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Review Article

Nanosuspension Technologies for Delivery of Poorly Soluble Drugs

Roya Yadollahi,[1] Krasimir Vasilev,[1,2] and Spomenka Simovic[3]

[1] *Mawson Institute, University of South Australia, Mawson Lakes, Adelaide, SA 5095, Australia*
[2] *School of Engineering, University of South Australia, Mawson Lakes, Adelaide, SA 5095, Australia*
[3] *Ian Wark Research Institute, University of South Australia, Mawson Lakes, Adelaide, SA 5095, Adelaide, Australia*

Correspondence should be addressed to Spomenka Simovic; spomenka.simovic@unisa.edu.au

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Poor aqueous solubility of some drug molecules is a major problem in drug formulation. Drug nanosuspensions emerged as one solution to delivering such hydrophobic drugs. Scaling down to nanoparticles enhances drug aqueous solubility and bioavailability by increasing drug surface area that comes into contact with biological media. Nanosuspensions that have attracted particular attention are those sterically stabilised by steric polymers such as polyethylene glycol (PEG) with a typical size range of 10–100 nm. These nanoparticles are capable of accumulating in targeted areas such as cancer tissues and infarct zones with minimal damage to healthy tissues. Nanosuspensions are often prepared by commercially available methods such as high pressure homogenization, media milling, emulsification, and melt emulsification. Solidification and surface modification methods are post-processing techniques used to add particular properties for advanced therapies. In this review, we firstly describe preparation methods for nanosuspensions. Secondly, we highlight typical characterization techniques. Finally, we describe several practical application of applications for drug delivery design and different administration routes such as parenteral, pulmonary, oral, and ocular.

1. Introduction

More than 40% of new chemical entities (NCE) are lipophilic compounds. Currently, poorly soluble drugs make up 1/3 of United States Pharmacopeia recognised drugs [1, 2]. Lipophilic compounds have poor aqueous solubility and imperfect dissolution profile which causes their low bioavailability. Bioavailability is percentage of the drug which reaches the systemic circulation [3]. Therefore, formulating new poorly water soluble molecules to obtain an adequate bioavailability has become a serious and challenging scientific, industrial, and medical issue. "Grease ball" and "brick dust" molecules are two types of poorly soluble drug compounds [4]. Grease ball molecules are highly lipophilic with high log P due to no interactions with water. Brick dust molecules have melting point above 200°C and low log P. Their poor solubility in water is caused by the strong intermolecular bonding and high lattice energy in solid state. Log P or partition coefficient is defined as logarithm of the ratio of concentration of a compound in a mixture of two immiscible solvents which are typically octanol and water. Log P determines the hydrophobic or lipophilic nature of molecules [5, 6].

Poorly water soluble molecules are typically formulated using various excipients with the aim of improving dissolution rate and storage stability. Excipients increase drug dissolution rate by increasing active drug surface area in contact with the dissolution medium [7]. Examples of excipients include

(i) cosolvents such as PEG-400 [8],

(ii) wetting agents such as sorbitan ester derivatives [9],

(iii) disintegrants such as croscarmellose sodium [10],

(iv) cyclodextrins such as β-cyclodextrins [11–16],

(v) micelles and lipid-based systems such as emulsions [17, 18], microemulsions, liposomes [19], solid lipid nanoparticles [20], and solid dispersions [21–23].

The use of excipients in formulations of poorly soluble drugs has been demonstrated to increase dissolution rate.

However, limitations such as toxicity of surfactants which are often used in high doses to keep drug in the dispersed state and limited drug loading have been identified [24]. Micronization is another approach used to increase drug solubility. Colloid mills or jet mills are examples of the micronization technique. The obtained particle size varies in the range from 0.1 μm to 25 μm and very small fraction of drug particles is below 1 μm [25]. Transferring micron size drug particles into nanoscale was the next development stage [26, 27]. Gassmann et al. produced drug nanoparticles using a precipitation method [28]. The limitation of this technique is the requirement for the drug to be soluble in at least one solvent and that solvent needs to be miscible with a nonsolvent [29]. To overcome these problems, in 1995, Müller et al. [30, 31] prepared nanosuspensions by a dispersion method. These workers have demonstrated that pure drug particles within the size range of 10 to 1000 nm became stable in the presence of surfactants and polymers. Since these pioneering reports, nanosuspensions have been defined as drug carriers with particle size range within 10–1000 nm [32]. It is now well established that nanosizing increases drug saturation solubility and dissolution rate [33]. Furthermore, nanosuspensions reduce drug administration doses, side effects, and cost of therapy [34]. Specific type of nanosuspensions is PEGylated nanoparticles in the size range 10–100 nm for passive targeting. PEGylated nanoparticles are colloidal structures with a cargo space for drugs, segregated from the environment by hydrophilic PEG corona that prevents recognition by macrophages and enables long-term circulation upon intravenous (i.v.) administration [35]. The size of the nanoparticles (10–100 nm) permits their extravasation and accumulation in tumour and infarct sites, known as enhanced permeability and retention (EPR) effect [36]. Passive targeting is based on pathophysiological characteristics unique to solid tumours: hypervascularity, irregular vascular architecture, potential for secretion of vascular permeability factors, and the lack of effective lymphatic drainage that prevents efficient clearance of macromolecules [37].

