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Review Article

Nanosuspension: Novel Approach for Drug Delivery

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ABSTRACT

Nanosuspensions have emerged as a encouraging strategy for the efficient delivery of hydrophobic drugs because of their multipurpose features and unique advantages. Techniques such as media milling and high pressure homogenization have been used commercially for producing nanosuspensions. Recently, the engineering of nanosuspensions employing emulsions and microemulsions as templates has been addressed in the literature. The unique features of nanosuspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels. Rapid strides have been made in the delivery of nanosuspensions by parenteral, peroral, ocular and pulmonary routes. Currently, efforts are being directed to extending their applications in site-specific drug delivery.

***Key Words*: Nanosuspension, Bioavailability, Nanosuspension application, Nanosuspension technology**

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1. INTRODUCTION

Modern drug discovery is very successful at choosing promising molecules and rejecting non-promising ones in a very short time,[1] but the same discovered molecules may not satisfy both therapeutic and formulation requirements.[2] Up to 40% of new chemical entities (NCEs)[3] discovered in the pharmaceutical industry today are compounds with low solubility. Conventional formulations of poorly water-soluble compounds are often associated with low and variable bioavailability. The formulation approaches available for drugs with low solubility include aqueous mixtures with an organic solvent[4, 5] (e.g., water-ethanol), solubilization,[6]formation of complexes (e.g. using β-cyclodextrins),[7-9] solid dispersions,[10-12] and pH control or salt form.[13] These formulation approaches have limitations, and their limited success is clearly demonstrated by the relatively low number of products in the market that are based on such technologies. The growing percentage of NCEs displaying solubility issues demands the development of new technologies for enhancing drug dissolution. Some approaches involve either chemical or mechanical modification of the environment surrounding the drug molecule (in a solution) or physically altering the characteristics of coarse drug particles.

The saturation solubility and dissolution rate of a drug substance can be mainly altered on two levels, through material engineering of a drug substance or through formulation approaches.[14] Nanotechnology has been applied to develop drug delivery systems like microemulsions, solid lipid nanoparticles, liposomes, and polymeric nanoparticles. But the cost involved in their preparation and their large-scale production feasibility is a primary concern. Thus, it would be much smarter to have a simple, universal formulation approach for such molecules. Micronization has been a universal approach widely used to improve bioavailability of drugs with poor solubility. The significant increase in surface area obtained by particle size reduction greatly improves the dissolution properties of a drug, thereby allowing a wider range of formulation approaches and delivery technologies. The recent advances in particle-size engineering methods have widened the formulation opportunities for relatively water-insoluble drugs. Several reports have shown significant improvement in saturation solubility and dissolution rate when the drug was reduced

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to nanometer size.[15-18] The nanosuspension of drugs has rapidly evolved into a mature drug-delivery strategy, and research interest is increasing in this area. This upward growth can be seen from the number of research articles and patents filed in the recent past. Consequently, drug nanosuspensions have arisen as a nanotechnology-based formulation approach, and they have been given increased attention due to their pharmaceutical advantage and pharmacoeconomic value, i.e., better performance in terms of cost and effect as compared to other approaches. Figure 1 shows the decision tree[19] for various formulation approaches for a drug, highlighting the importance of nanosuspensions, which comprise the only options for drugs with high melting points, high log P, and high dose requirements. However, considering the fact that more than 40–60 % of NCEs are low water solubility, have high log P, and have high melting points, nanosuspension is now preferred as a simple and universal formulation approach for a large number of drugs.[16,20] Nanosuspensions involve colloidal dispersion of nanosized drug particles that are produced using an appropriate method and are stabilized by a suitable stabilizer.[21,22] Nanosuspension technology offers major advantages of general applicability to most drugs and simplicity of method; it could become a universal formulation approach to processing drugs with low solubility. An important advantage of drug nanosuspensions is that they can be applied to various administration routes: oral,[23] parenteral,[24,25] ocular,[26,27] pulmonary,[28] dermal. In addition, they have shown great superiority over their traditional formulation counterparts.

Various articles have explained the production and applications of nanosuspensions,[29-31] and some have focused on their stability.[32, 33] But the complete picture of evolution of this system remains unclear. The aim of this review is to provide an overview of various approaches for preparation, characterization, applications, and advances in the field of nanosuspension technology, with special emphasis on the latest research developments and patents on nanosuspensions.

