CHAPTER

5

Nanoparticulate treatments for oral delivery

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1. Introduction

In 1959, when Dr. Richard Feynman [1] gave what is deemed to be one of the first lectures on engineering at the atomic scale, there was no doubt that "There is plenty of room at the bottom." This was one of the most enigmatic, yet accurate scientific prophecies that we have seen realized. What Dr. Feynman was talking about was engineering techniques to manipulate information at the atomic level. Since then, rapid progress has been made in the application of the concept of modifying materials at the atomic level to various fields such as industrial applications, e.g., refining of crude oil using mesoporous sieves, water treatment, e.g., filtration/ultrafiltration, and also drug delivery.

Mathematically speaking, a nanometer (nm) is defined as 1 billionth of a meter (1×10^{-9} m). However, the definition of a "nanoparticle" is not as well defined. According to the International Standards Organization, a nanoparticle is a "discrete nano-object where all three cartesian dimensions are less than 100 nm." However, the European Union contended with a slightly wider range for defining the confines of a nanoparticle indicating that it is a "natural, incidental, or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1−100 nm" [2]. Regardless of the exact definition, it is generally accepted that certain distinctive phenomena occur in the size range 1−100 nm such as catalytic properties of gold prepared in reverse micelles [3], liposomal nanoparticles, polymeric nanoparticles (PNs), and metal oxide nanoparticles [4] to name a few. It is this unique behavior that has had groundbreaking applications for nanotechnology over

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the last few decades (Table 5.1). Clearly, over time, the applicability and relevance of the enablement of nanotechnology have touched practically every aspect of human existence and effected flourishment of the quality of life for humankind. Particularly in recent years, focus on the application of nanotechnology in medicine has taken center stage.

2. Need for nanotechnology in oral solid dosage forms

One of the top 10 most prescribed medications in the United States is OSD forms (Fig. 5.1) [7]. While the new generation of treatments such as biologics and proteomics seems to favor parenteral dosage forms, the omnipotence and acceptability of OSDs has certainly made the pharmaceutical industry focus on developing newer medications primarily as OSDs.

However, in spite of the obvious advantages such as ease of administration, freedom from pain, and noninvasiveness, for most of the drugs administered via the oral route, some of the biggest challenges include solubility of the drug, permeability, and dissolution of the drug from the oral dosage form. While multiple approaches have been proposed to predict in vivo behavior based on in vitro properties (dissolution), the accuracy of the predictability of these modeling approaches still remains ambiguous at best. This is accentuated by the variability in conditions in the gastrointestinal tract under fed and fasting conditions. There is also some variability that can be afforded to the differences in metabolism between different individuals. Physiological characteristics such as enzymatic metabolism, pH [8], and bacterial colonization present several hurdles to the absorption of orally administered drug before it can reach systemic circulation. As a result, most of the orally administered drugs exhibit low bioavailability [9].

This multitude of challenges opens up new opportunities to still achieve efficacious oral

TABLE 5.1 Chronological advancement of nanotechnology over the last few decades [5].

Year	Chronology of nanotechnology developments for drug delivery
1974	Norio Tanuguchi coins the term nanotechnology. [6].
1981	Invention of the scanning tunneling microscope developed by Gerd Binnig and Heinrich Rohrer at IBM Zurich Research Laboratory. This invention has found application in the characterization of nanomaterials.
1985	Fullerenes (carbon nanotubes) were discovered by Harry Kroto, Richard Smalley, and Robert Curl. Carbon nanotubes have since been researched for application for cancer treatment via oral dosage forms.
1990s	Conception of early nanotechnology companies such as Nanophase Technologies Inc., Helix Energy Solutions Inc., and Zyvex Technologies Inc.
1999	Chad Mirkin (Northwestern University) invented dip-pen nanolithography based on the atomic force microscopy principle. This technology enabled transcription of electronic circuits, biomaterials on different substrates, and other applications. This technology later found applications in incorporating anticounterfeiting for oral solid dosage (OSD) forms.
2000	Elan Pharmaceuticals received approval for Sirolimus, reformulated using their proprietary technology called Nanocrystal. This technology worked on improving bioavailability by enhancing aqueous solubility.
2012	Marquibo (vincristine sulfate encapsulated in liposomes) was approved by the Food and Drug Administration for the treatment of acute lymphoid leukemia.

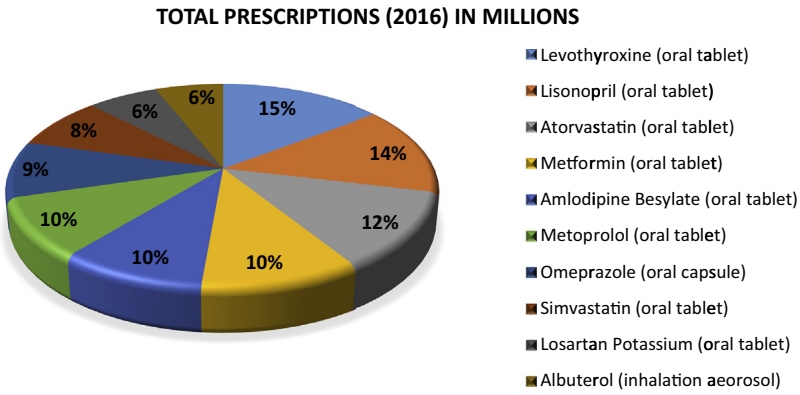

FIGURE 5.1 Top ten prescribed medications (2016).

drug delivery via the oral route by resorting to application of nanotechnology for the development of oral dosage forms. If the challenges of preventing drug degradation/metabolism and improving the absorption rate are overcome, this can significantly improve the possibility of oral drug delivery. Enteric protection using different types of polymers is well known wherein polymer chemistry allows for protection of the orally delivered drug dosage form in the acidic environment in the stomach for the duration of residence time of the dosage form. Once the dosage form reaches the higher pH environment in the small intestine, the enteric polymer film dissolves resulting in release of the drug from the dosage form. In spite of the various enhancements to an oral drug dosage form, the drug may still exhibit low bioavailability, especially large molecule drugs such as peptides, hormones, or proteins.

