND® (aprepitant) and MEGACE® ES (megestrol acetate). RAPAMUNE® is an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants. The pills should not be crushed, chewed or split. Patients unable to take the tablets should be prescribed the solution form and instructed on its proper use [136]. TRICOR® is a lipid-regulating agent available in tablet form for oral administration. Each tablet mainly contains GRAS additives such as hypromellose 2910 (3 cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate. TRICOR® is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia [137]. EMEND® is a substance P/neurokinin 1 (NK1) receptor antagonist. It is indicated (in combination with other antiemetic agents) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin, and the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) for the prevention of postoperative nausea and vomiting (PONV) [138]. Each capsule contains a GRAS additive such as sucrose, microcrystalline cellulose,

hydroxypropyl cellulose and sodium lauryl sulfate [138]. MEGACE® ES oral suspension is a progestin indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS). MEGACE® ES also contains the following GRAS inactive ingredients: alcohol, artificial lime flavor, citric acid monohydrate, docusate sodium, hypromellose, natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose [139].

The Self-Emulsifying Drug Delivery System (SEDDS) has been intensively studied to enhance the bioavailability of poor water-so1uble drugs. SEDDS is an anhydrous pre-concentrated system of microemulsion, which is composed of oil, surfactant and co-surfactant, and SMEDDS is capable of self-microemulsification after coming in contact with the physiological fluids on ingestion under gentle agitation. The agitation required for self-emulsification comes from native stomach and intestinal motility [140-142]. There are several products (NEORAL® and NORVIR®) that are commercially available as SMEDDS formulations in the US [143]. In spite of the various advantages of SEDDS, the large amount of surfactant and co-surfactant in these systems is associated with high levels of biological toxicity [143].

1.4 APPROVED NANOPHARMACEUTICAL PRODUCTS: DERMAL AND TRANSDERMAL DRUG DELIVERY

For dermal and transdermal drug delivery, liposomal nanomedicines have been shown to enhance drug permeation into the epidermis and dermis following localization of active agents at the targeted site of action as well as reduce the loss of these active agents due to percutaneous absorption [62, 144]. Liposomal nanomedicines can greatly enhance the penetration of macromolecule drugs as well as small molecule drugs. Enhancement of skin permeation via liposomal nanomedicines has been mainly due to the presence of specific types and ratios of phospholipids and cholesterol [145]. The formulation factors of liposomal nanomedicines are likely due to the thermodynamic lamellar phase of the liposome bilayer such as liquid crystalline state, gel state, crystalline state, size, charge, and lamellar structure such as multilamellar, unilamellar or non-lamellar hexagonal [44].

Lipid nanoparticles are attractive carriers for topical pharmaceutical (and cosmetics) products because of their occlusive properties, ability to increase skin hydration, ability to tailor drug release, protection of the drug against degradation, increase of skin penetration associated with targeting, and avoidance of systemic uptake [65, 146]. Although there are only cosmetic products on the market containing lipid nanoparticles at the present time, the market launch of pharmaceutical topical products is expected in the near future [65].

One of the most intensively researched areas for topical/transdermal drug delivery is that of submicron emulsions. This is due to the their higher solubilization capacity for both lipophilic and hydrophilic drugs, ease of

formulation, thermodynamic stability and ability to enhance skin permeation [147]. Despite these advantages, microemulsion systems present safety issues in long-term applications due to skin irritation by the presence of large amounts of surfactants and co-surfactants [148, 149].

Micelle Nanoparticles (MNP) have been developed for transdermal delivery of active agents. ESTRASORB® (Novavax Inc., USA) is the first nano-engineered topical dosage form that is approved by the FDA for hormone replacement therapy, thereby representing commercial validation of the MNP technology [150]. The *in vitro* Franz cell diffusion study was conducted using human cadaver skin, and three formulations of ESTRASORB® were evaluated [150]: (i) one containing about 9% w/w ethanol; (ii) a commercial estradiol gel containing about 40% w/w ethanol; and (iii) a 100% ethanolic solution of estradiol. ESTRASORB® is commercially manufactured on a kiloton scale and GRAS additives are used [151]. MNP drug delivery offers a potentially fast and inexpensive pharmaceutical development model by using drugs already proven safe and effective to create new proprietary formulations [150].

1.5 APPROVED NANOPHARMACEUTICAL PRODUCTS: PULMONARY DRUG DELIVERY

The lung is an attractive target for drug delivery because it offers a noninvasive means to provide not only local lung effects but also possible high systemic bioavailability, avoidance of first-pass metabolism, faster onset of therapeutic action, and the availability of a large surface area [5, 152]. Nanomedicines for pulmonary drug delivery have many advantages [5, 153], such as the ability to:

- achieve a relatively uniform drug distribution;
- enhance the solubility of the drug beyond its own aqueous solubility;
- achieve a sustained-release effect of the inhaled nanodrug;
- deliver macromolecules;
- reduced toxic side effects;
- improve patient compliance; and
- increase drug internalization by cells.

