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Review Article

Increasing Possibilities of Nanosuspension

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Nowadays, a very large proportion of new drug candidates emerging from drug discovery programmes are water insoluble and thus poorly bioavailable. To avoid this problem, nanotechnology for drug delivery has gained much interest as a way to improve the solubility problems. Nano refers to particles size range of 1–1000 nm. The reduction of drug particles into the submicron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. Nanosuspensions are part of nanotechnology. This interacts with the body at subcellular (i.e., molecular) scales with a high degree of specificity and can be potentially translated into targeted cellular and tissue-specific clinical applications designed to achieve maximal therapeutic efficacy with minimal side effects. Production of drugs as nanosuspensions can be developed for drug delivery systems as an oral formulation and nonoral administration. Here, this review describes the methods of pharmaceutical nanosuspension production including advantages and disadvantages, potential benefits, characterization tests, and pharmaceutical applications in drug delivery.

1. Introduction

One of the problems facing nanotechnology is the confusion and disagreement among experts about its definition. Nanotechnology is an umbrella term used to define the products, processes, and properties at the nano-microscale that have resulted from the convergence of the physical, chemical, and life sciences. The National Nanotechnology Initiative (NNI) defines, "Nanotechnology as research and development at the atomic, molecular, or macromolecular levels in the sub-100-nm range (w0.1–100 nm) to create structures, devices, and systems that have novel functional properties" [1]. A complete list of the potential applications of nanotechnology is too vast and diverse to discuss in detail, but without doubt, one of the greatest values of nanotechnology will be in the development of new and effective medical treatments [2]. In few words, nanotechnology can be said as "the technology at nanoscale" [3].

2. Nanomedicine

Burgeoning interest in the medical applications of nanotechnology has led to the emergence of a new field called nanomedicine, which involves the use of nanotechnology in drug development and offers ever more exciting promises of new diagnoses and cures [4]. It has been defined as "the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures." Therefore, nanomedicine adopts the concepts of nanoscale manipulation and assembly to applications at the clinical level of medical sciences [1]. Most broadly, nanomedicine is the process of diagnosing, treating, preventing disease and traumatic injury, relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body. In short, nanomedicine is the application of nanotechnology to medicine [5].

Applications of nanotechnology in medicine are potentially enormous. It is recognized that as particles get smaller, the surface area increases with a greater proportion of atoms/molecules found at the surface compared to those inside [4].

2.1. Nanosuspension. A nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as very finely colloid, biphasic, dispersed, and solid drug particles in an aqueous vehicle, size below 1 μm, without any matrix material, stabilized by

surfactants and polymers, and prepared by suitable methods for drug delivery applications, through various routes of administration like oral, topical, parenteral, ocular and pulmonary routes [6]. The particle-size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [7]. A nanosuspension not only solves the problem of poor solubility and bioavailability but also alters the pharmacokinetics of drug and that improves drug safety and efficacy. In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems, nanosuspensions are used as a formulation approach. Nanosuspension formulation approach is most suitable for the compounds with high $\log P$ value, high melting point, and high dose. The use of nanotechnology to formulate poorly water-soluble drugs as nanosuspension offers the opportunity to address nature of the deficiency associated with this class of drugs. Nanosuspension has been reported to enhance absorption and bioavailability; it may help to reduce the dose of the conventional oral dosage forms. Drug particle size reduction leads to an increase in surface area and consequently in the rate of dissolution as described by the Nernst-Brunner and Levich modification of the Noyes-Whitney equation. In addition, an increase in saturation solubility is postulated by particle size reduction due to an increased dissolution pressure explained by the Ostwald-Freundlich equation. An increasing amount of amorphous drug fraction could induce higher saturation solubility. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability. Drugs encapsulated within nanosuspensions exist in pharmaceutically acceptable crystalline or amorphous state. Nanosuspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption [6].

2.2. Potential Benefits of Nanosuspension Technology for Poorly Soluble Drugs [6, 8–10]. We have the following.

(1) Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, area under plasma versus time curve, onset time, peak drug level, reduced variability, and reduced fed/fasted effects. Due to the particle size reduction, the penetration capability of topical nanosuspension preparations increases significantly (Figure 1).

(2) Nanosuspensions can be used for compounds that are water insoluble but which are soluble in oil. On the other hand, nanosuspensions can be used in contrast with lipidic systems, and successfully formulate compounds that are insoluble in both water and oils.

(3) Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption.

(4) A pronounced advantage of nanosuspension is that there are many administration routes for nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.