2. PREPARATION OF NANOSUSPENSIONS

Several techniques are used to produce nanosuspensions. The existing technologies can be divided into “bottom-up” and “top-down” technologies, or a combination of both. A simple schematic representation of the two technologies is given in Fig. 1. The topdown technologies are disintegration methods that basically rely on mechanical attrition to render large crystalline particles into nanoparticles. The bottom-up approaches rely on controlled precipitation and/or crystallization. These processes involve dissolving the drug in a solvent and precipitating it in a controlled manner to nanoparticles through the addition of an antisolvent. Top-down technologies are more widely used than bottom up technologies because top-down technologies yield better control over the processing parameters. This conclusion has been drawn based on the survey of marketed products based on nanosuspension technology.

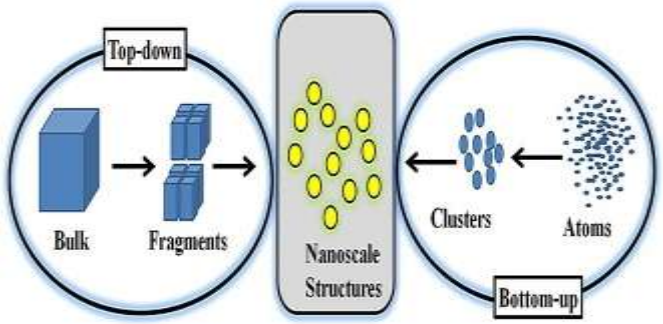

Figure 1. Schematic representation of top-down and bottom-up approaches.

The performance of nanosuspensions mainly depends on the particle size and the polydispersity index (PI) of the system, which is greatly affected by the method of preparation. The size and polydispersity obtained using various methods are not predictable, and obtained particle size and PI depends upon drug and process parameters. The PI is an important parameter governing the physical stability of nanosuspensions; it 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. The acceptable PI values may differ with method of administration. For intravenous administration, a small mean particle size and a narrow particle-size distribution are necessary. Specifically, the

number of particles greater than 5 µm should be sufficiently low after production and should remain within a limit during storage to avoid capillary blockade after intravenous injection. Various methods reported for preparation of nanosuspensions are depicted in Fig. 2. Of these, few methods have already demonstrated a scaling-up possibility a prerequisite for introduction of a product to the market. The recovery and yield of these methods at a small scale has been established by many researchers. Niwa et al. developed simple and easy method of preparing oral nanosuspension of pharmaceutical candidates with low water solubility to support the drug discovery and preclinical studies using animals (for 50 mg to 30 g of drug). The nanoparticles were successfully recovered with high yield (>95%) using this method.[34]In this section, various existing nanosuspension methods are briefly described. Technical notes have been provided regarding recent research work and patents employing these techniques.

2.1 Precipitation

Bottom-up technology starts at the molecular level and proceeds (via molecular association) to the formation of a solid nanosized particle. In bottom-up techniques, the drug is dissolved in an organic solvent, and this solution is mixed with a miscible antisolvent to initiate fast precipitation of a finely dispersed product. Drug solubility plays an important role in the precipitation technique.