As early as 1990, nanotechnology has enabled formulation of oral dosage forms that have been used for treating cancer [10] (Table 5.2). Formulation of small molecules such as doxorubicin (Doxil), sevelamer hydrochloride (Renagel), and fenofibrate (Tricor) into oral dosage forms with enhanced pharmacokinetics for the drugs has laid the foundation for the formulation of more complex, larger molecules, using nanotechnology, into oral dosage forms. The primary motivation for use of nanotechnology for OSDs is:

1. Bioavailability enhancement
2. Targeting specific regions of the physiology
3. Improved physiological stability
4. Sustained action

2.1 Bioavailability enhancement

The Biopharmaceutical Classification System (BCS) classifies drug compounds into four categories based on their solubility and permeability [11]. It stands to reason that BCS class II exhibiting low solubility will cause absorption to be rate limited by the dissolution rate of these drugs (Fig. 5.2).

This may result in poor bioavailability. Likewise, for BCS class IV drugs (low solubility, low permeability), dissolution rate and permeability will both rate limit absorption and inhibit bioavailability. Several new nanotechniques have been implemented to effect improved bioavailability for low soluble drugs such as nanomilling, which was first patented by Elan Nanosystems [12]. This unique methodology

TABLE 5.2 Food and Drug Administration (FDA)-approved nanopharmaceuticals [10].

Marketed trade name	Active ingredient	Type of nanoparticle treatment	Indication	Manufacturer	FDA approval
Adagen	PEG (polyethylene glycol) ylated adenosine deaminase enzyme	Polymer nanoparticles	Severe combined immunodeficiency disease	Sigma Tau	1990
Oncaspar	PEG-asparaginase		Acute lymphocytic leukemia	Sigma Tau	1994
Copaxone	Glatiramer acetate		Multiple sclerosis	Teva	1996
Renagel	Amine-loaded polymer (sevelamer hydrochloride)		Serum phosphorus control in patients with chronic kidney diseases on dialysis	Genzyme	2000
Doxil	PEGylated-stabilized liposomal doxorubicin	Liposomal nanoparticles	AIDS-related Kaposi's sarcoma, refractory ovarian cancer, multiple myeloma	Janssen	1995
Amphotec	Liposomal amphotericin B		Invasive aspergillosis	Alkopharma	1996
Ontak	Interleukin-2 diphtheria toxin fusion protein	Protein nanoparticles	Cutaneous T-cell lymphoma	Eisai	1999
Abraxane	Albumin protein-bound paclitaxel		Metastatic breast cancer	Celgene	2005
Emend	Aprepitant nanocrystal particles	Nanocrystal nanoparticles	Chemotherapy-related nausea and vomiting	Merck	2003
Tricor	Fenofibrate		Hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia	Abbott	2004

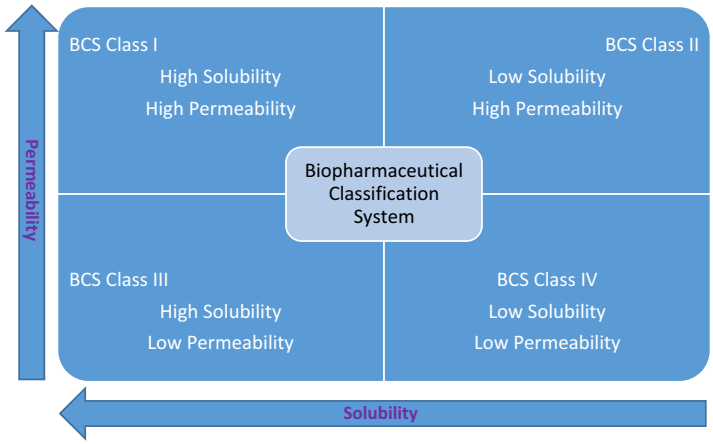

FIGURE 5.2 Biopharmaceutical classification system.

relied on high-shear media mills using inert media beads such as glass, zirconium dioxide, or highly cross-linked polystyrene resin to break the drug particles down to the nanometer size range using high energy. This "surface modification" resulted in significant reduction in particle size of the drug yielding a significantly high surface-to-volume ratio, thereby improving the solubility characteristics of the drug. This also resulted in significant improvement in the bioavailability of the drug. Several drugs were commercialized using this technology.

Surface enlargement is a phenomenon that results in increase in the number of drug crystals by way of particle size reduction of the parent crystals, but also results in a significant increase in the surface-to-volume ratio (Fig. 5.3).

Typically, wet media mills have the ability to operate in multiple modes, including batch, continuous, and recirculation (Fig. 5.4). While the batch mode serves to process small-scale batches at the lab scale, the continuous mode serves to process production of larger quantities of milled material. A receiving tank would be added to the process flow, which allows for continuous collection of the milled suspension. The scale integration capability allows for multiple mills to be stacked in series allowing a cascade flow of the input suspension through the multiple mills resulting in precise control of the particle size.

This is particularly noteworthy since the implementation of continuous manufacturing in the pharmaceutical industry is gaining traction. This methodology relies on increasing the surface area-to-volume ratio exponentially from a crystal form of the active pharmaceutical ingredient (API) by way of reducing the particle size significantly (by several orders of magnitude). As may be evident, this technology may have limitations, especially when the nanocrystals are suspended in aqueous media. Over time, the nanocrystals might face Ostwald ripening leading to a reduction in the surface charge causing issues such as aggregation, which can impact long-term stability of the suspension product.

Other novel approaches to size reduction based on increased bioavailability include homogenization (Dissocubes), deep-freeze homogenization (Nanopure), precipitation (Nanoedge), opposite stream or nanojet technology (Nanojet), emulsification-solvent evaporation technique, hydrosol, and supercritical fluid method [15]. While these methods rely on different mechanisms and equipment to effect particle size reduction, the common element is being able to reduce the particle size and hence increase the surface area-to-volume ratio. As per the Noyes–Whitney equation [16], this phenomenon potentially increases the dissolution rate of the milled drug nanoparticles. Because of the high surface free energies along with their thinner diffusion boundary layers, the dissolution of these particles is enhanced [17].

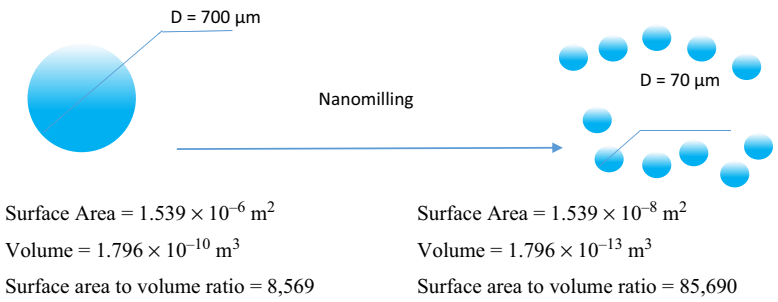

FIGURE 5.3 Example of increase in surface area-to-volume ratio with reduction in particle size.