Nanosuspensions have been demonstrated to have a number of advantages compared to traditional forms of drug delivery. These advantages are summarised below:

(i) solving the problem of poor aqueous solubility and poor bioavailability of the drugs from biopharmaceutical classification systems (BCS) II and IV. BCS allocates drugs to one of 4 classes: high solubility, high permeability (class I); low solubility, high permeability (class II); high solubility, low permeability (class III); low solubility, low permeability (class IV) [38]. Table 1 shows examples of drugs which belong to the different biopharmaceutical classes [39, 40]. For example, nanosizing of azithromycin has proven to increase considerably its dissolution rate; that is, more than 65% was dissolved after 5 hours compared to just 20% that was dissolved from microsized system [34];

(ii) increased drug bioavailability [41];

(iii) applicability to most drugs which are poorly soluble in both aqueous and organic media;

Table 1: Examples of drugs in different BCS classes.

BCS class	Drug examples
I	Propranolol, metoprolol, and theophylline
II	Piroxicam, naproxen, and cyclosporine
III	Ranitidine, cimetidine, and metformin
IV	Furosemide, hydrochlorothiazide

(iv) simple production methods [29];

(v) possibility to incorporate nanosuspensions in various dosage formats such as tablets, pellets, and capsules following standard manufacturing techniques. For example, ketoprofen nanosuspension has been successfully transformed into pellets [42];

(vi) lower fed/fasted variability [43].

2. Production Methods for Preparing Nanosuspension

2.1. Media Milling. The media milling technique was developed by Liversidge et al. [45, 46]. In this method high-shear media mills or pearl mills are used to produce nanosuspension. The media mill consists of a milling chamber, a milling shaft, and a recirculation chamber (Figure 1). The milling media or balls are framed in ceramic-sintered aluminium oxide or highly cross-linked polystyrene resin. The milling chamber is fed with an aqueous suspension of the drug, stabilizer, and the milling media or pearls rotate at a very high shear rate. This procedure can be carried out under controlled temperature. The friction and collisions among drug particles and pearls generate nanoparticles. Ease of scale-up and little batch-to-batch variation are the advantages of media milling. Disadvantage of this method is the erosion of pearls which leads to contamination of the final product and subsequently problems upon administration [47]. Table 2 shows examples of marketed nanosuspensions that have been produced by media milling technique [48, 49].

2.2. High Pressure Homogenization. High pressure homogenization is a commonly employed method for producing nanosuspensions of poorly soluble drugs [50–55]. This method involves forcing a suspension, which contains drug and stabilisers, through a valve with a small orifice under pressure.

High pressure homogenization is often classified into two groups:

(i) Dissocubes (homogenization in aqueous media),

(ii) Nanopure (homogenization in water-free media or water mixtures).

Dissocubes operates at high pressure of up to 1500 bar where a suspension passes through a small gap. This causes an increase in the dynamic pressure with simultaneous reduction in the static pressure which reduces the boiling point of water to room temperature. Consequently, at room temperature water starts boiling creating gas bubbles. When the

