



# Nanonization strategies for poorly water-soluble drugs

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Poor water solubility for many drugs and drug candidates remains a major obstacle to their development and clinical application. Conventional formulations to improve solubility suffer from low bioavailability and poor pharmacokinetics, with some carriers rendering systemic toxicities (e.g. Cremophor<sup>®</sup> EL). In this review, several major nanonization techniques that seek to overcome these limitations for drug solubilization are presented. Strategies including drug nanocrystals, nanoemulsions and polymeric micelles are reviewed. Finally, perspectives on existing challenges and future opportunities are highlighted.

## Introduction

One of the major obstacles to the development of highly potent pharmaceuticals is the poor water solubility of many drugs. Approximately 40% of potential new drugs identified by pharmaceutical companies are poorly soluble in water, which greatly hinders their clinical translations [1]. Low water solubility limits the bioavailability and absorption of these agents [2]. Several strategies and formulations have been employed to overcome these limitations. Although existing strategies such as complexing drugs with cyclodextrins [3], conjugation to dendrimers [4], salt formation of ionizable drugs [5] and the use of co-solvents [6,7] have been shown to improve drug solubility, universal solubilization methods that can improve the drugs' bioavailability significantly are still highly desirable.

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. These strategies include increasing the surface area to volume ratios of drug powders, changing the crystalline forms and designing novel nanomaterials that can act as carriers for controlled release [8,9]. Nanonization

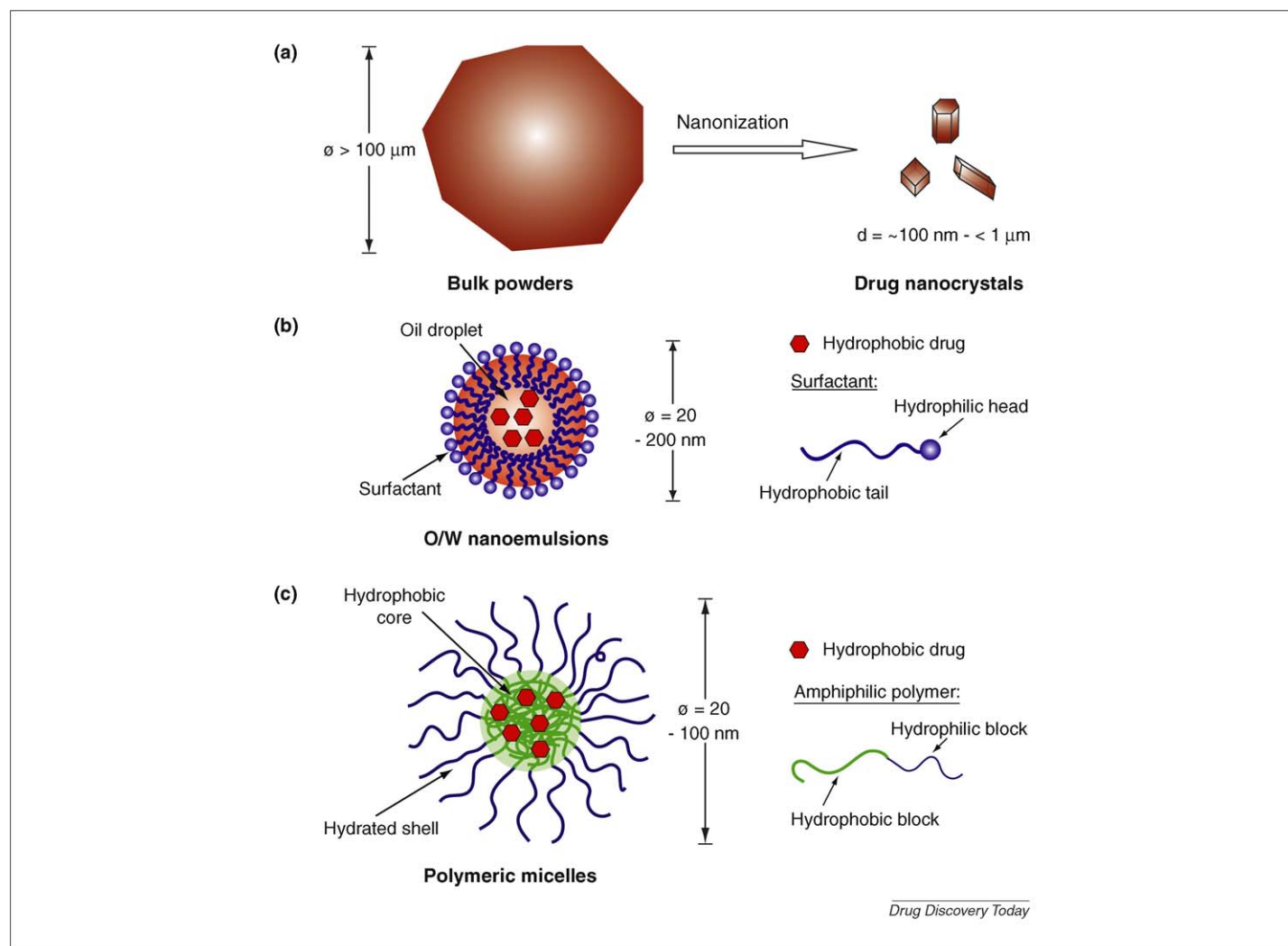
can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects [10].