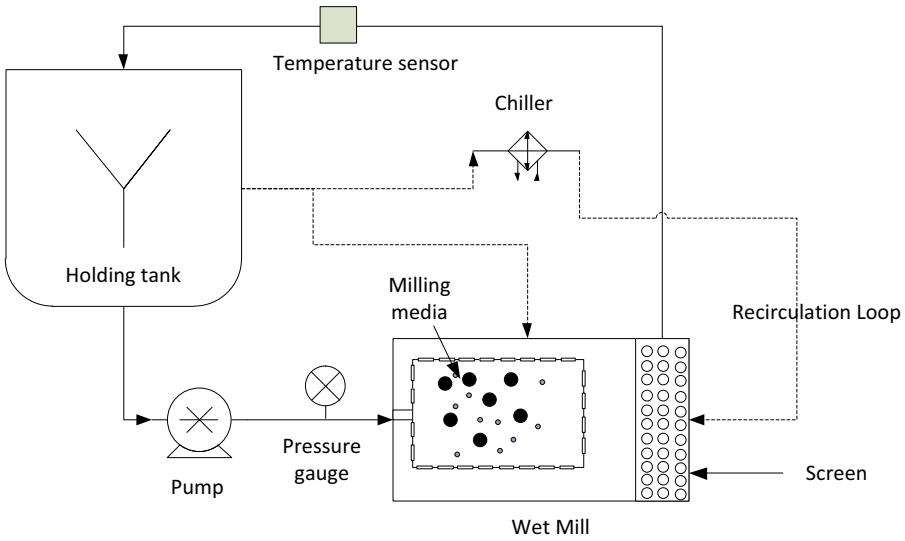

FIGURE 5.4 Schematic representation of the wet milling process [14].

2.2 Targeting specific regions of the physiology

As early as the 16th century [18], physicians started developing an understanding of the epidemiology of cancer and developing rudimentary methods of detecting and treating different forms of cancer. However, these methods often involve removal of the tumor if it had not "damaged" nearby tissue. However, this method was not very effective in late stages of cancer. Radiation therapy emerged in the early 20th century as a means for removal of smaller tumor growths. Soon after, chemotherapy treatments were considered effective as an adjuvant therapy. Chemotherapeutic agents act to destroy the rapidly dividing cells. However, the human body has healthy cells such as bone marrow cells, macrophages, digestive tract cells, and hair follicles, which also exhibit fast growth. Thus chemotherapy inadvertently also targets these healthy cells resulting in significant side effects such as immunosuppression, anemia, and hair loss [19]. Thus, because of the nature of the ominous disease, it was considered imperative to develop medications or treatments that could specifically target the malignant cells.

New advents in nanotechnology-based cancer treatments include methodologies such as active targeting. Surface-modified nanoparticles containing chemotherapeutic agents are used to target defective cells. These modifying agents may include targeting moieties such as synthetic polymers or lipids. Some critical characteristics of tumor-targeting nanoparticles include particle size, shape, and surface chemistry of the targeting agents [20]. Breakthrough research done by Cabral et al. on drug-loaded sub-100 nm polymeric micelles [21] showed that 1,2-diaminocyclohexaneplatinum(II)-loaded polymeric micelles, which were less than 30 nm, could penetrate into the interstitium of pancreatic tumor in vivo, whereas the larger ones mostly accumulated at the periphery of tumors. Another important characteristic that impacts tumor targeting and penetration is shape. Popović et al. [22] showed that penetration of specific shapes of surface-modified nanoparticles such as nanorods in mammary tumors was approximately double the volume of nanospherical-shaped nanoparticles having the same hydrodynamic diameter in mice. Smith et al. [23] compared the tumor penetration of

spherical quantum dots and single-walled carbon nanotubes in mouse tumor models and showed that difference in shape (assuming similar volumes) does impact tumor penetration capability and capacity.

2.3 Improved physiological stability

Oral delivery of large molecules like peptides and proteins such as insulin has been one of the most significant challenges facing researchers given the trade-off between stability and efficacy of the large molecules. Additionally, with the ability to target specific regions of the human physiology, the need to establish stability of the large molecules at the site of action is also paramount. Gou et al. [24] found that solid lipids encapsulated within nanoparticulate cores rendered these loaded systems spherical in shape and stabilized not only the nanoparticle cores by enhancing the thermodynamic stability of the nanoparticle but also the chemical stability of the block copolymer in the gastrointestinal environment. Pharmacokinetic studies conducted by Gou et al. showed improved bioavailability of core-stabilized oral larotaxel as compared to the lipid-free nanoparticles or larotaxel solution. Studies performed comparing binary lipids with single lipid formulations [25] showed that binary lipid matrix-based nanoparticles (using stearic acid and tristearin for the lipid core and Pluronic-F68 as the stabilizer) exhibited superior drug-loading and drug release characteristics. These binary lipid matrices were more stable in gastrointestinal fluids and showed improved storage stability compared with single lipid formulations.

2.4 Sustained or controlled release effect

Solid lipid nanoparticles (SLNs) affect sustained release of the entrapped active pharmaceutical ingredients because of their improved drug release characteristics and have been employed for delivery of small as well as large molecules. Gupta et al. [26] developed a sustained drug delivery colloidal system comprising poly(DL-lactide-*co*-glycolide) (PLGA) nanoparticles for sparfloxacin to effect ophthalmic delivery by prolonging precorneal residence time and ocular penetration. PLGA nanoparticles have also been used to encapsulate savoxepine and develop sustained release intramuscular and intravenous depot injections [27]. Similarly, PLGA systems have also been used to formulate poorly soluble drugs such as carbamazepine via the solvent emulsification evaporation technique. In this case, Tummala et al. [28] were able to show not only improved solubility of the drug, but also sustained release over a period of 24 h. Organically modified silica-based nanoparticles synthesized using the microemulsion technique have been used to entrap doxorubicin. Roy et al. [29] developed a sustained release system for this drug by modulating the nanoparticle size such that the drug can be release over a period of up to 2 weeks.