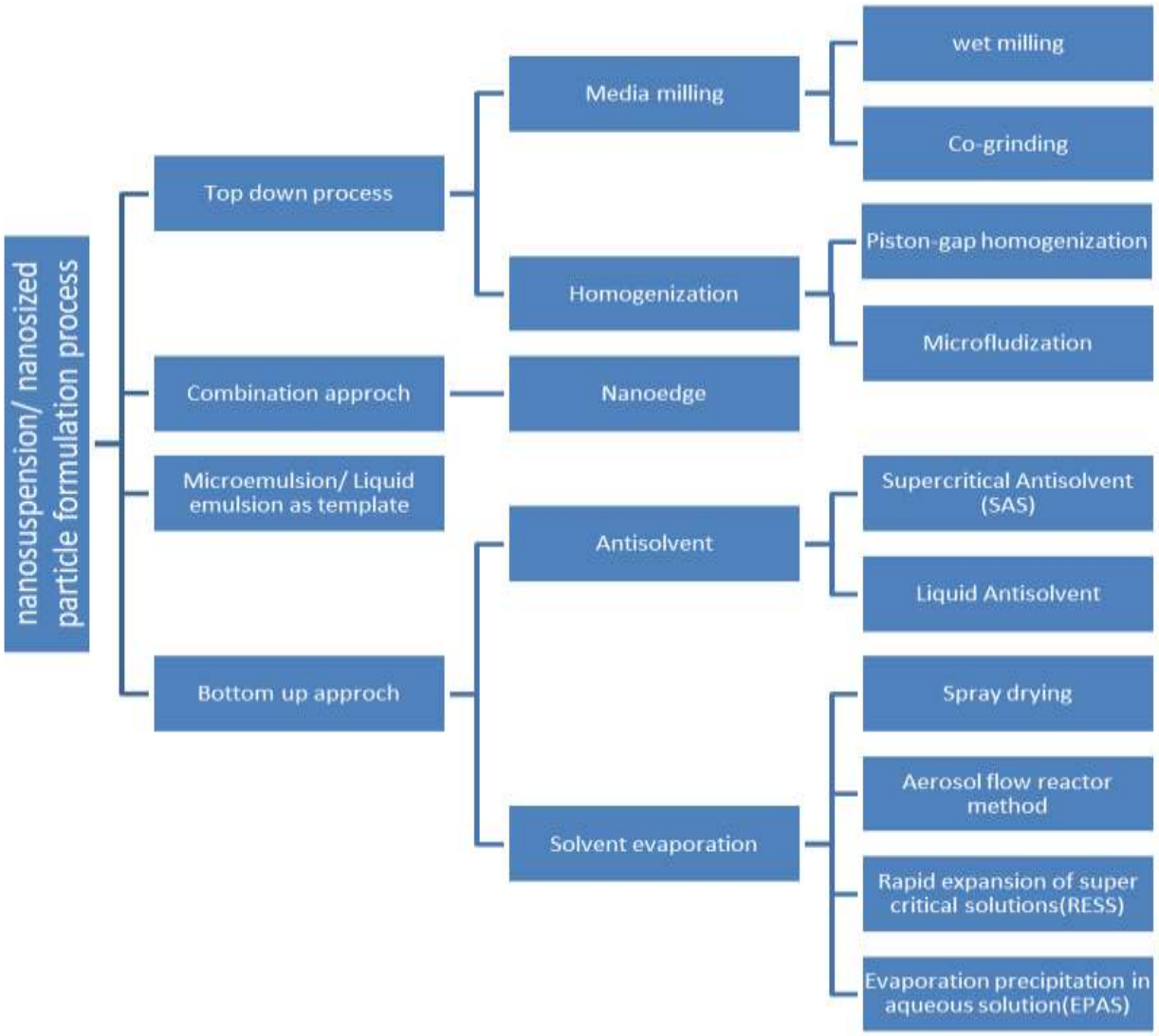

Figure 2. Methods for preparation of nanosuspensions

Nucleation and growth kinetics dictate the final particle size and size distribution and are controlled via supersaturation, which can be achieved by controlling process parameters and modifying API solubility.[35] Reproducibility and control over particle size in precipitation

techniques are the major factors considered. The key factors to controlling the size and stability of drug nanoparticles are the choices of solvents and stabilizers and the mixing process. The mixing step is crucial to producing a rapid and uniform supersaturated solution that facilitates the formation of uniform drug nanoparticles. Other crucial factors include drug concentration, volume ratio of antisolvent to solvent, temperature, and viscosity. The precipitation method, a bottom-up method, has been employed successfully for preparing nanosuspensions. [36, 37] Examples of the precipitation technique include hydrosols, Nanomorph, supercritical fluid (SCF) technology, and other precipitation approaches. The precipitation method has the advantages of technical simplicity, simple equipment requirements, and easy scalability. SCF methods require special equipment, but the particle size control is better with these methods. The disadvantages of the precipitation method include the requirement that a drug be soluble in at least one solvent, the miscibility of that solvent with nonsolvent, solvent residues, and the preservation of the nanoparticle structure

2.2 Hydrosols

The hydrosols were developed by Sucker et al. of the Sandoz Company (now Novartis, Inc.).[38] In this approach, the drug is dissolved in a solvent, and this solvent is added to a nonsolvent to initiate rapid precipitation of a finely dispersed product. To achieve this, it is necessary to pass the so-called Ostwald–Mier area very quickly, which means reducing the solvent quantity very quickly.[39] This is achieved by adding the solvent to a nonsolvent (i.e., doing it the other way around would lead to the formation of larger crystals). The formed nanocrystals need to be stabilized by surfactants or polymers to avoid growth of the nanocrystals to microcrystals. In general, it is recommended that the product be lyophilized to preserve the nanosize of the particles. This technology is, to some extent, complex (e.g., the preservation of particle size), and it excludes all molecules that are poorly soluble in aqueous and organic media. But unfortunately, no products based on this technology have been marketed. An additional problem is solvent residue; its removal makes the process more costly.