(5) Nanosuspension of nanoparticles (NPs) offers various advantages over conventional ocular dosage forms, including reduction in the amount of dose, maintenance of drug release over a prolonged period of time, reduction in systemic toxicity of drug, enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, and suitability for poorly water-soluble drugs, and smaller particles are better tolerated by patients than larger particles; therefore, nanoparticles may represent auspicious drug carriers for ophthalmic applications.

(6) Nanosuspension has low incidence of side effects by the excipients.

(7) Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.

(8) Increased resistance to hydrolysis and oxidation and increased physical stability to settling.

(9) Reduced administration volumes, essential for intramuscular, subcutaneous, and ophthalmic use.

(10) Finally, nanosuspensions can provide the passive targeting.

2.3. Ingredients Used in the Formulation of Nanosuspension. We have the following:

stabilizer;

organic solvents;

cosurfactants;

other additives like buffers, salts, polyols, osmogents, and cryoprotectants [11].

3. Preparation Methods of Nanosuspensions

For manufacturing nanosuspensions, there are two converse methods "bottom-up" and the "top-down" technologies. Conventional methods of precipitation are called "bottom-up technology". The "top-down technologies" are the disintegration methods and are preferred over the precipitation methods. These include media milling (Nanocrystals), high-pressure homogenization in water (Dissocubes), high-pressure homogenization in nonaqueous media (Nanopure) and combination of precipitation and high-pressure homogenization (Nanoedge).

Techniques like emulsion as templates and microemulsion as templates are also used for preparing nanosuspensions [12].

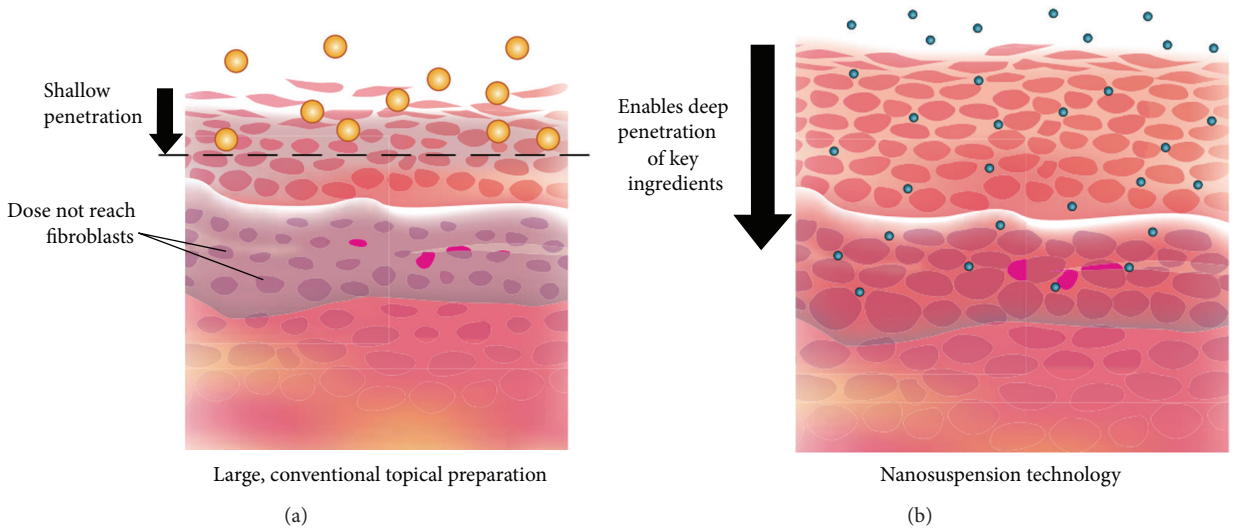

Figure 1: Penetration capability of nanosuspension over conventional topical preparation.

3.1. Different Methods of Nanosuspension Preparation [12]. See Figure 2.

3.2. Media Milling (Nanocrystals). This method was discovered by Liversidge et al. in 1992 and first patented by "Nanosystems" group, and now this patent transferred to "Elan drug delivery."

Here, the particle size is reduced by the high shear rate. And the total process is performed under controlled temperature. Otherwise, at high shear rate, some temperature will build up which will degrade some of the ingredients in the dosage form.

This equipment is known as high shear media milling or pearl mills (Figure 3).

This mill consists of three major columns:

(a) milling chamber;

(b) milling shaft;

(c) recirculation chamber.

3.2.1. Principle. Here, the main principle involved in the size reduction is "impaction". By this shear, the microparticles are braked down into nanoparticles. And it is connected to the recirculating chamber so that continuous production will be carried out. It is suitable for both batch operation and continuous operation. By this, we can reduce the particle size up to <200 nm in 30–60 min only [13].

3.3. High-Pressure Homogenization (Dissocubes). The process was developed by R. H. Muller, and first patent was taken by DDS Gmbh. Later, patent was transferred to Skype pharmaceuticals.