The inhalation devices for pulmonary drug delivery can be divided into three different categories: nebulizers, pressurized Metered Dose Inhalers (pMDIs), and dry powder inhalers (DPIs) [152]. In most cases, nanomedicines can be delivered to the lungs by nebulization of colloidal dispersions or by using pMDIs and DPIs in solid form [5]. Because of the small size and strong particle-to-particle interaction of nanomedicines, particle agglomeration and settlement can easily occur in colloidal dispersions. Also, chemical instability of colloidal dispersions is an issue due to carrier hydrolysis and drug degradation [11]. To overcome these physical and chemical instabilities, there have been several research approaches such as freeze-drying, spray-drying, spray freeze-drying, or supercritical fluid preparation of nanocarriers to provide a storage form [154]. The delivery of nanomedicines to the lungs is limited as individual nanocarriers

do not deposit efficiently in the lungs via diffusion, sedimentation or impaction, resulting in the exhalation of a majority of the inhaled dose [11, 152]. Therefore, micron-sized powder carriers containing nanoparticles or agglomerated nanoparticles can be designed to improve the inhalation aerosol delivery of nanoparticles for deep lung delivery by DPIs [155].

The field of nanopharmaceuticals for pulmonary delivery is in its infancy as basic research is conducted in this critically important area. For liposomal drug delivery, the marketed pharmaceutical phospholipid-based product for the treatment of respiratory distress syndrome is SURFAXIN® which is a synthetic lung surfactant in combination with the recombinant surface-active polypeptide, KL_4 [156]. In lung cancer nanomedicine pulmonary delivery research, the liposomal combination of paclitaxel and cyclosporin A was evaluated in mice animal models for pulmonary metastases of renal-cell carcinoma [157]. Pulmonary metastases were also achieved in a murine renal carcinoma model with nanoliposomal 9-Nitrocamptothecin inhalation aerosols [158]. The proof-of-concept of proliposome formulations of liposomal nanomedicines has been demonstrated using spray-dried DPI powders [159-162].

Solid lipid nanoparticles (SLNs) can be investigated for non-invasive pulmonary delivery of therapeutic drugs [163-165]. SLNs could deliver insulin via the pulmonary administration route with both *in vitro* and *in vivo* stability as well as prolonging hypoglycemic effect [163]. The thymopentin-loaded SLNs could enhance drug absorption and offer a sustained drug-release effect [165]. Epirubicin-loaded SLNs have been prepared as an inhalable formulation for treatment of lung cancer [164]. In animal models, these SLNs resulted in higher drug concentrations in the lungs and in plasma following inhalation of epirubicin-SLNs as compared to those following administration of an epirubicin solution [164].

1.6 CONCLUSIONS AND FUTURE PROSPECTS

Active agents that failed as conventional formulations due to unacceptable toxicity profiles, poor bioavailability, solubility issues, or physical/chemical inability may be reconfigured as nanoformulations. Additionally, with targeting ligands, nanomedicines can be innovative therapeutic agents for the enhancement of cellular uptake into tissues of interest. From a business perspective, nanopharmaceuticals offer the ability to extend the economic life of proprietary drugs and create additional revenue streams, thereby significantly affecting the drug commercialization landscape [3].

There has been a classic lifecycle management option practiced by drug companies in case of reformulation with nanotechnology. Nanopharmaceuticals are usually not bioequivalent to their parent versions, and hence, cannot apply for FDA approval via an Abbreviated New Drug Application (ANDA) under section 505(b)(j) of the Federal Food, Drug, and Cosmetic Act [3]. In other words, a nanodrug is generally not bioequivalent to a microcrystalline or solubilized form of the same drug (i.e., nano is not always bioequivalent to its bulk

counterpart). Hence, a New Drug Application (NDA) under the 505 (b)(1) route may need to be filed at the FDA. Obviously, if a nanopharmaceutical is bioequivalent to its parent version, an ANDA can be filed to seek regulatory approval. Therefore, when warranted, the FDA should treat nanoversions of active ingredients as NCEs. This will ensure that drugs, biologics, etc. that have been previously approved by the FDA but later modified as nanoversions will undergo a new and rigorous round of safety testing in order to obtain premarket approval [3, 169].

Nanomedical advances and the FDA system for governing it are inevitably intertwined. However, the "baby steps" the FAD has undertaken over the past decade have led to regulatory uncertainty [166-169]. Whether the FDA eventually creates new regulations, tweaks existing ones, for the time being it should at least look at nanomedical products on a case-by-case basis [168, 169].

The toxicity of many nanoscale materials will not be fully apparent until they are widely distributed and their exposure is felt by a diverse population [169]. Therefore, postmarket tracking or a surveillance system must be adopted to assist in nanomedical product recalls [169]. Although toxicological testing for health risks of such products is not currently a complete science [170], nevertheless, it is crucial to monitor their unique properties (if any) that may lead to serious adverse effects and toxicity. Because it is well established that premarket testing of nanodrugs will not detect all adverse reactions [171], it is essential that long-term testing of nanoscale materials be in place to allow safety testing. In this regard, toxicity data specific to nanomaterials needs to be collected and an effective risk research strategy devised [169]. Currently, there are few reliable means to identify marketed "nano-containing" products, and consumers are unable to judge for themselves which ones may be toxic. Hence, the FDA should seriously contemplate nano ingredient labeling on a case-by-case basis.