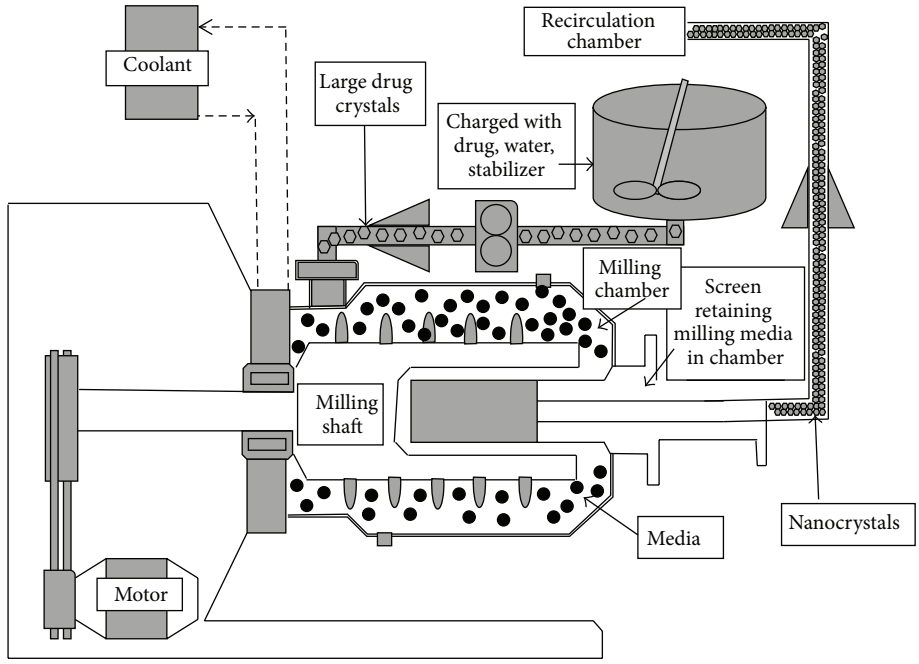

Figure 1: Schematic of media milling process. Adopted from [44].

Table 2: Examples of marketed nanosuspensions produced by media milling technique.

Trade name	Drug	Indication	Dosage form	Company	Status
Rapamune	Sirolimus	Immunosuppressive	Oral suspension/tablet 1-2 mg	Wyeth	Marketed in 2000
Tricor	Fenofibrate	Hypercholesterolemia	Oral tablet 48–145 mg	Abbott	Marketed in 2004
Emend	Aprepitant	Antiemetics	Oral capsule 80–125 mg	Merck	Marketed in 2003
Megace ES	Megestrol	Antianorexia, cachexia	Oral suspension 125 mg/mL	Par Pharmaceuticals	Marketed in 2005

suspension departs the gap and the pressure returns to atmospheric level, the gas bubbles implode. This phenomenon is called cavitation. The combined forces of cavitation, high shear, and collisions lead to fracture of the drug microparticles into nanosized particles [56]. Homogenization pressure, number of homogenization cycles, hardness of drugs, and temperature (when thermosensitive drugs are processed) are factors that influence the physical characteristics (such as particle size) of the resulting nanosuspensions. Metal contamination due to the erosion is less pronounced in this technique than in media milling. High pressure homogenization is considered as a safe technique for producing nanosuspensions. Less than 1 ppm metal contaminations were detected under processing condition of 20 cycles and pressure of 1500 bar [56–58]. The main drawback of this method is the need for pretreatment to obtain microparticles before starting the homogenization process and the many cycles of homogenization [59, 60].

For some purposes such as dispersing drug nanocrystals in low molecular weight PEG or in oil, liquid nanosuspensions are dispersed in nonaqueous media or media with reduced water content. Because of the high boiling point and low vapour pressure of oily fatty acids and oils, the drop in pressure is not sufficient for cavitation and thus the latter is not a determining factor in this process. To compensate for insufficient drop in pressure, the Nanopure process is conducted at low temperature which is often referred to as "deep-freeze" method. Conducting the process at 0°C or even below the freezing point produces results comparable to those achieved using dissocubes [61]. Table 3 shows examples of drugs processed by high pressure homogenization and corresponding references.

2.3. Microprecipitation-High Pressure Homogenization (Nanoedge Technology). Nanoedge Technology was developed by Müller et al. [75]. The technology consists of two processes:

Table 3: Some examples of drugs produced by high pressure homogenization technique.