Commonly used homogenizer is the APV Micron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany). And another type is piston-gap homogenizers. And it is manufactured by Avestin (Avestin Inc., Ottawa, Canada). And another one is Stansted (Stansted Fluid Power Ltd. Stansted, UK).

The main principle is high pressure that is 100–1500 bars. By this pressure we can easily convert the micron size particle, into nanosize particle. And it initially needs the micron range particle that is <25 micrometer, so that we have to get the sample from the jet mill because by using jet mill we can reduce the particle size up to <25 micrometer (Figure 4).

And we can use this equipment for both batch and continuous operations. Capacity is also 40 mL to thousand litres. Here, first, we have to convert the particles into presuspension form (after jet milling).

3.3.1. Principle. High shear and high pressure are due to particle collisions; the particle size will be reduced. Here, we have to add viscosity enhancers to increase the viscosity of nanosuspension. In this methods we have to mainly concentrate on two parameter called pressure and homogenization cycles (depending on particle hardness analyzed by particle size and polydispersibility index) [13].

3.4. Emulsion as Template [13]. These emulsions are also useful for the preparation of nanosuspensions. The drugs which were insoluble in volatile organic solvents or partially soluble in water are prepared by this method.

This method is done by two types: as shown in Figure 5.

3.5. Microemulsion as Template. Microemulsions are thermodynamically stable and isotropically clear dispersion of the two immiscible liquids such as oil and water, and they were stabilized by an interfacial film of surfactant and cosurfactant. In this, firstly, the microemulsion was prepared the dug solution was mixed to that prepared emulsion and drug loading efficiency was tested [13].

3.6. Precipitation Method. Precipitation has been applied for years to prepare submicron particles within the last decade, especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in a solvent. Then, this solution is mixed

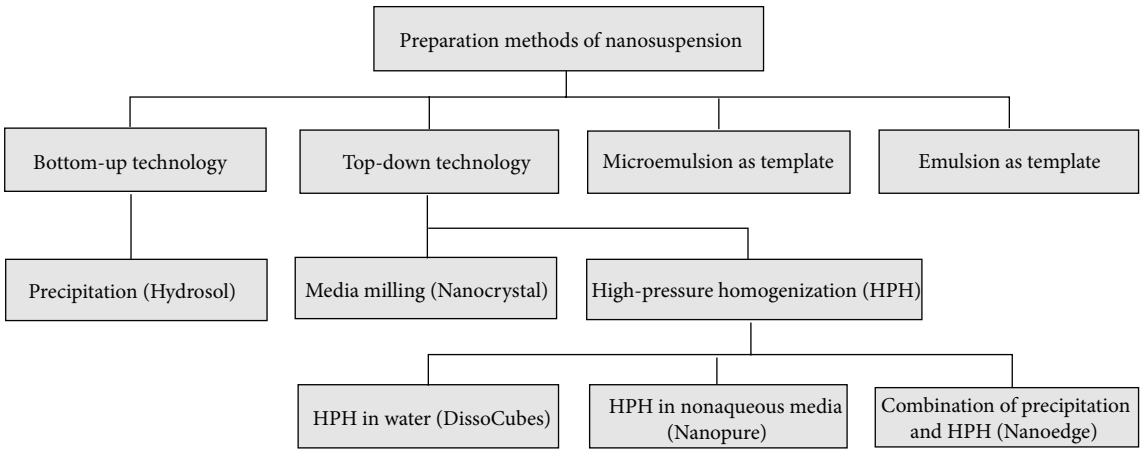

Figure 2: Schematic diagram of preparation methods of nanosuspension.

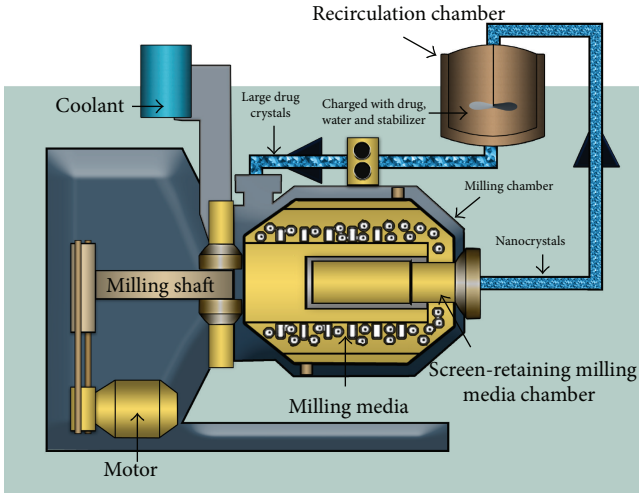

Figure 3: Schematic representation of the media milling process [11].