Nanonization of hydrophobic drugs generally involves the production of drug nanocrystals through either chemical precipitation or disintegration [8]. Alternatively, nanotechnology-based drug delivery systems such as nanoemulsions and polymeric micelles can be used [9] (Fig. 1). During the past decade, several drug nanoformulations have been clinically approved or are under clinical investigation (Table 1) [8,9]. Major research efforts have been focused on the development of enabling nanoformulation technologies, new pharmaceutical materials and quality control to improve product properties while reducing production costs. New technological advances and unmet clinical needs provide the key driving force for the research and development of nanonization strategies.

## Drug nanocrystals

Drug nanocrystals are nanoscopic crystals of the parent compound with dimensions less than 1  $\mu\text{m}$ . According to the Noyes–Whitney equation [11], a decrease in particle size will lead to an increase in effective surface area in the diffusion layer, which, in turn, increases the drug dissolution rate. Drug nanocrystals are one of the most important strategies to enhance the oral bioavailability of

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**FIGURE 1**

Schematic of different nanonization strategies to increase drug solubility and bioavailability.

hydrophobic drugs. Several preparation methods for drug nanocrystals have been investigated. Here, we review several key methods, including nanoprecipitation, high-pressure homogenization and media milling.

### Nanoprecipitation

The nanoprecipitation method involves the formation of crystalline or semicrystalline drug nanoparticles by nucleation and the growth of drug crystals. In a typical procedure, drug molecules are first dissolved in an appropriate organic solvent such as acetone, tetrahydrofuran or *N*-methyl-2-pyrrolidone at a supersaturation concentration to allow for the nucleation of drug seeds. Drug nanocrystals are then formed by adding the organic mixture to an antisolvent in the presence of stabilizers such as hydroxypropyl methylcellulose, polyvinylpyrrolidone, Tween 80, Poloxamer 188 or lecithin [12]. The choice of solvents and stabilizers and the mixing process are key factors to control the size and stability of the drug nanocrystals. A combination of several stabilizers is often used for optimal effect. The primary role of stabilizers is to inhibit excessive crystal growth or particle aggregation [13]. The mixing (also called micromixing) step is crucial to produce a rapid and

uniform supersaturated solution, which facilitates the formation of uniform and small drug nanoparticles [14]. Other crucial factors include the drug concentration, volume ratio of antisolvent to solvent, temperature and viscosity.

Nanocrystals of several drugs prepared using nanoprecipitation are in preclinical development. Recent progress in the nanoprecipitation technique has centered on efforts to improve the production efficiency of high-quality drug nanoparticles. For example, an antisolvent precipitation under high gravity was developed to mass produce nanoparticles from hydrophobic drugs such as danazol and cefuroxime axetil [15]. Drug nanoparticles have also been prepared by mixing an organic stream of drug and stabilizers with a continuously circulating aqueous phase under ultrasonication [16], directly spraying the solution into cryogenic substrate (e.g. liquid nitrogen) [17] or using controlled crystallization of drugs during a freeze-drying process [18]. The use of nonorganic solvent precipitation has also been investigated [13]. In this method, a basic solution can be used to precipitate drug molecules dissolved in an acidic solution to form drug nanoparticles. This approach is effective when the drug of interest has pH-dependent solubility, such as itraconazole [13].