2.3 Nanomorph

The precipitation method developed by Sucker generally yields crystalline particles, whereas another precipitation technique developed by Knoll (now owned by Abbott, Inc.) reportedly creates amorphous particles.[40] The product is called Nanomorph. The special feature of Nanomorph is an increase in the dissolution velocity due to the amorphous character of the product. The precipitation in the amorphous form is achieved by an aqueous polymer solution. However, for commercialization of this technique, the major challenge is to preserve the amorphous character during the shelf life, as any polymorphic change will result in changes in bioavailability. 3. Supercritical Fluid Technology Nanosized drug particles can be produced with supercritical fluids using various methods, such as the rapid expansion of supercritical solution process (RESS), the gas antisolvent (GAS) process, and the supercritical antisolvent process (SAS). The RESS process involves expanding the solution of the drug in a supercritical fluid through a nozzle. Upon expansion, supercritical fluid loses its solvent power, leading to precipitation of the dissolved drug as fine particles. Cyclosporine nanoparticles in the size range of 400 to 700 nm have been produced using this technique.[41] The GAS process involves pressurizing a solution of drug in a common solvent with CO2. As the solvent is removed and the solution gets supersaturated, the drug precipitates and forms fine crystals. The SAS process uses a supercritical fluid (in which the drug is poorly soluble) and a solvent for the drug (which is also miscible with the supercritical fluid). The method involves injecting a solution of the drug into the supercritical fluid. As the drug solution becomes supersaturated, the drug precipitates as fine crystals. Chattopadhyay et al. have applied this method for preparing nanosuspension of griseofulvin, an antifungal agent with poor aqueous solubility. The particle size and morphology of the nanoparticles were further controlled by subjecting the drug solution to an ultrasound field generated by a vibrating surface inside the supercritical media. The frequency of the vibration was varied to obtain particles with different sizes and morphologies.[42] The SAS method can lead to particle nucleation

overgrowth due to transient high supersaturation. With these methods, high supersaturating may also result in the development of an amorphous form or other undesired polymorphs. This is particularly true in the case of organic molecular crystals, in which the forces holding the molecules together in the lattice are relatively weak.

2.4 Other precipitation approaches

Recently, some new precipitation methods have been reported for preparing nanosized particles. These comprise

- High-gravity controlled precipitation (HGCP),
- Sonoprecipitation,
- The aerosol flow reactor method,
- Evaporative precipitation in aqueous solutions (EPAS), and
- Spray drying.

One of the most promising nanoprecipitation techniques available at the commercial production scale is HGCP. This technique comprises a rotating packed bed to strengthen mass and heat transfer by several orders in a multi phased system. The technique has subsequently been applied to the production of nanoparticulate drugs like cefuroxime axetil, azithromycin, danazol, cephadrine, and salbutamol sulphate.[43] Recently, sonoprecipitation (or sonocrystallization), a crystallization process which is mainly assisted by ultrasound, has been developed. The principle involves development of bubbles (cavitation) followed by collapse, which releases shock waves, thereby stimulating nucleation powered by changes in temperature and pressure. This technique has been successfully used for preparing nanosized particles of cefuroxime axetil.[44] The aerosol flow reactor method is a single-step continuous process like spray drying that involves atomizing the drug solution into a carrier gas for drying. The method has the potential to control the particle morphology and polymorphic form because this method provides more precise control over the temperature history and residence time of droplets. This method has been used to produce spherical nanoparticles of beclomethasone dipropionate.[45] Another precipitation method reported for nanoparticle preparation is EPAS. In this method, an organic solution of drug is preheated through a coil and injected under the surface of a heated aqueous solution with surfactant(s) added to stabilize the particles. Intensive atomization occurs below the liquid surface, which produces a large interface between the organic and aqueous solutions, causing rapid evaporation of the organic solvent and precipitation of particles. Cyclosporine A nanoparticles have been produced using this technique.[46] In spray drying, a drug solution (aqueous or organic) is atomized to fine droplets, which are evaporated in a warm air current to form dry particles. This method is not suitable for production of nanoparticles because spray drying has low cyclone collection efficiency for nanoparticles. With an electrostatic collector, it is now possible to collect spray-dried nanoparticles. The applicability of this approach has been demonstrated using bovine serum albumin solution.[47]