Model drug	Literature reference
Albendazole	[53]
Amphotericin B	[62]
Omeprazole	[50]
Fenofibrate	[63]
Azithromycin	[34]
Budesonide	[64]
Buparvaquone	[55, 65, 66]
Clofazimine	[67]
Glucocorticoid drugs	[68]
Paclitaxel	[29]
Spironolactone	[54]
Oridonin	[69]
Melarsoprol	[70]
Tarazepide	[71]
Nimodipine	[72]
Amphotericin B	[73]
Itraconazole	[74]
Nifedipine	[52]

precipitation of drug particles and their fragmentation by using high pressure homogenization. Generally, this technique includes mixing of two different solutions. The drug is dissolved in an organic solvent which is miscible with water and forms the organic phase. The stabilisers are dissolved in the aqueous phase in which the drug is insoluble. Mixing these two solutions causes precipitation of drug particles. The last step of the process is high pressure homogenization [76]. Nanosuspension of itraconazole is an example of "Nanoedge Technology" [77].

2.4. Emulsion Diffusion Method. This method uses partially water-miscible and volatile organic solvent such as butyl lactate, benzyl alcohol, triacetin, and ethyl acetate as the dispersed phase [78, 79]. The emulsion is prepared by dispersing the drug loaded in a mixture of solvents or an organic solvent and forming emulsion with water by high pressure homogenisation or other techniques. Dilution leads to formation of nanosuspensions by diffusion of the internal phase into the external phase when droplets convert into solid particles. The size of the emulsion droplets determines the particle size. The use of organic solvents such as ethyl acetate, ethanol, methanol, and chloroform and the presence of residual solvents in the final products are major drawbacks of this technology due to potential environmental hazards and human safety issues [78]. Acyclovir nanosuspensions have been produced by emulsion diffusion method [80].

2.5. Melt Emulsification Method. Melt emulsification method has been used to prepare solid lipid nanoparticles [81, 82]. Kocbek et al. [78] are the first authors to use the melt emulsification technique to prepare 100 nm ibuprofen nanosuspensions with traditional excipients such as Tween 80 and polyvinylpyrrolidone. The first step in melt emulsification involves dispersing the drug in aqueous solution with stabiliser. Secondly, the nanosuspension is heated above the melting point of the drug and homogenised with a high-speed homogeniser to produce an emulsion. During this procedure the temperature must be controlled and maintained above the melting point of the drug. The final step of the melt emulsification method is cooling off the emulsion to a suitable temperature, either at room temperature or in an ice bath. Factors affecting particle size include drug and stabiliser concentrations, type of stabiliser, and cooling condition. Solvent-free prepared nanosuspensions are particularly important from toxicity point of view. Therefore, the advantage of this method over solvent diffusion method is avoidance of organic solvents. Ibuprofen nanosuspensions prepared by this technique have been reported to increase the dissolution rate to over 65% after 10 min compared to just 15% for micronized ibuprofen dissolved after the same period [78].

3. Nanosuspension Characterisation

3.1. Size. The most important characteristics of nanosuspensions are particle size and polydispersity index (PI: particle size distribution). Particles size of nanosuspensions critically determines the following characteristics of nanosuspensions [56]:

(i) drug saturation solubility,

(ii) physical stability,

(iii) dissolution rate,

(iv) bioavailability.

According to Noyes-Whitney equation (1), which is based on Fick's first law of diffusion, decreasing particle size causes an increase in particle surface area that in turn increases drug solubility in aqueous media contributing to an enhanced dissolution rate [83, 84]:

$$\frac{dM}{dt} = \frac{DA}{h}\left(C_{\text{Bulk}} - C_{\text{Eq}}\right), \tag{1}$$

where dM/dt is the rate of dissolution, D is the average diffusion coefficient, A is the surface area of the solid, C_{Bulk} is the concentration of drug in the bulk solution, C_{Eq} is the concentration of drug in the diffusion layer surrounding the drug, and h is the diffusion layer thickness.

Increased solubility with reduction of particles size is also demonstrated by Ostwald-Freundlich equation (2) [41, 85]:

$$C(r) = C(\infty)\exp\left(\frac{2\gamma M}{r\rho RT}\right), \tag{2}$$

where $C(r)$, $C(\infty)$ are the solubilities of a particle of radius r and infinite size, M is the molecular weight, ρ is the density of the particle, γ is the interfacial tension, r is the particle radius, R is the gas constant, and T is the temperature.