TABLE 1

**Representative nanoformulations of water-insoluble drugs that are approved for clinical use or under clinical trials.**

<i>Nanonization strategy</i>	Trade name	Drug	Inactive ingredients	Indication	Dosage form	Developer, status
<b>High-pressure homogenization</b>	Triglide <sup>®</sup>	Fenofibrate	Carboxymethylcellulose sodium, croscarmellose sodium, lecithin, sodium lauryl sulfate	Hypercholesterolemia	Oral tablet	SkyePharma/Sciele, approved in 2005
<b>Media milling</b>	Rapamune <sup>®</sup>	Sirolimus	Providone, poloxamer 188	Immunosuppression	Oral tablet	Elan/Wyeth, approved in 2000
	Emend <sup>®</sup>	Aprepitant	Hydroxypropyl cellulose, sodium lauryl sulfate	Antiemetics	Oral capsule	Elan/Merck, approved in 2003
	Tricor <sup>®</sup>	Fenofibrate	Hydroxypropyl methylcellulose, sodium lauryl sulfate, crospovidone	Hypercholesterolemia	Oral tablet	Elan/Abbott, approved in 2004
	Megace ES <sup>®</sup>	Megestrol	Hydroxypropyl methylcellulose, docusate sodium	Antianorexia, cachexia	Oral suspension	Elan/Par Pharmaceuticals, approved in 2005
	Invega <sup>®</sup> , Sustenna <sup>™</sup>	Paliperidone palmitate	Polysorbate 20, polyethylene glycol 4000	Schizophrenia	Intramuscular suspension	Elan/Johnson & Johnson, approved in 2009
<b>Nanoemulsion</b>	Estrasorb <sup>®</sup>	Estradiol	Soybean oil, polysorbate 80, ethanol	Vasomotor symptoms associated with menopause	Topical emulsion	Novavax/Graceway, approved in 2003
	Flexogan <sup>®</sup>	Camphor, menthol, methyl salicylate	Medium chain triglycerides, lecithin	Analgesics	Topical emulsion	AlphaRx, approved in 2001
	BF-200 ALA-gel	5-Amino levulinic acid	Miglyol, lecithin	Actinic keratosis for photodynamic therapy	Topical gel	Biofrontera, Phase III
	Restasis	Cyclosporine	Castor oil; polysorbate 80; carbomer 1342	Chronic dry eye disease	Ophthalmic emulsion	Allergan, approved in 2002
<b>Polymeric micelles</b>	NK911 <sup>®</sup>	Doxorubicin	Poly(ethylene glycol)-co-poly(L-aspartic acid)	Solid tumors	Lyophilized powders for suspension	Nippon Kayaku, Phase II
	NK105 <sup>®</sup>	Paclitaxel	Poly(ethylene glycol)-co-poly(L-aspartic acid)	Solid tumors	Lyophilized powders for suspension	NanoCarrier/Nippon Kayaku, Phase II
	Genexol-PM	Paclitaxel	Poly(ethylene glycol)-co-poly(D,L-lactic acid)	Solid tumors	Lyophilized powders for suspension	Samyang, Approved in South Korea in 2007, Phase II in the US

**High-pressure homogenization**

Production of drug nanoparticles via the top-down disintegration mechanism generally involves high-pressure homogenization (HPH) or media milling. HPH has been widely used in the pharmaceutical industry since the Dissocubes<sup>®</sup> piston-gap homogenizer (SkyePharma) was developed in the mid-1990s. Nowadays, HPH is used for preparing drug nanocrystals such as Triglide<sup>®</sup>, a clinically approved product for the treatment of hypercholesterolemia or hyperlipidemia. Other examples include Nanopure, Nanocrystal<sup>™</sup>, Nanomorph<sup>™</sup> and Nanoedge<sup>™</sup> (Table 1) [19]. As an advanced nanonization strategy, HPH offers an excellent choice for producing high-quality drug nanoparticles on an industrial scale.