3. Formulation perspectives

As the field of nanotechnology has advanced in the last few decades, so has the perspective to formulate novel medications in various dosage forms. The multitude of advantages offered by the application of nanotechnology, in various forms, includes surface modification capability resulting in improved surface area-to-volume ratio resulting in improved solubility and bioavailability, ability to target specific regions of the human physiology, ability to construct complex nanosystems that enable sustained release of the active at the site of action, and most importantly the ability to manipulate at the atomic scale resulting in the capability of developing breakthrough medications for treating diseases like cancer or neurological disorders like Alzheimer's, Parkinson's, and multiple sclerosis.

The enigma of "nanotechnology" as it has unfolded in its several manifestations, especially in the most predominant dosage form, i.e., the OSD form, can be attributed to the different "nanotechniques" that have been developed over the decades (Fig. 5.5). It would be apt to take a walk through the details of these techniques, how they work, and what their applications are.

3.1 Solid lipid nanoparticles (SLNs)

SLNs are an advanced colloidal drug delivery system. They belong to the family of nanoemulsions where the active ingredient is incorporated into a lipid carrier such as high-melting point glycerides, fatty acids, steroids, and waxes. Biocompatible surfactants such as poloxamer, polysorbate, sodium glycocholate, and soybean lecithin are used to stabilize these SLNs [30]. Typically, SLNs are employed as drug carriers to PNs and can have particle sizes ranging between 50 and 1000 nm. The reduced particle size offers higher surface area resulting in various advantages such as prolonged release of drug and rapid uptake by cells [31]. Another significant advantage of SLNs because of the smaller particle size distribution is the ability to counter issues with poor solubility and bioavailability [32].

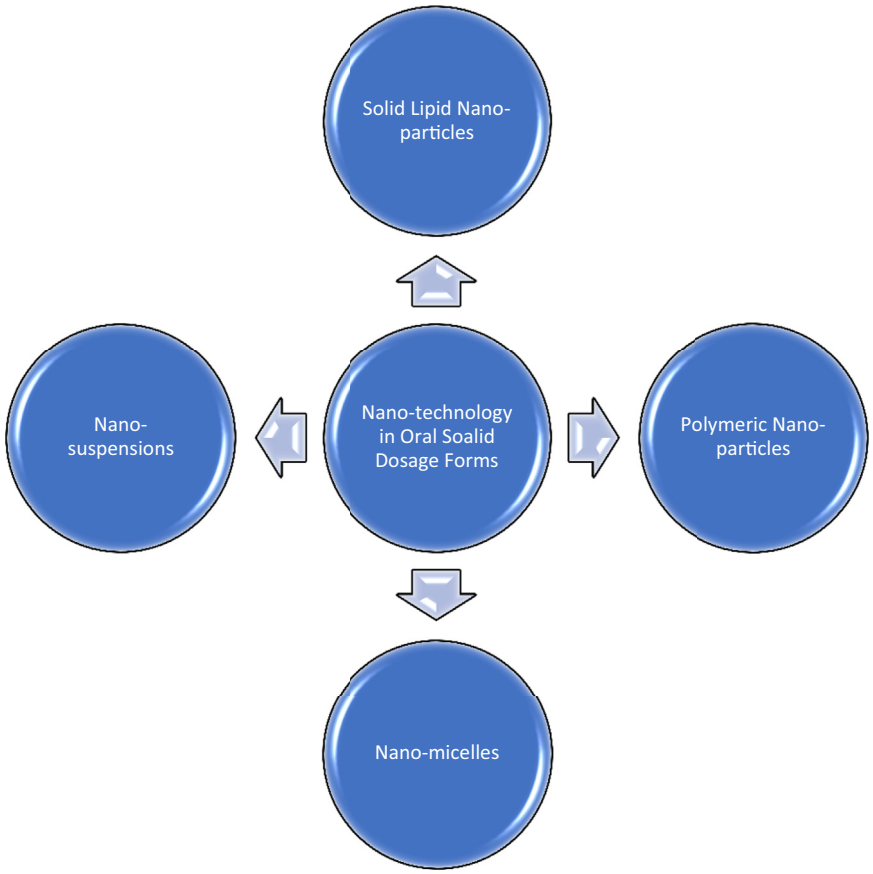

FIGURE 5.5 Applications of nanotechnology to different techniques for the formulation of oral solid dosage forms.

Various methodologies have been developed to produce SLNs, including:

1. Hot melt extrusion (HME) in combination with homogenizer
2. Solvent emulsification/evaporation
3. Hot/cold homogenization
4. Microemulsion
5. Supercritical fluid/ultrasonication

3.1.1 Hot melt extrusion

HME is a relatively old process developed in the early 1930s, when it was developed for use in plastics and the food industries. It was not until the 1970s that the application of HME to the pharmaceutical field took root. While HME has been employed for the development of OSD forms with multiple commercialized products such as Kaletra (lopinavir/ritonavir), Norvir (ritonavir), Onmel (itraconazole), and many others [37], its application for the production of SLNs is fairly recent. Fig. 5.6 shows a representation of the HME process developed by Patil et al. for the manufacture of SLNs for the model drug fenofibrate [38]. This was achieved by co-mixing the lipid phase and the aqueous phase with an emulsifier within the barrel of the hot melt extruder at temperatures exceeding the melting point of the lipid. Subsequently, particle size reduction to below 200 nm was achieved by linking a high-pressure homogenizer in sequence with the hot melt extruder.

Since the HME in series with high-pressure homogenization (HPH) can run on a continuous basis as long as input materials are being supplied to the process, this option presents a robust and scalable manufacturing process for SLNs. Some critical considerations for applying HME for SLN production are: physicochemical characteristics of the API, physicochemical characteristics of the lipid(s), choice of stabilizer, critical process parameters for the HME process such as screw design, screw speed, temperature zones, and limits for the temperatures in each zone, and critical process parameters for the HPH process.