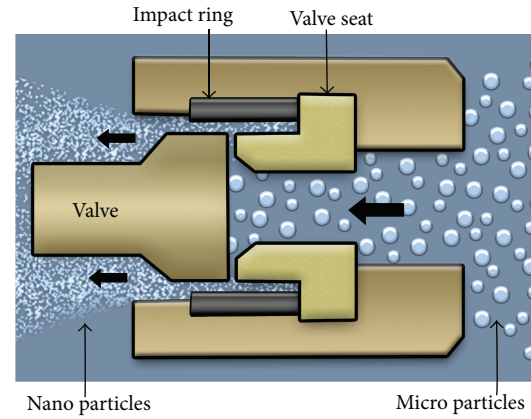

Figure 4: Schematic representation of the high-pressure homogenization process [11].

with a miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually water) leads to sudden supersaturation of drug in the mixed solution and generation of ultrafine crystalline or amorphous drug solids (Figure 6). This process involves two phases: nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate but low growth rate is necessary. Both rates are dependent on temperature: the optimum temperature for nucleation might lie below that for crystal growth, which permits temperature optimization [6].

3.7. Dry Cogrinding. Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported [15]. Colloidal particle formation of many poorly water soluble drugs like like griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS) [16]. Many soluble polymers and copolymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives have been used. Physicochemical properties and dissolution of poorly water-soluble drugs were improved by cogrinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. Dry cogrinding can be carried out easily and economically and can be conducted without organic solvents. The cogrinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained [12].

3.8. Some Other Methods for Nanosuspension Preparation [19, 20]. We have the following.

(i) Laser fragmentation.

(ii) Nanojet technology.

(iii) Emulsion solvent diffusion method.

(iv) Melt emulsification method.

(v) Supercritical fluid method.

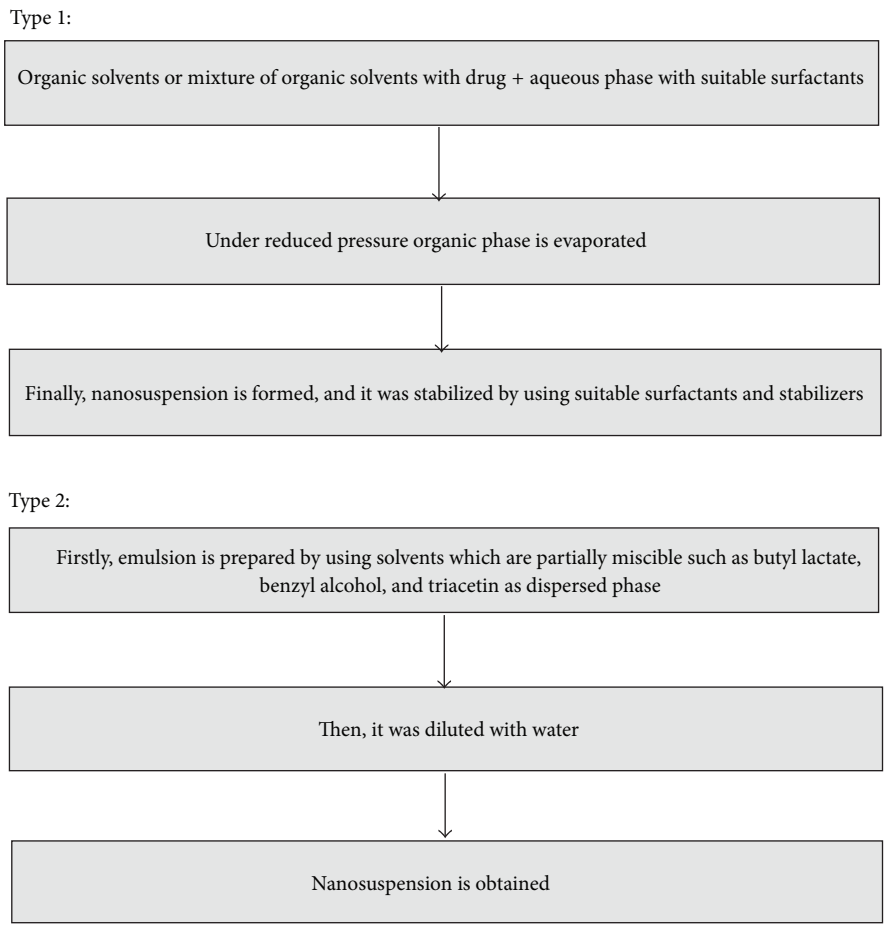

Figure 5: Schematic representation of the emulsion as template process.