Typically, HPH is carried out in either water or a nonaqueous media (e.g. PEG 400). The nonaqueous media is suitable for water-sensitive drugs. In a standard procedure, a suspension of crystalline drug and stabilizers is passed through the narrow gap of a homogenizer at high pressure (500–2000 bar). The pressure creates powerful disruptive forces such as cavitation, collision and shearing, which disintegrate coarse particles to nanoparticles [8]. Par-

ticle size depends on the number of cycles and the pressure and temperature of the homogenization process. Smaller nanocrystals can be obtained by increasing the homogenization pressure and the number of homogenization cycles [19]. The stabilizers also play an important part in decreasing particle size and avoiding aggregation of nanoparticles.

**Media milling**

Among the three methods reviewed, media milling has the longest track record for the production of drug nanocrystals. Commercial products from this method include Rapamune<sup>®</sup>, Emend<sup>®</sup>, Tricor<sup>®</sup>, Megace ES<sup>®</sup> and Invega<sup>®</sup> (Table 1). In this protocol, the milling chamber is charged with milling pearls, dispersion media (e.g. water), drug powders and stabilizers. The pearls are rotated at a very high speed to generate strong shear forces to disintegrate drug powders into nanoparticles [20]. Physical characteristics of the resulting nanocrystals depend on the number of milling pearls, the amount of drug and stabilizer, and milling time, speed and temperature. Recently, Takatsuka *et al.* [21] prepared drug nanocrystals by a wet milling procedure using a rotation/revolution mixer and

zirconia balls. The technique showed superior performance compared with the Beads mill, enabling drug nanocrystals to be produced in a quick process (approximately 5 min) using a small amount of zirconia balls. The potential shortcomings of media milling are difficulty in the removal of residual milling media from the final product and the loss of drug owing to adhesion to the inner surface of the milling chamber. Furthermore, the method is not suitable for drug powders with elasticity. Despite these limitations, the milling method is the most commonly used method in industry because of its low cost and capacity for rapid production.

#### *Dosage formulation after nanonization*

After nanonization, drug nanocrystals are frequently formulated in conventional dosage forms such as tablets, capsules, pellets and injectable suspensions. This step requires the removal of suspension solvent and incorporation of drug nanocrystals into the new dosage forms without compromising their physical, chemical and pharmaceutical properties [12]. Numerous techniques such as freeze drying, spray drying, centrifugation and ultrafiltration have been employed to dry or concentrate drug nanoparticles. Protectants such as mannitol, sucrose and trehalose are usually added to the nanoparticles to avoid agglomeration [12,22]. In the freeze-drying procedure, the nature and amount of protectants [23] and freezing rate [24] are important factors. For solid dosage forms, the addition of excipients such as fillers, binders, humectants, disintegrating agents and lubricants is crucial in retaining the properties of drug nanoparticles.

### **Nanoemulsions**

Nanoemulsions are a nonequilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid. Emulsions with nanoscopic droplet sizes (typically in the range of 20–200 nm) are often referred to as submicron emulsions. Nanoemulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules (Fig. 1). Although nanoemulsions have a tendency for phase separation, kinetically stable nanoemulsions can be achieved with sufficient shelf stability and no apparent flocculation or coalescence [25]. Advantages of nanoemulsions include increased drug loading and enhanced bioavailability. Commercial products that are nanoemulsions include Estrasorb<sup>®</sup> and Flexogan<sup>®</sup> (Table 1).

In a nanoemulsion, the oil droplets serve as the reservoir for hydrophobic drugs [26]. The most widely used oil molecules include saturated and unsaturated fatty acids, fatty acid esters and soybean oils. Surfactant molecules play a key part in stabilizing the nanoemulsions. Nonionic or amphoteric surfactants such as poloxamer, lecithin and Tween 80 are commonly used. Combinations of various surfactants have also been used to control droplet size and improve the stability of nanoemulsions.

The methods used for the production of nanoemulsions include HPH, microfluidization, ultrasonication and spontaneous emulsification [27]. In HPH, coarse emulsions form nanoemulsions owing to the disruptive forces created by high pressure. As with the formation of drug nanocrystals, the homogenization pressure and number of cycles are key parameters that affect droplet size and the size distribution of nanoemulsions [28]. Microfluidization uses a high-pressure pump to force the emulsions through many

microchannels in the central chamber of the microfluidizer. This technique generally results in the formation of nanoemulsions with narrow size distributions [29,30]. Ultrasonication utilizes ultrasound energy to disrupt macroscopic droplets, enabling them to reform in nanoscopic dimensions. Although the procedure is simple, it results in a less than optimal heterogeneous distribution of nanodroplet sizes. In addition, the high-energy output by ultrasound can cause structural damage to the ingredients. Spontaneous emulsification is a low-energy method, which can emulsify the oil phase using the interfacial instability originating from rapid diffusion of a solvent across the oil–water interface [31].