3.1.2 Solvent emulsification/evaporation

This method is of particular importance for the encapsulation of poorly soluble drugs within

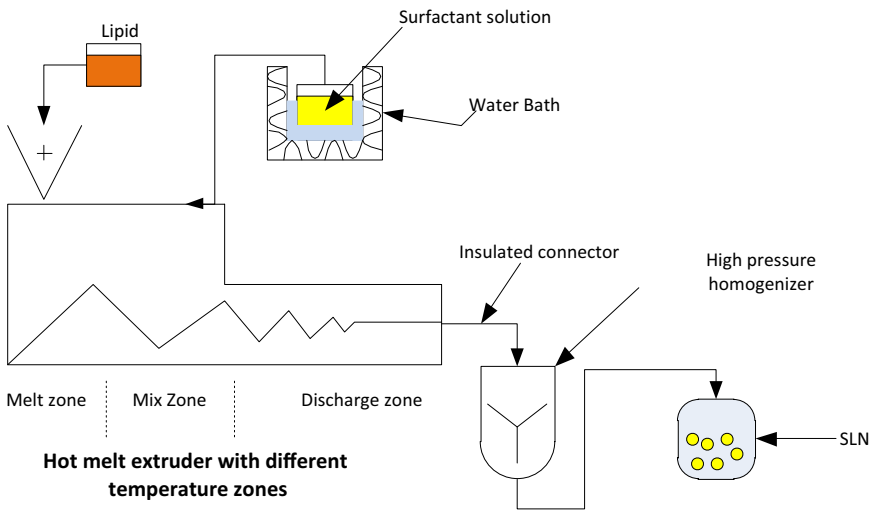

FIGURE 5.6 Schematic representation of continuous preparation of solid lipid nanoparticles (SLNs) using hot melt extrusion connected to a high-pressure homogenizer [38].

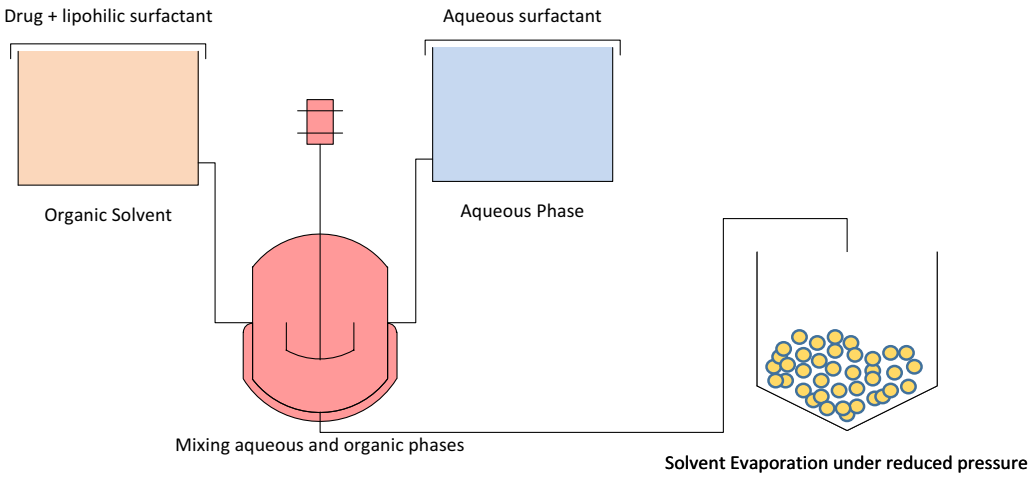

FIGURE 5.7 Schematic representation of the solvent emulsification/evaporation process.

a water-insoluble polymer. As shown in Fig. 5.7, this process starts with preparation of an emulsion, where the external phase is chosen based on the nature of the encapsulating polymer and the API used for the encapsulation. Once the organic and aqueous phases are mixed, the solvent is evaporated resulting in the formation of the microspheres/nanospheres. Nanoparticles loaded with drug can be achieved reproducibly with a mean particle diameter of up to 30 nm [39].

3.1.3 *Hot/cold homogenization [33,40]*

The process for the preparation of SLNs using hot high pressure homogenization requires temperatures higher than the melting point of the lipid. Drug-loaded lipid melt is prepared following which a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase is mixed using high shear mixing at the same temperature. This pre-emulsion is then homogenized at high pressure at a temperature that is above the melting point of the lipid. The processing temperature can be modulated to achieve various particle sizes of the SLNs. Typically, higher operating temperature yields lower particle sizes; however, caution has to be used to ensure that the higher temperatures do not adversely impact the stability of the drug and the carrier. The critical process parameters that can be optimized based on the desired particle size characteristics include operating homogenization temperature, homogenizer speed, and number of homogenization cycles (Fig. 5.8).

Similar to the hot high pressure homogenization process, the cold homogenization process starts with dispersion or solubilization of the drug within the molten lipid. This phase is subsequently rapidly cooled to ensure uniform dispersion of the drug within the lipid. This step is followed by micronization of the drug containing solid lipid to yield particles in a size range of 50–100 microns. These particles are chilled in an emulsifier solution. Freezing of the solid lipid increases the fragility of the solid lipid and eases milling. Finally, temperature-controlled HPH yields drug-loaded SLNs. While cold homogenization offers certain advantages over hot homogenization in terms of ensuring stability of the lipid by limiting the exposure of the lipid and/or drug to higher temperatures, it also limits control on the polydispersity and overall particle size as compared to hot homogenization.

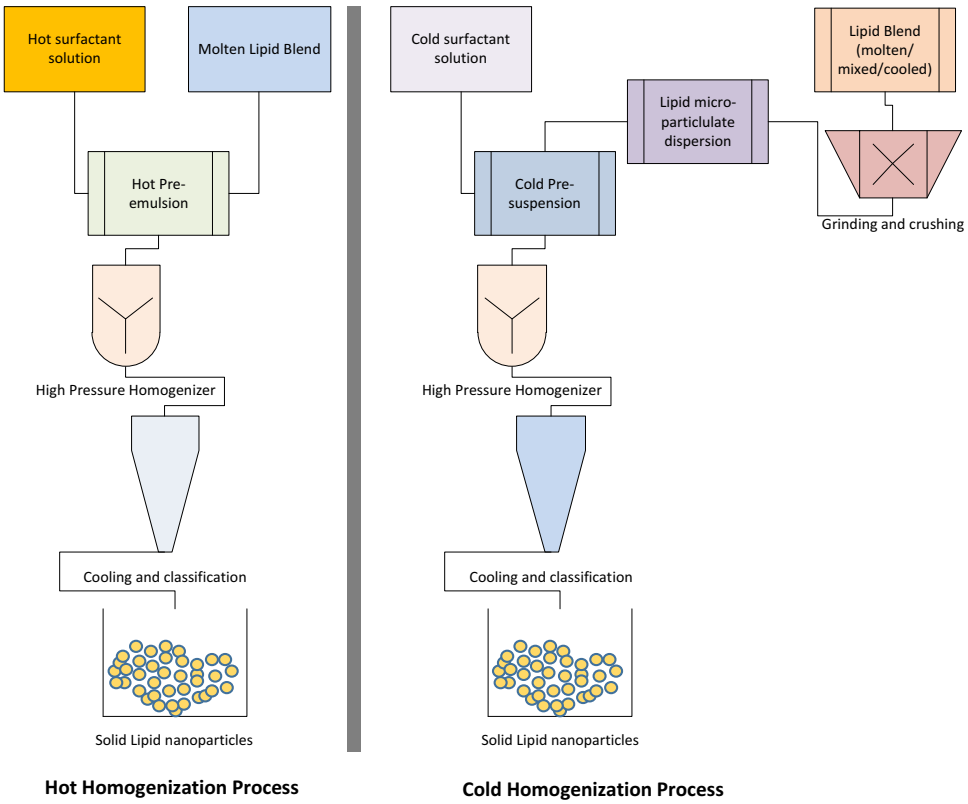

FIGURE 5.8 Schematic representation of hot and cold homogenization processes for solid lipid nanoparticle production.