Figure 2 shows surface area as a function of particle size [86]. It has been experimentally demonstrated that particle size affects drug saturation solubility and dissolution rate. *In vivo* studies of Wang et al. [87] have demonstrated that

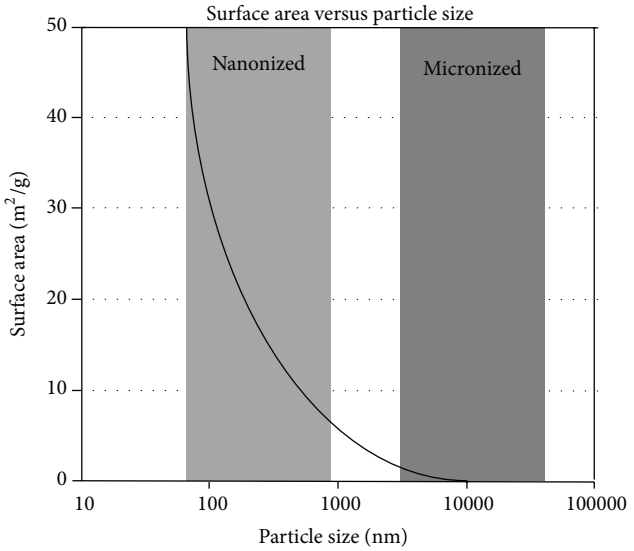

FIGURE 2: Surface area as a function of particles size. Adopted from [86].

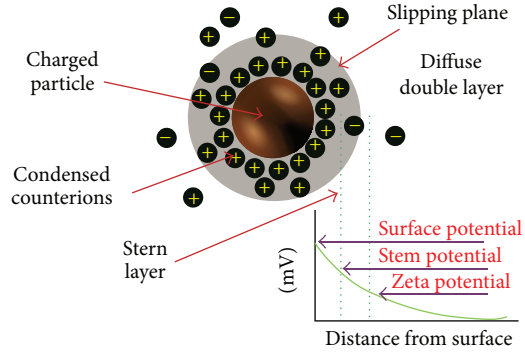

FIGURE 3: Schematic of the electric double layer formed around a charged particle.

particle size affects drug pharmacokinetic characteristics. In addition, from a perspective of practical application, drug particles have to be within specific size ranges. For example, capillaries typically have diameters of 5-6 μm [84] so the presence of large particles in parenteral formulations leads to embolism and capillary blockage. Photon Correlation Spectroscopy (PCS) (also known as Dynamic Light Scattering) is a technique often used to determine particle size and PI of drug nanosuspensions. PCS is capable of accurate measurements of particle sizes in range of 3 nm to 3 μm. However, this technique is not accurate when particles size is above 3 μm [56, 88]. In this technique, the Brownian motion (movement in random direction) of particles is measured as a function of time. Larger particles move with lower velocity than smaller particles. In addition, larger particles may settle out of the measurement zone. Hence, these factors limit capability for measuring particle sizes above 3 μm [89]. Laser Diffraction (LD) is typically used to measure particle size range of 0.05–80 μm up to 2000 μm. This technique can also be used to detect and quantify particle size ranges during the production procedure [56, 88]. Other techniques routinely used for measuring particle size are optical and electron microscopy. Scanning Electron Microscopy (SEM) [90, 91], Atomic Force Microscope (AFM) [90–92], and Transmission Electron Microscopy (TEM) [91–93] are also routinely used to characterize nanoparticles size and morphology. Furthermore, the Coulter Counter analysis can be used to determine the absolute number of particles per unit volume for different particle sizes [88]. Fluorescence Correlation Spectroscopy (FCS) [94, 95], Nanoparticle Tracking Analysis (NTA) [94, 96], and Flow Field Flow Fractionation (FIFFF) are other examples for size analyses of nanoparticles [94, 97]. Details are available in [98].

3.2. Crystalline State and Particle Morphology. The high energy amorphous form of drugs is thermodynamically unstable and changes to a crystalline form during storage. The amorphous form is preferred due to superior dissolution characteristics and consequently higher bioavailability of the drugs [99]. Transformation from amorphous to crystalline forms over storage is one of the issues that should be considered when formulating nanosuspensions. In order to investigate amorphous and crystalline fractions X-ray powder diffraction (XRPD) is used. XRPD is sometimes considered to be the most appropriate method for evaluating drug crystalline structure, since each crystal has a specific diffraction pattern [100]. However, it should be taken into consideration that there is a slight difference in the crystal structure of the same drug as observed by Tian et al. who studied the crystalline forms of carbamazepine [101]. Terahertz spectroscopy is a relatively new analytical method used to evaluate crystalline form of drugs where each crystalline polymorph form exhibits specific terahertz absorption spectrum [102–104]. Differential Scanning Calorimetry (DSC) is another commonly used technique for determining crystalline and amorphous fractions. It measures the temperatures and heat flows associated with the transition in drugs from crystalline to amorphous state as a function of time and temperature in a controlled atmosphere. DSC can also be used in conjunction with XRPD [105, 106].