Lipid nanoemulsions of hydrophobic drugs have been shown to improve the oral bioavailability of drugs by increasing drug absorption rates through the gastrointestinal tract [32]. Nanoemulsions have also been used for the parental, ocular and transdermal delivery of drugs. Lipophilic antineoplastic agents such as dacarbazine, paclitaxel, curcumin and tamoxifen are encapsulated in nanoemulsions to increase cytotoxicity and to overcome multi-drug resistance [30,33–35]. In addition, nanoemulsions can also be used for the intravenous delivery of lipophilic drugs that cause venous irritation by encapsulating the drugs in the oil phase to prevent the exposure of the drug to the vessel endothelium [36]. Nanoemulsions have also been used in the transdermal delivery of lipophilic drugs because of their high drug-loading capacity, enhanced skin permeability and host tolerance [26]. The skin permeation rates of many drugs such as genistein, celecoxib, methyl salicylate and menthol are increased significantly in nanoemulsions secondary to lipid interactions with the stratum corneum of skin, high drug concentration gradients and the small diameters of nanodroplets [28,37–39]. In addition, nanoemulsions have recently been reported to improve the sublingual and intranasal delivery of drugs because of their mucoadhesive properties and ability to enhance the permeability of the mucous layer [40].

### **Polymeric micelles**

#### *Structural compositions*

Polymeric micelles have received considerable attention in the past two decades as a new multifunctional nanoplatform for the delivery of hydrophobic drugs. Polymeric micelles are nanosized (typically in the range of 20–100 nm) supramolecular constructs (Fig. 1) formed from the self-assembly of amphiphilic block copolymers in aqueous environments [41]. In water, the hydrophobic segment of the block copolymer self-associates into a semisolid core, with the hydrophilic segment of the copolymer forming a coronal layer. The resulting core–shell architecture is important for drug delivery purposes; the hydrophobic core serves as a reservoir for water-insoluble drugs, and the outer shell protects the micelle from rapid clearance in circulation [42].

Poly(ethylene glycol) (PEG) is most commonly used for the hydrophilic segment. PEG molecules are biologically inert. Moreover, they are shown to prevent nonspecific protein adsorption to the micelle surface prolonging the blood circulation time of the micelles. Other polymers, such as poly(*N*-vinyl pyrrolidone) and poly(*N*-isopropyl acrylamide), are also used as hydrophilic blocks but with much less frequency [43]. Compared with the hydrophilic blocks, the chemistry of core-forming hydrophobic polymers is much more diverse. Polyesters and poly(*L*-amino acids) are the most widely used polymers because of their biocompatibility

and biodegradability. Examples include, but are not limited to, poly(lactic acid) (both L-isomer, or PLA and D,L-isomer, or PDLLA); poly( $\epsilon$ -caprolactone); poly(L-aspartic acid) (pAsp); and poly(L-glutamic acid) [44]. Recently, a new hydrotropic polymer design was reported to form polymeric micelles with high drug loading and excellent physical stability [45]. This process involves the screening of hundreds of pharmaceutically safe molecules to identify candidate structures that enable heightened solubility for a chosen drug; then, the structural motif is incorporated as the hydrophobic segment to enhance its interactions with the drug. Using this approach, Park and co-workers have developed hydrotropic copolymers consisting of PEG and poly(4-(2-vinylbenzyloxy-N-picolyl-nicotinamide)) that provide efficient encapsulation of paclitaxel with high loading [45]. This method might provide a universal strategy to produce tailor-made polymeric micelles that can achieve high drug loading and stable encapsulation of a wide variety of drugs.