3.1.4 *Microemulsion [41]*

In this methodology, the solid lipid is melted. The drug is either dissolved or dispersed in the lipid depending on the solubility and lipophilicity characteristics of the drug (Fig. 5.9).

The aqueous mixture/solution of drug is then added to the molten lipid blend. A surfactant and/or cosurfactant is added to the lipid/drug mixture at a temperature that is higher than the melting point of the lipid. This results in the formation of a clear water-in-oil (W/O) emulsion. This W/O emulsion is then mixed with water, surfactant, and cosurfactant (which act as stabilizers) under stirring. The resulting suspension of nanoparticles is washed with dispersion medium using ultrafiltration yielding SLNs.

3.1.5 *Supercritical fluid*

Another methodology used for the production of SLNs is rapid expansion of supercritical solution. It can be looked at as a "greener" way to produce SLNs since the use of solvents can be avoided (depending on the solubility and lipophilicity of the lipid and drug components). In this process, a solution in the supercritical state (at a temperature that is above the critical point, where liquid and gas phases do no distinctly exist) is sprayed through a narrow capillary nozzle. Because of a sudden change in the orifice diameter, the sprayed solution experiences a drastic change in density resulting in highly supersaturated SLNs. This method has been successfully employed to develop OSD

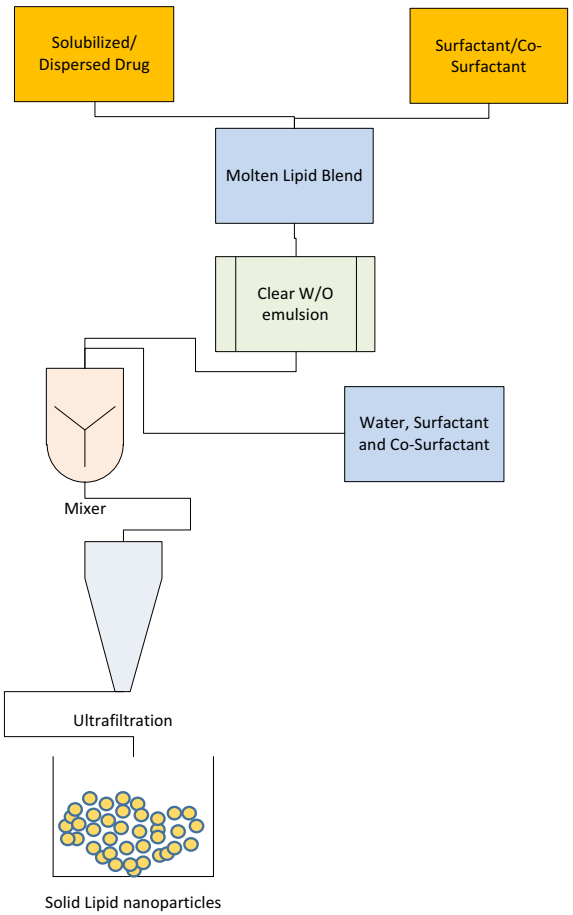

FIGURE 5.9 Method of manufacture for microemulsions. *W/O*, Water in oil.

forms using several small molecules such as carbamazepine [42], indomethacin, ketoprofen, and bovine serum albumin [43].

3.2 Polymeric nanoparticles

As the name suggests, PNs basically stem from use of biodegradable polymeric materials such as gelatins, polyglycolic acid, poly(lactic-*co*-glycolic) acid, polyethylene glycol, and poly(-methylmethacrylate). The FDA has approved the use of multiple polymeric materials to be used as therapeutic agents for human use such as (PLGA) copolymer and poly(lactic) acid. Application of PNs for gene therapy treatment of cancer, use as antimicrobials, and also for development of biomaterials has been well known for more than a decade. Most prominent of these applications is the development of oral dosage forms. This manifestation addresses some of the common problems [44] faced with drug absorption, which can be limited in oral dosage forms by three key parameters of the dosage form, namely dissolution, solubility, and permeability.

PNs can be classified into two main categories [44,45]: nanoshells and nanospheres. Nanoshells

represent layered structures that contain a (drug) core and a polymeric shell, whereas nanospheres represent homogeneous structures where the active is matrixed with the polymeric material. These two types of PNs can be generated from preformed polymers or customized polymeric structures synthesized using specific monomers (Fig. 5.10). These PNs can be manufactured using several techniques. Many techniques for direct polymerization such as emulsification and interfacial polymerization have been employed. Researchers have also reported in situ polymerization within microspheres fabricated with biocompatible polymers [46].

There are multiple benefits of employing PNs in the formulation of oral dosage forms. By manipulating the size of the PNs, it may be possible to bypass physiological obstacles (gastric bypass, enzyme action, renal clearance, and others) [47]. Also, PNs can be employed via surface modification to target (actively or passively)-specific tumor sites. Long circulating PNs can also be loaded with drugs to prolong the exposure of the drug at the specific tumor sites [48].

In the past two decades, a number of PN drug products (oral) have been approved by the FDA (Tables 5.3–5.5). Both glatiramer acetate and sevelamer hydrochloride/carbonate are examples of synthetic polymers.