2.5 High-Pressure Homogenization

High-pressure homogenization (HPH) is a disintegration method based on the top-down approach. Two homogenization principles are applied: piston gap fluidization and microfluidization. In the first method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high-pressure homogenizer, and particle-size reduction is based on the cavitation principle. The particle cavitation forces are sufficiently high to convert the drug microparticles into nanoparticles. Particles are also reduced due to high shear forces and the collision of the particles against each other. The major concerns associated with this method are the need for drug particles to be in micronized state before loading and the number of homogenization cycles required.[48] The size of the drug nanocrystals that can be achieved depends mainly on the power density of the homogenizer, the number of homogenization cycles, and temperature. Drug factors also have an important effect on the HPH process. An important determining factor for the final size of the drug nanocrystals is the hardness of the drugs. For soft drugs such as paclitaxel, it is possible to obtain a particle size as low as 250 nm; but it is very difficult to achieve a particle size of 250 nm for

harder drugs, such as azodicarbonamide, irrespective of homogenization cycles and pressure. During the size reduction process, the particles and/or crystals break preferentially at weak points (i.e., imperfections). The number of imperfections decreases with decreasing particle size; thus the remaining crystals become more and more perfect. Therefore, the force required to break the crystals increases with decreasing particle size. The particles will not further diminute, even when additional homogenization cycles are applied, if the force (i.e., power density) in the homogenizer is equal to the interaction forces in the crystal. The second method is microfluidization, which is based on a jet stream principle. Here, the suspension is accelerated and passes with a high velocity through a specially designed homogenization chamber (either Z shaped or Y shaped), leading to a reduction in particle size due to the collision of particles and the shear forces generated. Techniques based on the HPH processes include hydrosol, Nanomorph, nanocrystals, dissocubes, Nanopure and Nanoedge. The HPH method has been used successfully by various researchers to achieve nanosuspensions.[49-51]

2.6 Lipid emulsion/ microemulsion template

Lipid emulsion and/or microemulsions are also used as templates for the preparation of nanosuspensions. These systems are applicable for drugs that are soluble in either volatile organic solvents or that are partially water-miscible solvents. In this technique, an organic solvent or mixture of solvents loaded with the drug is added slowly to an aqueous medium with stirring at a high speed that leads to formation of small droplets (containing drug dissolved in organic solvent) emulsified in the aqueous vehicle. As the stirring progresses at high speed, the droplet size is further reduced. The process is also accompanied by slow evaporation of the organic solvent from the droplets. Once the organic solvent is evaporated completely, pure drug particles stabilized by surfactant are left behind, suspended in the aqueous vehicle. The advantages of lipid emulsions/microemulsions as templates for nanosuspension formation are that they are easy to produce by controlling the emulsion droplet and that this procedure is easy to scale up. However, the use of organic solvents affects the environment, and large amounts of surfactant or stabilizer are required. This approach was investigated for improving dissolution properties of drugs with low water solubility.[52]

2.7 Milling Techniques

Milling techniques are now being widely used for preparation of nanosuspensions. Nanosuspensions obtained using milling techniques are prepared either by wet milling or dry co-grinding.

Wet Milling

Nanocrystal is a patent-protected technology developed by Liversidge et al.[53] This technique involves mechanical attrition of suspended drug particles using suitable milling media like glass, (yttrium-stabilized) zirconium oxide, or highly crosslinked polystyrene resins. The milling chamber is charged with drug, surfactant and milling media, and a milling medium (usually water), and the contents are subjected to a very high shear rate. The high energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. A majority of nanosized products in the market are based on this technique. The advantages of this method include easy scale up, the possibility of handling a large quantity of drugs, and little batch-to-batch variation. The limitations include lengthy process, possible contamination with milling media, and chances of formation of unstable drug particles due to prolonged milling. This method has been used for formulating nanosuspensions of glyburide, itraconazole, fluticasone, etc.[54-56]

Dry Co-grinding

Preparation of nanosuspensions by dry-milling techniques has been reported.[57] It involves dry grinding of a drug with additives (i.e., co-grinding) and is a simple, organic, solventfree preparation process. Formation of drug nanoparticles occurs when the ground mixtures of drug with polymer and/or surfactant are dispersed in water. Water-

soluble polymers and surfactants have been used as additives for effective size reduction of drug particles as well as to inhibit particle agglomeration and to improve their dissolution. Improvement in physicochemical properties and dissolution of poorly water-soluble drugs due to cogrinding can be attributed to an improvement in the surface polarity and transformation from a crystalline to an amorphous form.[3] Dry co-grinding can be performed easily and economically without organic solvents and can reduce particles to the submicron level, often yielding a stable amorphous solid. This method is promising for preparation of nanosuspensions of dihydroartemisinin, albendazole, danazol, and felodipine.[58, 59]

2.8 Combination technologies

The previous nanosuspension methods are combined in some cases to gain better size reduction and improved stability of the system. The combination of these methods has resulted in improved advantages associated with nanosuspension technology. Nanoedge is a patented technology based on the combination of precipitation and homogenization.