3.3. Particle Charge (Zeta Potential). Particle charge plays an important role in ensuring stable nanosuspensions. The electric charge on a particle surface provides electrostatic repulsion between the drug nanoparticles and in this way prevents particles from aggregation and precipitation. The schematic in Figure 3 provides an illustration of the electric double layer around a charged particle. The double layer consists of a stern layer and a diffusion layer of opposite ions. The electric potential at the shear plane is known as the zeta potential [107]. It is considered that a minimum zeta potential of ±30 mV is required to ensure pure electrostatic stabilisation. When electrostatic stabilisation is combined with steric stabilisation (by using appropriate polymers), zeta potential of ±20 mV could be sufficient to prevent drug particles from aggregation and precipitation [64]. Steric stabilisation is defined as stabilisation caused by the adsorbed and hydrated polymer layers on the dispersed

particle [108]. Particles charge is typically determined by measuring electrophoretic mobility upon application of an electric field which is then converted to zeta potential by using the Helmholtz-Smoluchowski equation [109]. The zeta potential can also be measured by applying an ultrasound wave which induces the so-called electroacoustic phenomena [110].

3.4. Stability. Reduction in particle size results in increased surface energy due to the greater number of unstable surface atoms and molecules. This destabilises the colloidal suspension. Therefore, the use of stabilisers is often necessary to avoid particle agglomeration and reduce the possibility for Ostwald ripening [111]. Common stabilisers used to formulate nanosuspensions include polysorbates, povidones, poloxamer, lecithin, polyoleate, and cellulose polymers [111, 112]. Mixture of surfactants and polymers has been found to be beneficial for long-term stabilisation of nanosuspensions [78, 113, 114]. Polymeric materials and surfactants act as an ionic barrier and/or inhibitors of the close interaction between particles. Surfactants can increase the electrostatic repulsion and improve particle stability by altering the zeta potential [115]. Precipitation of particles is another phenomenon that should be taken into account when considering stability of nanosuspensions. According to Stoke's law (3), decreasing particle size, reducing the density difference of solid phase, and increasing the viscosity of the medium decrease the precipitation velocity [116]:

$$V = \frac{2r^2 (\rho_1 - \rho_2) g}{(9\eta)}, \tag{3}$$

where V is the precipitation velocity, r is the particle size, ρ_1 is the mass density of particles, ρ_2 is the mass density of fluid, g is the gravitational acceleration, and η is the viscosity of the medium.

The stability of nanosuspension system can also be increased by increasing the uniformity of particle sizes by using centrifugation or other techniques to remove larger particles [117].

4. Postproduction Processing

4.1. Solidification Techniques. Nanosuspensions are thermodynamically unstable. Solidification techniques transform nanosuspensions into solid dosage forms such as tablets, capsules, and pellets. Solid dosage forms increase the storage stability of nanosuspensions. It is also convenient from marketing perspective and is practically important for patient convenience. Pelletization, granulation, spray drying, and lyophilisation are the unit-operations of the solidification technique [118, 119]. Matrix formers (e.g., mannitol, cellulose derivatives) are usually added to the nanosuspensions before solidification to prevent destabilisation of particles due to creating additional thermal stresses such as heating during spray drying or freezing during lyophilisation. For example, microcrystalline cellulose was used by Bernard et al. as a matrix former during the freeze drying process of itraconazole nanosuspensions [120].

4.2. Surface Modification Techniques. Rapid or burst release of nanosuspensions may cause toxicity and severe side effects. Hence, surface modification is required in order to control drug release and/or prolonged residence at the site of action. For instance, nanosuspensions used for targeting the monocyte phagocytic system (MPS) in the treatment of lymphatic-mediated diseases [121] can cause toxicity due to accumulation of drug. Surface modification can be understood if we compare drug release from coated and uncoated surfaces. Tan et al. showed that by layer-by-layer nanogels coating of procaine hydrochloride decreases the burst release of drug [122]. Another example is comparison between buparvaquone nanosuspensions with and without mucoadhesive polymers. A significant reduction in the infective score of *Cryptosporidium parvum* after oral administration of buparvaquone nanosuspensions with mucoadhesive polymers was attributed to adhesion and prolonged residence of drug particles at the absorption sites in the gastrointestinal tract (GIT) [55, 123]. The surface engineering by surface coating is important for targeted drug delivery systems. PEG is commonly used to modify nanoparticle surface. This leads to reduced protein adsorption and opsonization of nanoparticles and leads to prolonged systematic circulation time [124]. Longer circulation time is required to allow nanoparticles sufficient time to leak out of vasculature in infective and inflammatory areas including cancer tissues [125, 126]. Carefully engineered nanoparticles surface can also effectively target the diseased tissue. For instance, Kreuter et al. have demonstrated that polyisobutyl cyanoacrylate nanoparticles stabilised by classic surfactants (Tween 20, 40, 60, and 80) can deliver peptide dalargin across blood-brain barrier [127].