3.3 Nanomicelles

Micelle formation occurs with amphiphilic molecules. Amphiphilic molecules contain both hydrophilic and hydrophobic (nonpolar) groups. Hence, when exposed to any solvent, they exhibit the unique property of self-assembly. Typically, there are three types of nanomicelles based on the disposition of the functional groups and their alignment relative to each other (Fig. 5.11). Normal micelles manufactured in aqueous media will self-assemble in such a way that the hydrophobic groups will be grouped inward with their hydrophilic ends pointing outward toward the aqueous media. Reverse micelles are formed in nonaqueous or organic media wherein the functional groups self-assemble such that the hydrophilic groups are directed inward and the hydrophobic groups are stabilized outward. Unimolecular micelles are classified by a core and shell covalently bonded together. Some of the commonly used amphiphilic molecules for preparing nanomicelles are lipids, polymers, oligopeptides, and polysaccharides. Critical micellar concentration (CMC) is an important quality attribute of polymers that determines the viability of use of a particular polymer to being formulated with a drug either as a normal or reverse micelle. Since low CMC polymers portend a longer circulation time within the systemic circulation and hence

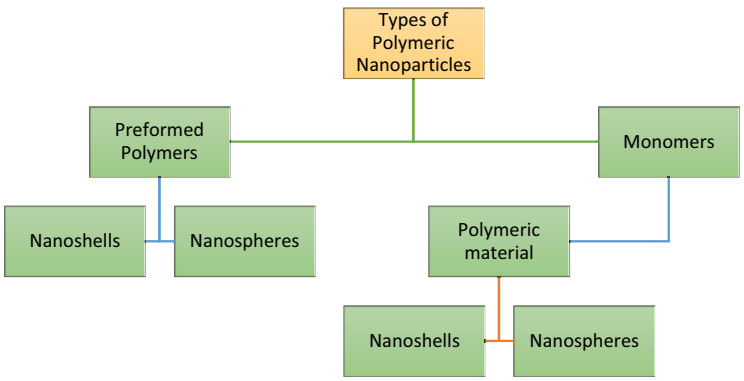

FIGURE 5.10 Classification of polymeric nanoparticles.

TABLE 5.3 List of Food and Drug Administration (FDA)-approved drugs commercialized using NanoCrystal technology [13].

Active ingredient	Brand name	Manufacturer	FDA approval year
Tizanidine hydrochloride	Zanaflex	Covis Pharmaceuticals Inc.	2002
Fenofibrate	Tricor	Abbvie Inc.	2004
Megestrol acetate	Megace	Endo Pharmaceuticals Inc.	2005
Fenofibrate	Triglide	SkyePharma AG	2005
Aprepitant	Emend	Merck and Co. Inc.	2006
Paliperidone	Invega	Janssen Pharmaceuticals Inc.	2008
Sirolimus	Rapamune	PF Prism CV	2010
Aripiprazole lauroxil	Aristada	Alkermes Inc.	2015

TABLE 5.4 Application of solid lipid nanoparticles (SLNs) to improve the bioavailability of multiple active pharmaceutical ingredients (APIs).

API	Application	Type	Manufacturing methodology	References
Fenofibrate	Enhancement of oral bioavailability	SLN	High-pressure homogenization	[33]
Carvedilol	Improvement of oral bioavailability and bypassing hepatic first-pass metabolism	SLN	Microemulsion	[33]
Clozapine	Enhancement of oral bioavailability	SLN	Hot homogenization followed by ultrasonication	[34]
Simvastatin	Improvement of oral bioavailability	SLN	Emulsification solvent evaporation	[35]
Paclitaxel	Improvement of absorption in plasma and lymph node	SLN	Hot sonication method	[36]

TABLE 5.5 Examples of polymer nanoparticle drugs formulated into oral solid dosage forms [13].

Brand name	Generic name	Dosage form	Indication	Year approved
Copaxone	Glatiramer acetate	Oral solution	Multiple sclerosis	February 2002
Renevela	Sevelamer carbonate	Tablet	Control of serum phosphorus in adults and children	October 2007
Renagel	Sevelamer hydrochloride	Tablet		July 2000

prolong action of the drug contained within the micellar microstructure; generally, polymers with low CMC lend themselves favorably to sustained action drugs [49].

Lynn David et al. reported the development of a pH-sensitive biodegradable polymer (poly(β-amino ester)) for aiding in diagnostics and therapy for cancer [50]. Similarly, Feng et al. also demonstrated development of pH-modulated nanomicellar carriers for paclitaxel and superparamagnetic iron oxide for potential cancer therapy [51].

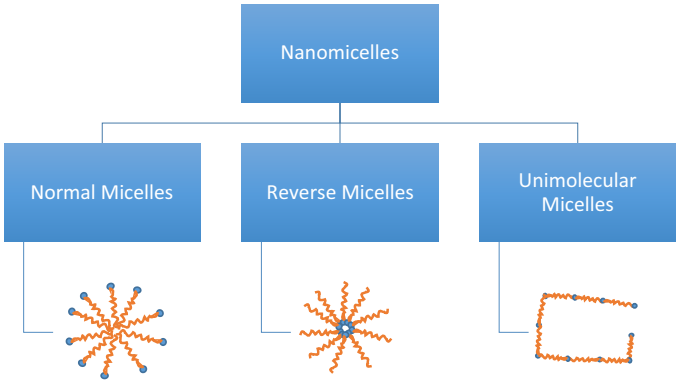

FIGURE 5.11 Types of nanomicelles.

Although many therapies are under development, commercial drug products using the nanomicelle technology are limited to only a handful, including CEQUA for ocular delivery targeted for dry eye treatment (approved by the FDA in 2018) and XELPROS for ophthalmic suspension delivery for the treatment of open-angle glaucoma or ocular hypertension (approved by the FDA in 2018).

3.4 Nanosuspensions

Another variant of liposomal nanostructures or PNs are nanosuspensions. Nanosuspensions are colloidal dispersions of drug micro/nanoparticles stabilized using surfactants. One of the distinctive advantages that nanosuspensions is a drastic improvement in the saturation solubility of a drug. This assists with drugs having poor aqueous solubility in enabling the formulation of these drugs into an oral dosage form with improved solubility and potentially improved bioavailability as well. The manufacturing processes for nanosuspensions have evolved through two paradigms: ascendant and descendant. The "ascendant" paradigm refers to an "assembly" method or integration approach (precipitation, microemulsion, melt emulsification) leading to the formation of nanosuspensions. The "descendant" paradigm refers to a "disintegration" approach (milling, HPH) to forming nanosuspensions [52]. Examples of nanosuspensions formulated into oral dosage forms approved by the FDA are indicated in Table 5.6.

TABLE 5.6 Examples of nanosuspensions formulated into oral dosage forms approved by the FDA [13].