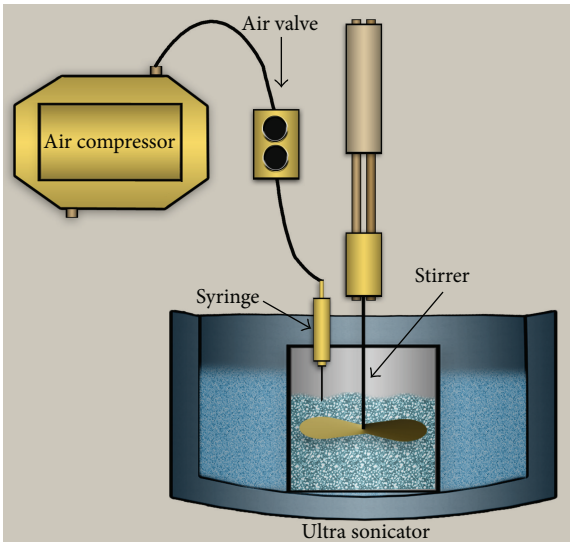

Figure 6: Schematic representation of the precipitation method [14].

Table 1 describes different preparation methods of nanosuspension technologies with their advantages and disadvantages.

4. Characterization Tests [8]

Chemical

(i) Active ingredient
(ii) Degradation products
(iii) Moisture (for lyophilized and solid dosage forms)
(iv) Preservatives
(v) pH.

Physical

(i) Particle-size distribution
(ii) Particle-size distribution in response to accelerated ageing and shipping (freeze/thaw, mechanical agitation, and centrifugation)
(iii) Drainability (from sides of container)
(iv) Syringeability, and injectability
(v) Resuspendability
(vi) Dissolution in water or biorelevant medium
(vii) Compatibility after admixture
(viii) Zeta potential (electrostatic self-repulsion of particles).

Table 1: Advantages and disadvantages of different preparation methods of nanosuspension technologies [7, 13, 17, 18].

Preparation methods	Advantages	Disadvantages
Precipitation	(i) Simple process (ii) Economical production (iii) Ease of scale-up	(i) Drug has to be soluble at least in one solvent and that this solvent needs to be miscible with a nonsolvent (ii) Growing of crystals needs to be limited by surfactant addition
High-pressure homogenization	(i) General applicability to most drugs (ii) For dilute and high concentrated nanosuspensions preparation (iii) Simple technique (iv) Sterile products preparation (v) Drugs which belong to BCS CLASS II and IV (vi) Ease of scale-up and little batch-to-batch variation	(i) High number of homogenization cycles (ii) Prerequisite micronized drug particles (iii) Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer (iv) Presuspension is required (v) High number of homogenization cycles
Emulsion/microemulsion template	(i) High drug solubilization (ii) Long shelf life (iii) Large-scale preparation (iv) Low cost (v) Simple manufacturing method (vi) Some organic solvents like ethyl acetate and ethyl formate can be used	(i) Used organic solvents are much unsuitable as human health cost (ii) Use of high amount of surfactant and stabilizers
Media milling	(i) Little batch-to-batch variation (ii) Ease of handling large quantities of drugs	(i) Generation of residue of milling media (ii) Time-consuming process (iii) Prolonged milling may induce the formation of amorphous leading to instability (iv) Scale-up is not easy due to mill size and weight
Dry cogrinding	(i) Easy process (ii) No organic solvent (iii) Requiring short grinding time	Generation of residue of milling media

Biological

(i) Sterility

(ii) Pyrogenicity

(iii) *In vivo* pharmacokinetics.

The essential characterization parameters for nanosuspensions are as follows.

4.1. Mean Particle Size and Particle-Size Distribution. The mean particle size and the width of particle-size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability and even biological performance of nanosuspensions. It has been indicated by Müller and Peters (1998) that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug [21]. Photon correlation spectroscopy (PCS) (B. W. Müller and R. H. Müller, 1984) can be used for rapid and accurate determination of the mean particle diameter of nanosuspensions [22].