#### *Micelle preparation*

Several methods, including dialysis, solvent evaporation and film sonication, have been established to produce drug-loaded micelles [46]. In the dialysis method, an organic solution of the copolymer and drug mixture is placed in a dialysis device submerged in water or an aqueous buffer. The micelles are formed by the slow replacement of the organic medium with water through dialysis. In solvent evaporation, a mixture of the copolymer and drug in an organic solvent (e.g. ethyl acetate) or a combination of solvents is added into water under vigorous mixing [47]. The organic solvent is allowed to evaporate slowly (4–24 hours) to form the micelles. In the film sonication method, drug and copolymer mixtures are dissolved in an organic solvent and allowed to dry and form a blended film. The film is then hydrated in water and sonicated using an ultrasonic mixer to produce polymeric micelles. The choice of organic solvent(s) in all three methods is crucial for forming stable, uniformly sized micelles with high drug-loading content. Currently, approved micelles for clinical use include doxorubicin-loaded PEG–pAsp micelles (NK911<sup>®</sup>) produced using the dialysis method [48] and paclitaxel-loaded PEG–PDLLA micelles (Genexol-PM) produced by the film sonication method [49].

#### *Pharmaceutical properties*

Polymeric micelles offer many pharmaceutical advantages for the delivery of hydrophobic drugs, such as high stability with improved hemocompatibility and drug pharmacokinetics. As a result, polymeric micelles are often used to deliver anticancer drugs with narrow therapeutic indices given via intravenous administration. They have been shown to improve the biological efficacy of antineoplastic agents while reducing systemic toxicity over conventional formulations. Kataoka and co-workers prepared doxorubicin micelles from a PEG–pAsp block copolymer, resulting in significantly improved preclinical antitumor efficacy [48]. The micelle formulation, currently in clinical trials under the name NK911<sup>®</sup>, nearly tripled the blood half-life of the free drug (from 48 min to 2.3–2.8 hours) [50]. Paclitaxel is another commonly used anticancer drug with very low water solubility (1.5  $\mu\text{g}/\text{cc}$ ). Currently, the clinically approved carrier to solubilize the drug is Cremophor<sup>®</sup> EL (Taxol<sup>®</sup>), a polyethylene-glycol-modified castor

oil. Although useful in drug solubilization, the delivery agent itself has negative side-effects and can lead to hypersensitivity reactions (HSRs) and neuropathy. In comparison, Genexol-PM (i.e. paclitaxel in PEG–PDLLA micelles) showed no HSRs and a lower degree of myelosuppression. Consequently, Genexol-PM enables a considerable increase in maximum tolerated dose, to 390  $\text{mg}/\text{m}^2$  compared with 230  $\text{mg}/\text{m}^2$  for Cremophor<sup>®</sup> EL [51]. This formulation was approved first in South Korea in 2007 and subsequently in several other Asian countries for cancer treatment.

In addition to the previously mentioned advantages, polymeric micelles allow a multifunctional design to achieve integrated diagnostic and therapeutic ('theranostic') functions and molecular targeting capabilities. For example, superparamagnetic iron oxide nanoparticles have been co-loaded with drugs inside polymeric micelles, and magnetic resonance imaging is able to visualize the tumor-targeting specificity of micelles encoded with a cancer-targeting peptide [52–54]. Multifunctional nanomedicine holds considerable promise for the molecular diagnosis of disease phenotypes, customized therapy to exploit unique pathological targets, and the simultaneous treatment and monitoring of therapeutic efficacy. This modular design with 'theranostic' functions might prove essential in achieving personalized medicine for many challenging diseases such as cancer [55].

#### **Comparison of different nanoformulation strategies**

Table 2 summarizes the advantages and disadvantages of three nanoformulations. Each strategy has its own strengths and weaknesses that need to be carefully considered. Currently, the formation of drug nanocrystals is the most established technique among the three strategies discussed in this review, with multiple clinically approved products. Large-scale production of drug nanocrystals is feasible with excellent reproducibility. This technique can formulate drugs with a wide range of solubility profiles, including drugs that are not soluble in either water or oils. The precipitation methods can also formulate drugs into amorphous or semicrystalline nanoparticles, whereas homogenization and media milling methods work better with drugs that have a high degree of crystallinity. Drug nanocrystals also have fast dissolution rates, which make them an excellent choice for oral delivery. However, this strategy sometimes requires high-energy input, resulting in high production costs. Moreover, formulated nanocrystals often require surface stabilization. Owing to the fast dissolution kinetics and a lack of controlled release mechanism, nanocrystal formulations are not suitable for cytotoxic drugs with small therapeutic indices such as anticancer agents.