Brand name	Generic name	Dosage form	Indication	Year approved
Emend	Aprepitant	Oral suspension	Antiemetic	2015
Tricor	Fenofibrate	Oral tablet	Hypercholesterolemia	2004
Megace ES	Megestrol	Oral suspension	Antianorexic	2005
Zanaflex	Tizanidine hydrochloride	Oral capsule	Treatment of muscle spasms	1996

TABLE 5.7 Ongoing clinical trials for oral nanoformulations [53].

Study drug	Study phase	Indication	Sponsor	Study start date
Silver biomaterial	Phase I/II	Bactericidal	University of Utah	December 2010
BPM31510—oral nanosuspensions	Phase I	Cholesterol treatment	Berg LLC	January 2017
Cannabidiol nanolipospheres	Early phase I	Pain treatment	Haddasah Medical Organization	April 2019
MK-1439 (nanoformulation)	Phase I	Treatment of HIV-1	Merck Sharp and Dohme	September 2015
Encochleated amphotericin B (CAMB/MAT2203) Lipid crystal nanoparticle formulation of amphotericin B	Phase IIa	Treatment of mucocutaneous candidiasis infections in patients who are refractory or intolerant to standard nonintravenous therapies	Matinas BioPharma Nanotechnologies, Inc.	September 2016
AZD4635 50 mg nanosuspension	Early (basic science) stage	Not disclosed (assessment of food effect, pH effect, and bioavailability)	Astrazeneca	November 2018
Nanoluteolin (natural extract)	Early phase I	Assessment of apoptotic activity on tongue squamous cell carcinoma cell line	Cairo University	November 2017

There are more than 50 nanoformulations that are currently at the investigational stage and undergoing clinical trials. Most of the information is not available publicly because of proprietary reasons. Ongoing/completed early-phase clinical trial information for some of the early-stage development oral nanoformulations is summarized in Table 5.7.

4. Challenges

Although nanotechnology has persisted in its implementation and promise for different applications in various fields, its manifestation for developing commercial pharmaceutical drug products has been, to a large extent, limited because of the significant challenges faced while proving the safety aspect of the "nano" medicines (Fig. 5.12). The FDA formed a Nanotechnology Task Force (NTF) in August 2006. The main responsibility of this group within the FDA is to provide sound guidance and pathways for industry to aid in developing and commercializing innovative, safe, and effective medications based on the use of nanotechnology. Since its inception, the NTF has aided in rolling out guidance enabling the commercialization of "nano" medicines for the treatment of different types of cancer, multiple sclerosis, arthritis, and many others. That being said, the FDA continues to face numerous challenges as breakthrough advancements in nanomedicine are being made.

The first challenge is the evaluation of sufficiency of the current regulatory framework as

FIGURE 5.12 Challenges faced for commercializing nanomedicines.

it stands with respect to the dedicated resources within the FDA to evaluate these advanced therapies and also updating/introducing new guidance to align with the risk mitigation strategies associated with the newer nanotechnologies. Since material behavior at the nanoscale differs significantly from the macroscale, digging deeper into the definitions of these materials and their characteristics from both a chemical and physical viewpoint needs to be evaluated—or rather reevaluated. Current guidance and procedures may apply to existing products, but the increasing advancements in nanotechnology and the complexities it brings forth warrant continuous evaluation and updating of the regulatory processes to leverage risk with opportunity [54].

Another challenge relates to the new risks posed by the unique nanoscale properties and whether these would stand to impact the adequacy of traditional safety and efficacy requirements. Pertinent risks persist in relation to novel nanomaterials concerning existing safety and clinical protocols and their appropriateness, and also if the abbreviated review (for generic medications to novel nanomedicines) fits within the current Abbreviated New Drug Application paradigm. Approval of a generic medicine in the pharmaceutical market is primarily contingent upon establishing therapeutic equivalence, which is a combination of pharmaceutical equivalence and bioequivalence with respect to the reference product. However, for nanomedicines, because of the behavioral differences between macroscale and nanoscale materials, this standard may or may not be applicable to ensure equivalency with

respect to the reference product, and hence may need to be reviewed [55].

Next, the challenge of designing robust processes for manufacturing nanoscale materials and incorporating them in finished oral dosage forms also presents challenges. Understanding the nanoscale material behavior throughout the manufacturing processes and instituting in-process controls to monitor and control the quality of the nanoscale product reproducibly is paramount to developing a robust control strategy for the manufacturing processes [56].

Yet another challenge has to do with patient awareness of the nanomedicine products. The FDA is working to enable and enhance patient engagement by reaching out to the industry and obtaining critical input for labeling requirements for nanomedicines [54].

5. Conclusions

Nanoparticles for pharmaceutical applications are truly on the rise. Commercial applications of multiple classes of nanoparticles for oral delivery have been commercialized for the treatment of various onerous ailments, including cancer, HIV, multiple sclerosis, and other central nervous system disorders. New and innovative technologies are being developed to make these nanoparticulate treatments more specific, potent, and yet safe and effective. This review has discussed various formulation perspectives that focus on the development of various different types of nanoparticulate oral treatments such as SLNs, polymeric NPs, nanosuspensions, and nanomicelles. Various novel manufacturing methodologies for the fabrication of these different nanoparticulates were also discussed. Depending on the intended benefit, whether it is improvement in bioavailability, specific targeting, physiological stability, or sustained action, the specific nanoparticulate genre can be chosen along with the complementing manufacturing methodology. In spite of the tremendous innovation in the field of nanotechnology in medicine, challenges abound. Innovation and collaborative efforts between industry and regulatory agencies pave the way for breakthrough treatments using nanotechnology. This is clearly evident from the increasing number of approvals for nanomedicines and also the continuous outreach by the FDA through the numerous comprehensive guidelines detailing the development pathway and the regulatory approval pathways for these groundbreaking treatments. As we make our way into the future, we tread with confidence armed with the knowledge of a new realm (at the nanoscale) and a deeper understanding of the various capabilities of nanotechnology. We are poised favorably to bring revolutionary treatments to ominous diseases that have plagued humankind for a long time and to make this world a truly better place.

Abbreviations

API	active pharmaceutical ingredient
BCS	Biopharmaceutical Classification System
CMC	critical micellar concentration
DPN	dip-pen nanolithography
FDA	Food and Drug Administration
HME	hot melt extrusion
HPH	high-pressure homogenization
NTF	Nanotechnology Task Force
OSD	oral solid dosage
PLGA	poly(DL-lactide-*co*-glycolide)
PN	polymeric nanoparticles
SLN	solid lipid nanoparticles
W/O	water-in-oil

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