Moreover, PCS can even be used for determining the width of the particle-size distribution (polydispersity index (*PI*)). The *PI* is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A *PI* value of 0.1–0.25 indicates a fairly narrow size distribution whereas a *PI* value greater than 0.5 indicates a very broad distribution. No logarithmic normal distribution can definitely be attributed to such a high *PI* value. Although PCS is a versatile technique, because of its low measuring range (3 nm to 3 μm) it becomes difficult to determine the possibility of contamination of the nanosuspension by microparticulate drugs (having particle size greater than 3 μm). Hence, in addition to PCS analysis, laser diffractometry (LD) analysis of nanosuspensions should be carried out in order to detect as well as quantify the drug microparticles that might have been generated during the production process. Laser diffractometry yields a volume size distribution and can be used to measure particles ranging from 0.05 to 80 μm, and in certain instruments, particle sizes up to 2000 μm can be measured. The typical LD characterization includes determination of diameter 50% LD (50) and diameter 99% LD (99) values, which indicate that either 50 or 99% of the particles are below the indicated size. The LD analysis becomes critical for nanosuspensions that are meant for parenteral and pulmonary delivery. Even if the nanosuspension contains a small number of particles greater than 5-6 μm, there could be a possibility of capillary blockade or emboli formation, as the size of the smallest blood capillary is 5-6 μm. It should be noted that the particle size data of a nanosuspension obtained by LD and PCS analysis are not identical as LD data are volume based and the PCS mean diameter is the light intensity weighted size. The PCS mean diameter and

the 50 or 99% diameter from the LD analyses are likely to differ, with LD data generally exhibiting higher values. The nanosuspensions can be suitably diluted with deionized water before carrying out PCS or LD analysis. For nanosuspensions that are intended for intravenous administration, particle-size analysis by the Coulter counter technique is essential in addition to PCS and LD analysis. Since the Coulter counter gives the absolute number of particles per volume unit for the different size classes, it is a more efficient and appropriate technique than LD analysis for quantifying the contamination of nanosuspensions by microparticulate drugs [11].

4.2. Crystalline State and Particle Morphology. The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Additionally, when nanosuspensions are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug nanoparticles generated during the production of nanosuspensions. The changes in the physical state of thedrug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis [23, 24] and can be supplemented by differential scanning calorimetry [25]. In order to get an actual idea of particle morphology, scanning electron microscopy is preferred [23].

4.3. Particle Charge (Zeta Potential). The determination of the zeta potential of a nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension. The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension, a minimum zeta potential of 30 mV is required, whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of 20 mV is desirable [26].

4.4. Saturation Solubility and Dissolution Velocity. The determination of the saturation solubility and dissolution velocity is very important as these two parameters together help to anticipate any change in the *in vivo* performance (blood profiles, plasma peaks, and bioavailability) of the drug. As nanosuspensions are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter. The saturation solubility and dissolution velocity of the drug nanosuspensions in different physiological buffers as well as at different temperatures should be assessed according to methods reported in the pharmacopoeia. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained release dosage forms based on nanoparticulate drugs [11].

4.5. In Vivo Biological Performance. The establishment of an in vitro/in vivo correlation and the monitoring of the in vivo performance of the drug are an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected nanosuspensions since the *in vivo* behavior of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins. In fact, the qualitative and quantitative composition of the protein absorption pattern observed after the intravenous injection of nanoparticles is recognized as the essential factor for organ distribution [27–31]. Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of *in-vivo* behavior. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity [32], whereas 2D PAGE [27] can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals [11].

5. Applications of Nanosuspension

Applications of nanosuspensions had landmarking history. Among these few applications are given below.

5.1. Oral Drug Delivery. Most of the time the oral route is preferred because it has numerous well-known advantages. Some orally administered antibiotics such as atovaquone and Buparvaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The oral administration of naproxen nanoparticles lead to an area under the curve (AUC) (0–24 h) of 97.5 mg-h/L compared with just 44.7 mg-h/L for naprosyn suspensions and 32.7 mg-h/L for anaprox tablets. Oral administration of the gonadotropin inhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2%. A nanosuspension of amphotericin B showed a significant improvement in its oral absorption in comparison with the conventional commercial formulation [6].

5.2. Bioavailability Enhancement. The poor oral bioavailability of the drug may be due to poor solubility, poor permeability, or poor stability in the gastrointestinal tract (GIT). Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation. The therapeutic effect was significantly enhanced, which indicates higher bioavailability. This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min) [18].

5.3. Parenteral Drug Delivery. Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via Intraperitoneal to intravenous injection. For administration by the parenteral route,

the drug either has to be solubilized or has particle/globule size below 5 μm to avoid capillary blockage. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspensions revealed their superiority over taxol in reducing the median tumour burden [33]. Similarly, aphidicolin, a poorly water soluble new anti parasitic lead molecule, when administered as a nanosuspension resulted in an improvement in EC50 in comparison to DMSO-dissolved drug [34]. Clofazimine nanosuspension, a poorly water-soluble antileprotic drug, revealed an improvement in stability and efficacy over the liposomal clofazimine in *M. avium*-infected female mice [35]. Rainbow and coworkers reported an intravenous itraconazole nanosuspension enhanced efficacy of antifungal activity relative to a solution formulation in rats [7]. Intrathecal delivery of nanosuspension busulfan to a mouse model of neoplastic meningitis led to a significant increase in survival [36].