So far, the process of converting basic research in nanomedicine into commercially viable products has been difficult. Securing valid, defensible patent protection from the US Patent & Trademark Office [172, 173] along with clearer regulatory and safety guidelines from the FDA [168, 169] are critical to any commercialization effort pertaining to nanopharmaceuticals.

In the future, novel "multifunctional" nanopharmaceuticals will be designed as new generations of drug delivery systems to target specific organs or specific tissues. Currently, nanodrug delivery systems are being developed to target even individual cells or organelles. As we rapidly enter the age of nanotheranostics, it is likely that nanopharmaceuticals will become prime tools in treating numerous diseases [174, 175]. However, even though the use of nanotechnology for drug delivery is promising and a highly attractive application area, additional funding, basic research and translational research from "bench-to-bedside" is needed.

1.7 DISCLOSURES AND CONFLICT OF INTEREST

The authors declare that they have no conflict of interest and have no current financial involvement with any organization or entity discussed in this chapter. Dr. Bawa is Scientific Advisor to Teva Pharmaceuticals, Ltd. (Israel). No writing assistance was utilized in the production of this manuscript and the authors have received no payment for preparation of this chapter. The findings and conclusions here reflect the current views of the authors. They should not be attributed, in whole or in part, to the organizations with which they are affiliated, nor should they be considered as expressing an opinion with regard to the merits of any particular company or product discussed herein. Nothing contained herein is to be considered as the rendering of legal advice.

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Dr. Chun-Woong Park received an M.S. in 2005 in pharmaceutics and Ph.D. in physical pharmacy in 2008 from Sungkyunkwan University, Republic of Korea. From 2010 to 2011, he was a postdoctoral visiting scholar at the University Of Kentucky College Of Pharmacy, Department of Pharmaceutical Sciences-Drug Development Division, USA. Currently, he is an assistant professor at the College of Pharmacy at Chungbuk National University, Republic of Korea. His current research focuses on advanced particle engineering design for dry powder inhalation aerosols and gastroretentive drug delivery system using a PUMICETM matrix system.

Dr. Raj Bawa is president of Bawa Biotech LLC, an Ashburn, VA based biotech/pharma consultancy and patent law firm he founded in 2002. He is an inventor, entrepreneur, professor and a registered patent agent licensed to practice before the U.S. Patent & Trademark Office. Trained as a biochemist and microbiologist, he has been an active researcher for the past two decades. He has extensive expertise in pharmaceutical sciences, biotechnology, nanomedicine, drug delivery and biodefense-related scientific, FDA regulatory and patent law issues. Since 1999, he has held various adjunct faculty positions at Rensselaer Polytechnic Institute in Troy, NY where he is currently an adjunct professor of biological sciences and where he received his Ph.D. degree (Biophysics/Biochemistry; 1987-1990). Since 2004, he has been an adjunct associate professor of natural and applied sciences at the Extended Learning Institute of NVCC in Annandale, VA. Since 2012, he has been a scientific advisor to Teva Pharmaceutical Industries, Ltd., Israel. He previously served as patent legal advisor at Sequoia Pharmaceuticals, Gaithersburg, MD and as senior scientist at SynerGene Therapeutics, Inc., Potomac, MD. He recently served as principal investigator of two National Cancer Institute/SBIR contracts titled "Targeted nanocomplexed iron oxide for early detection with concurrent hyperthermia treatment of cancer" and "A targeted nanocomplex for early detection of lung cancer." In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office, including primary examiner (6 years) and instructor at the US Patent Academy. He is a life member of Sigma Xi, founding director of the American Society for Nanomedicine, and co-chair of the Nanotech Committee of the American Bar Association. He has authored over 100 publications, co-edited two books and presented or chaired at over 200 conferences worldwide. He serves on the editorial boards of 16 peer-reviewed journals, including *Pharmaceutical Patent Analyst, International Journal of Nanomedicine, Cancer Nanotechnology, Applied Scientific Reports, Recent Patents on*

Biomedical Engineering, Nanotechnology Law and Business, Recent Patents on Nanotechnology, Journal of Epidemiology and Preventive Medicine, WIRE's Nanomedicine and Nanobiotechnology, JSM Biotechnology & Biomedical Engineering, Nanomedicine: NBM. Some of Dr. Bawa's awards include the Innovations Prize from the Institution of Mechanical Engineers, London, UK (2008); Appreciation Award from the Undersecretary of Commerce, Washington, DC (2001); a Research Fellowship from Rensselaer (1989-90); the Key Award from Rensselaer's Office of Alumni Relations (2005); and Lifetime Achievement Award from the American Society for Nanomedicine (2014).

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