Nanoemulsions offer some crucial benefits over other nanonization techniques. High drug-loading content can be achieved easily using many clinically approved pharmaceutical ingredients (e.g. small molecular surfactants, lipids and oils). The production process is also inexpensive. Nanoemulsions are used for topical administration with several clinically approved products. Other routes of administration for drugs with large therapeutic indices are also used clinically. Drug nanoemulsions often suffer from poor stability, with the possibility of flocculation and coalescences upon storage. The lack of a controlled release mechanism is also a limitation for this nanoformulation technique to deliver cytotoxic agents.

Polymeric micelles have been explored extensively in the past decade because they can achieve improved blood stability and



TABLE 2

**Comparison of the advantages and disadvantages of different nanoformulations.**

<b>Nanoformulations</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Nanocrystals</b>	Established manufacturing techniques Good reproducibility with large-scale production Good compatibility with drugs having different solubility profiles Fast dissolution rates Excellent for oral formulations	High-energy input Require stabilizers Not suitable for cytotoxic drugs with small therapeutic indices Lack of controlled release Not ideal for intravenous administration
<b>Nanoemulsions</b>	High drug-loading content Suitable for various administration routes Approved pharmaceutical ingredients Low-cost productions	Potential flocculation and coalescence Lack of controlled release Poor blood stability
<b>Polymeric micelles</b>	Excellent blood stability Passive and active targeting to tumors Controlled release functions Multifunctional design Suitable for intravenous administration	Limited number of polymers for clinical use Concerns over nanotoxicity Concerns over storage stability

have excellent controlled release properties. The higher hemostability of micelles allows prolonged circulation, enabling passive and active targeting to tumors for cancer treatment. In addition, a multifunctional design for polymeric micelles can also be achieved by incorporating imaging agents and therapeutic agents in the same micelle. Polymeric micelles are also suitable for intravenous administration to deliver a variety of cytotoxic drugs, a potential advantage over nanocrystals and nanoemulsions in cancer chemotherapy. The disadvantages of micelles include concerns over the safety of polymer carriers; only a few polymers, such as PLA, are clinically approved.

### Challenges

Although multiple nanonization products have been clinically approved in the past decade, major challenges inhibit their widespread adoption. Scientifically, comprehensive structure–function relationships between the nanoparticle structure and pharmacological properties still need to be fully established. The size, shape, composition and surface properties of nanocarriers need to be precisely controlled and their effects on drug pharmacokinetics and pharmacodynamics need to be clearly elucidated. The US Food and Drug Administration (FDA) has recognized the importance and promise of nanomedicine and begun to create and implement necessary regulatory policy. The characterization of product quality and pharmacological evaluation of absorption, distribution, metabolism and excretion (ADME) are emerging as the new focus for assessing the safety and efficiency of various nanoformulations [56]. Other technological challenges remain, such as a lack of valid methods for nanoparticle characterization and reference standards for assessing the quality and safety of nanoproducts. During the production process, real-time monitoring of intermediate nanoparticles and assurance tests of final products are necessary. Parameters that are innate to nanoparticles – such as particle size, size distribution, morphology, surface chemistry, crystallinity

and aggregation state – need to be controlled precisely because they will affect ADME and toxicity of nanoformulations. Undoubtedly, many existing guidelines for preclinical studies including drug pharmacokinetics, genetic toxicity and mutagenicity for free drugs will also be applicable to nanoparticles [56]. The FDA has recently approved Emend<sup>®</sup> as a new antiemetic treatment based on the complete studies of safety and toxicity that are unique to nanoparticles. Accurate assessment of the risk and benefit of nanomedicine will be essential to realize the clinical potential of this novel paradigm of therapy.

### Concluding remarks

In summary, numerous studies have demonstrated the feasibility of nanonization strategy to improve solubility, dissolution kinetics and bioavailability of hydrophobic drugs. Multiple nanoformulations have recently been approved for clinical use, and several products are still in the pipelines of preclinical and clinical trials. The diverse nanonization strategies provide flexible options to develop tailor-made nanotherapeutics for different drugs and administration routes. These techniques can also be used to revive the clinical efficacy of toxic drugs or facilitate the clinical translation of drug candidates that are deemed failures simply because of lack of solubility. With rapid scientific and technological advancements, nanonization of hydrophobic drugs can potentially be vital for clinical applications of highly potent drugs.

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