5.4. Pulmonary Drug Delivery. Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in lungs. The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. At the same time, the increased adhesiveness of the drug to mucosal surfaces offers a prolonged residence time for the drug at the absorption site. This ability of nanosuspensions offers quick onset of action initially, and then controlled release of the active moiety is highly beneficial and is required by most pulmonary diseases. Budesonide drug nanoparticles were successfully nebulized using an ultrasonic nebulizer [6].

5.5. Ocular Drug Delivery. Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids [6]. The protective barriers of the eye make drug delivery difficult without tissue damage. Poor drug absorption and penetration of drugs to intraocular tissues limit the delivery of drugs. Use of nanoparticles and nanosuspensions for drug delivery to the intraocular tissues is being developed. One example is cross-linked polymer nanosuspensions of dexamethasone, which show enhanced anti-inflammatory activity in a model of rabbit eye irritation [20].

5.6. Targeted Drug Delivery. Nanosuspensions can be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. The engineering of stealth nanosuspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems [11]. Kayser formulated a nanosuspension of aphidicolin to improve drug targeting against Leishmania-Infected macrophages. He stated that the drug in the conventional form had an effective concentration (EC 50) of 0.16 mcg/mL, whereas the nanosuspension formulation had an enhanced activity with an (EC 50) of 0.003 mcg/mL [61].

Scholer et al. showed an improved drug targeting to the brain in the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii using a nanosuspension formulation of atovaquone [62].

5.7. Mucoadhesion of the Nanoparticles. Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT, for example, Cryptosporidium parvum. Mucoadhesive Buparvaquone nanosuspensions, because of their prolonged residence at the infection site, revealed a 10-fold reduction in the infectivity score of Cryptosporidium parvum as compared to the Buparvaquone nanosuspensions without mucoadhesive polymers [6].

5.8. Nanosuspension: Breaking the Barrier of the Skin. Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form and thus enhancing the diffusion of the drug into the skin (Figure 1) [7].

5.9. Central Nervous System. Nanosuspensions afford a means of administering increased concentrations of poorly water-soluble drugs to the brain with decreased systemic effects. Significant efficacy has been shown with microparticulate busulfan in mice administered intrathecally. The work has advanced to Phase I in patients afflicted with neoplastic meningitis, administered via an Ommaya reservoir for intraventricular delivery and via lumbar puncture. The drug was well tolerated and resulted in delayed progression of disease. Epidural injection of a 10% butamben suspension for cancer pain was well tolerated in dogs and humans. Future work will probably also involve less invasive routes, utilizing either passive targeting (via PEGylation, as has been done for liposomes) or active targeting to the brain following intravenous administration of nanosuspensions. In these latter publications, it was found that use of the agent Polysorbate 80 in the formulation led to deposition of apolipoprotein E on the nanoparticles, which facilitated brain uptake by receptors on the brain endothelial cells [8].

5.10. Nanosuspension Formulations for Treating Bioweapon-Mediated Diseases. Several concepts of targeting of nanosuspension dosage forms for treatment of bioweapon-mediated diseases have been developed at the Baxter Healthcare Corporation. Alterations of pharmacokinetic profiles of existing antibiotics can lead to enhanced efficacy with reduced side effects. This has been shown for a nanosuspension formulation of the antifungal agent itraconazole. Secondly, viral sanctuaries breed resistance and often include the brain and lymphatics. These may be targeted by loading nanoparticulate

Table 2: Summary of drug nanosuspensions.

Drug	Drug delivery route	Manufacturing method	Indication
Silybin	Oral, IV	HPH	Human prostate cancer [37, 38]
All-trans retinoic acid (ATRA)	IV, oral, and skin	Modified precipitation method	Antiproliferative drug against tumor [14, 39]
Mitotane	Oral	Emulsion as template	Symptomatic treatment of advanced adrenocortical carcinoma (ACC) [38, 40, 41]
Clofazimine	Intravenous	High-pressure homogenization	Murine *Mycobacterium avium* infection [42]
Cyclosporin A	Inhalation	Antisolvent precipitation	In immunosuppression [43, 44]
Amphotericin B	Ocular	Solvent displacement process	Management of ophthalmic fungal infections [45]
Olmesartan medoxomil	Oral	Media milling	Antihypertensive agent [46]
Simvastatin	Oral	Nanoprecipitation	Lipid-lowering agent [47]
Azithromycin	Oral	HPH	Antimicrobial [38, 41]
Nifedipine	Oral	Dry cogrinding	Treatment of vascular diseases [48–50]
Salbutamol sulfate	Pulmonary inhalation.	HPH	Antiasthmatic [51]
Diclofenac	Transdermal	Emulsification	NSAID [52]
Oridonin	IV	HPH	Antitumor [53, 54]
Albendazole	Oral	HPH	Lipophilic anthelmintic drug [55]
Loviride	IV	Milling	Antivirotic [56, 57]
Naproxen	I.P	Precipitation	Analgesic activity [58]
Paclitaxel	IV	HPH	Anticancer [8, 36]
Nevirapine	Parenteral	HPH	Antiretroviral [57]
Ibuprofen	Ocular	Emulsion solvent diffusion method	Ocular anti-inflammatory activity [6, 59]
Megestrol acetate	Oral	Laser fragmentation and media milling	Anorexia and cachexia [19, 60]