5. Application of Nanosuspensions

Nanosuspensions are used as oral, parenteral, ocular, and pulmonary drug delivery systems.

5.1. Oral Administration. Oral administration is the first patient choice because of painless and noninvasive administration [128, 129]. In addition, oral formulations have several advantages for the pharmaceutical industry such as easy manufacturing, short production time, and reasonable production cost [128]. Oleanolic acid, which has many applications such as hepatoprotective, antitumour, antibacterial, anti-inflammatory, and antiulcer effects, has low aqueous solubility which results in erratic pharmacokinetics after oral administration. Applying oleanolic acid in the form of nanosuspension increases dissolution rate to about 90% in the first 20 min compared to just 15% for micronized drug powder [130]. Reduction of drug particle size to the nanoscale leads to an increased dissolution rate and can improve adhesion of the drug particles to the mucosa. Better contact with intestinal cells (bioadhesive phase) and a greater concentration gradient between blood and GIT increase drug intestinal absorption [130–132]. Nanosuspensions are also used to control infections. Atovaquone and buparvaquone for the treatment of leishmaniasis and opportunistic *Pneumocystis carinii* infections in HIV patients are effective in high doses due to low bioavailability. A comparative study of atovaquone

in the form of micronized particles and nanosuspensions showed that the latter decreased infectivity from 40% to 15% [29]. In another example, buparvaquone nanosuspensions reduced infection from 2.0 to 1.02 and micronized particles only to 1.47 [29].

5.2. Parenteral Administration. In emergency cases such as cardiac arrest and anaphylactic shock parenteral administration is the first choice [133]. Parenteral administration includes administration of dosage forms by subcutaneous, i.v., intramuscular, and intra-arterial methods [134]. Advantages of this type of administration include avoidance of first-pass metabolism, reliable doses, and higher bioavailability. Control over the dose and rate allows more predictable pharmacodynamic and pharmacokinetic profiles after i.v. administration compared to oral administration [135]. Administered drug particles are required to be smaller than 5 μm to prevent blockage of capillaries [32]. A study on mice investigated tumour growth inhibition rate and showed that oridonin in the form of nanosuspension decreased considerably the volume and weight of the tumour. Oridonin in the form of nanosuspension raised the rate of tumour inhibition to 60.23% compared to 42.49% for the conventional form [136]. Nanosuspensions improve therapeutic efficiency and reduce the cost of therapy through improved dosing efficiency and smaller injection volumes.

5.3. Pulmonary Drug Delivery. Pulmonary drug delivery aims at treating several respiratory conditions such as asthma and chronic obstructive pulmonary diseases [137, 138]. Advantages of pulmonary drug delivery over oral and parenteral drug administration include direct delivery to the site of action which leads to decreased dosage and side effects [139]. Conventional pulmonary delivery systems provide only rapid drug release, poor residence time, and lack of selectivity [140]. Nanosuspensions can solve problems of poor drug solubility in pulmonary secretions and lack of selectivity through direct delivery to target pulmonary cells. Adhesiveness of nanosuspensions to mucosal surfaces leads to improved selectivity because of minimal drug loss and prolonged residence time at target site [64]. Pulmonary nanosuspensions improve drug diffusion and dissolution rate and consequently increase bioavailability and prevent undesirable drug deposition in the mouth and pharynx. Surface engineered nanosuspensions may provide quick onset followed by controlled drug release which is optimal drug delivery pattern for most pulmonary diseases. Moreover, nanosuspensions for treating lung infections have demonstrated good proportion between actual and delivered drug concentrations in each actuation [141]. The internalisation rate for nanoparticles of 0.5 μm diameter into the pulmonary epithelial cell has been reported to be 10 times higher compared to particles of 1 μm and 100 times higher compared to particles of 2-3 μm [142, 143].

5.4. Ocular Administration. Major problems in ocular therapy include

(i) poor drug solubility in lachrymal fluids,

(ii) repeated instillation of conventional eye drops due to drainage through the nasolacrimal duct,

(iii) repeated instillation and systematic drug absorption often causing side effects [144].

Nanosuspensions as ocular drug delivery systems offer several advantages.

(i) Nanoparticle modified surface by appropriate bioerodible polymer causes prolonged residual time in cul-de-sac desired for effective treatment. Commonly reported polymers in ocular nanosuspensions are poly(alkyl cyanoacrylates), polycaprolactone, and poly(lactic acid)/poly(lactic-co-glycolic acid) [145]. Employing polymers in ocular drug delivery significantly prolongs drug ocular residence time and improves bioavailability [146].

(ii) Positively charged nanoparticles have strong adhesion to negatively charged mucin which extends the drug release. For example, polymer Eudragit RS 100 was used in ibuprofen nanosuspensions to increase drug residence time by creating positively charged surface which resulted in improved corneal adhesion [56]. Flurbiprofen nanosuspensions covered by Eudragit polymers RS 100 and RL 100 exhibited prolonged drug release [147]. Chitosan is another mucoadhesive cationic polymer used in ocular drug delivery to bond with negatively charged mucin and enhance drug residence time [146].

(iii) Reduced drug loss because of the natural adhesiveness of drug nanoparticles [56, 148].

(iv) Enhanced rate and extent of drug absorption: for instance, in a study by Kassem et al., nanosuspensions of hydrocortisone, prednisolone, and dexamethasone were prepared by high pressure homogenisation. Measured intraocular pressure of normotensive Albino rabbits demonstrated that glucocorticoid drugs in the form of nanosuspensions unlike conventional dosage forms significantly increase the absorption rate and the therapeutic efficiency [68].

Employing polymers with the ability of *in situ* gelling (instilled in a liquid form and transformed to a gel in the cul-de-sac) controls the drug release. Study by Gupta et al. suggested that formulating forskolin nanoparticles in conjunction with *in situ* gel forming polymers noveon AA-1 polycarbophil/poloxamer 407 controls drug release through increased corneal contact time and slower drug diffusion within the viscous polymer medium [149].

6. Conclusions and Prospective

This review presents the recent progress in therapeutic nanosuspensions produced by various techniques such as high pressure homogenisation, media milling, and emulsification. Attractive characteristics of nanosuspensions such as uniform nanosized particles, improved solubility in biological media and adhesiveness (sugar versus ground sugar), increased drug concentrations, and residence time at the absorption sites enable the innovative design of a new class of drug delivery systems. Such nanosized drug formulations

have a number of benefits for drug therapies including high surface area, controllable nanosize dimensions, and tailored surface chemistry. However, in early stages, several *in vivo* studies clearly demonstrate the potential of these drug delivery vehicles in parenteral, oral, ocular, and pulmonary administration, where not only a controlled release but also an appropriate bioadhesion is required. The research on drug nanosuspensions is in its infancy. However, these systems carry flexibility and opportunity for further tailoring particles, surface properties to optimise *in vivo* responses, and generation of new clinical approaches for treating a number of diseases (heart, cancer, diabetes, Parkinson's, Alzheimer's, etc.) are required. Considering that nanoparticle uptake is size dependent, working on the size optimization of drug nanosuspension can help us prepare an appropriate nanosuspension formulation with better diffusion through the mucus gel layer. In addition, incorporation of polymers on the particle surface and size reduction can be regarded as the future step in nanosuspension research. To summarise future research directions include (a) increasing *in vivo* bioavailability and correlating *in vitro* and *in vivo* bioavailability data; (b) achieving controlled and sustained drug release over extended period of time using biocompatible matrix polymers; (c) development of stimuli-responsive systems such as magnetic field, light, temperature, and pH, which is particularly important for highly toxic drugs; (d) further studies that are necessary to understand the behaviour of nanosuspensions *in vivo*, including interactions with cells and different biological barriers such as the blood-brain barrier; (e) surface engineering of nanosuspensions for active or passive targeting in order to enhance their ability to reach the target. The aim of future studies is to combat the challenges associated with poorly soluble drugs in order to achieve high bioavailability, dissolution velocity, and bioadhesion of the drug.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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