drug into macrophages which target these organs, increasing antiviral drug concentration in these typically inaccessible regions. Finally, a strategy for dendritic cell vaccines has been developed for use against bioweapons [63].

Table 2 summarizes successfully manufactured nanosuspension of different drugs for different delivery routes with their manufacturing method and indication.

6. Recent Trend of Nanosuspension

In recent years, nanosuspension technology has been successfully applied to tackle the formulation issues of poorly soluble drugs [64]. Most recently, nanopowders have been used as a delivery system for oral administration to enhance the dissolution rates of poorly soluble drugs. Tween 80/poloxamer 188 stabilised nanosuspension of a hydrophobic antiretroviral drug; loviride was prepared on a laboratory scale by media milling, and sucrose cofreeze-dried nanopowders were obtained [65]. Pulmonary products are essentially feasible. Nanosuspensions can be aerosolized using commercial nebulizers, but no products have been created. The reason may be commercial and not technical. It makes little sense to replace a well-selling product with a nanosuspension simply because pulmonary deposition might be superior. The cost of market introduction is too high. Even with a new molecule, an established routine delivery technology is preferable [66].

In addition, injection of poorly water-soluble nanosuspension drugs is an emerging and rapidly growing field that has drawn increasing attention due to its benefits in reducing toxicity and increasing drug efficacy through elimination of cosolvent in the formulation [38]. The current approaches for parenteral delivery include salt formation, solubilization using cosolvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost, and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above [33].

Some recent studies based on stability have proved that nanosuspension could significantly improve the chemical and photo stability of Quercetin compared with the solution stored in the same conditions. Nanosuspension technology would be an effective route to improve the stabilization of the chemical labile drugs [64]. Tam et al. [67, 68] have recently attempted to achieve stable nanosuspensions via a novel design of flocs structure called "open flocs." Thin film freezing was used to produce BSA nanorods with aspect ratio of approximately 24. These BSA nanorods were found to be highly stable when dispersed into hydrofluoroalkane (HFA) propellant, with no apparent sedimentation observed for 1 year. Due to the high aspect ratio of BSA nanorods and relatively strong attractive van der Waals (vdW) forces at the

contact sites between the particles, primary nanorods were locked together rapidly as an open structure upon addition of HFA, inhibiting collapse of the flocs [68].

A nanosuspension of indinavir has been loaded into bone marrow derived macrophages and injected into HIV-1-challenged humanized mice. The targeted delivery system significantly reduced numbers of virus-infected cells in plasma, lymph nodes, spleen, liver, and lung and led to CD4 (+) T-cell protection [69]. Spironolactone (SP) is a mineralocorticoid widely prescribed in pediatric population. It is a poor water-soluble drug characterized by incomplete oral bioavailability, bitter taste, and tendency to destabilize in aqueous media. Regarding the good solubility of Spironolactone in lipid materials, lipid nanoparticles seemed to be an excellent way to overcome these issues [70].

To overcome the problems associated with oral absorption and bioavailability issues, various strategies have been utilized [71], and nanosuspension is emerged as a promising strategy for the efficient delivery of hydrophobic drugs nowadays [11].

7. Conclusion

The formulation of poorly soluble drugs has always been a challenging problem faced by pharmaceutical scientists. In this case, nanosuspension formulations can be considered as a promising candidate. Various techniques described in this review alone or in combination can be successfully used to solve the poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Nanosuspensions can be administered through oral, parenteral, ophthalmic, pulmonary, and topical routes. It can play a very important role for human betterment as the technology is simple, requires less excipients, and increases dissolution velocity and saturation solubility. By emphasizing this technology, our society will be benefited financially also. Thus, nanosuspension technology is able enough to bring enormous immediate benefits and will revolutionize the research and practice of medicine in the field of pharmacy.

Conflict of Interests

The authors report no financial or other conflict of interests relevant to the subject of the paper.

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