2.9 Nanoedge

The basic principles of Nanoedge are the same as those of precipitation and homogenization nanoprocesses. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawbacks of the precipitation technique, crystal growth and long-term stability, can be resolved using Nanoedge technology. In this technique, the precipitated suspension is further homogenized, leading to a reduction in particle size and avoiding crystal growth. Precipitation is performed in water using water-miscible solvents such as methanol, ethanol, and isopropanol. It is desirable to remove those solvents completely, although they can be tolerated to a certain extent in formulation. For effective production of nanosuspensions using Nanoedge technology, an evaporation step can be included to provide a solvent-free, modified starting material followed by HPH.[60]

3. EVALUATION OF NANOSUSPENSIONS

The unique qualities and performance of nanoparticulate systems as devices for drug delivery arises directly from their physicochemical properties. Hence, determining such characteristics is essential for achieving the mechanistic understanding of their behavior; this understanding allows prediction of in vivo performance as well as allowing particle designing, formulation development, and process troubleshooting to be conducted in a rational fashion. Nanosuspensions are generally characterized according to the following parameters: particle size, surface charge (i.e., zeta potential), crystalline state, saturation solubility, and stability.

3.1 Particle Size

The most basic and important property of any nanoparticulate system is particle size. The saturation solubility, dissolution velocity, physical stability, and even biological performance of these systems depend on particle size. Saturation solubility and dissolution velocity vary considerably with change in particle size of the drug.[61] The most frequently used techniques for size measurement of nanosized particles are dynamic light-scattering techniques, static light-scattering techniques, and microscopy. Each method has advantages as well as disadvantages. The mean size and width of distribution (polydispersity index, PI) is typically determined by photon correlation spectroscopy (PCS). This technique can be used for rapid and accurate determination of the mean particle diameter in nanosuspensions.[62] PCS records the variation in the intensity of scattered light on the microsecond time scale.[63, 64] The measuring range of PCS is limited to approximately 3 nm to 3 mm. Therefore, laser diffractometry (LD) is also used to detect any particles in the micrometer range or aggregates of drug nanoparticles. For nanosuspension intended for intravenous use, particle-size determination by Coulter Counter is also essential, as even a few particles with particle size greater than 5 μm may cause blockage of blood vessels. Depending on the type of equipment employed, the measured size range of particles is approximately 0.01–80 μm. The instrument used and the material to be analyzed are important parameters that affect accurate particle size measurement. The stability of the

sample during analysis is the most important requisite for correct and reproducible results.[65] Thus, all of these factors must be considered when selecting the appropriate technique for particle-size determination for a particular sample. A few examples that illustrate the importance of particle size on in vivo performance follow. Nowacek et al. demonstrated that physical characteristics such as particle size, surfactant coating, surface charge, and most importantly, shape are predictors of cell uptake and antiretroviral efficacy.[66] In vivo studies conducted by Ghosh et al. showed superior systemic exposure of drug in case of nanosuspension compared to non-micronized coarse suspension in dogs.[67] Detroja et al. showed enhanced antihypertensive activity of candesartan cilexetil compared to the plain drug in rats.[68]

3.2 Surface charge (Zeta potential)

Particle charge is a stability-determining parameter in aqueous nanosuspensions. It is measured by electrophoresis and is typically expressed as phoretic mobility [(mm/S)/(V/cm)] or zeta potential (mV). Zeta potential is used as a surrogate for surface charge and is often measured by observing the oscillations in signal that result from light scattered by particles located in an electric field.[69,70] A number of instrumental configurations with different approaches have been implemented in different equipment; the most commonly used is the Doppler shift. The zeta potential of a nanosuspension is governed by both the surfactant and the drug itself. For a physically stable nanosuspension solely stabilized by electrostatic repulsion, a minimum zeta potential of ±30 mV is required. In combined electrostatic and steric stabilization, ±20 mV is sufficient as a rough guideline.[71] Cerdeira et al. stabilized a miconazole nanosuspension by combining electrostatic and steric stabilization (-19±1 mV) for 6 months.[72] Zhang et al. showed that all-trans retinoic acid (ATRA) nanosuspensions with zeta potential of -37.9 ± 2.0 mV had sufficient electrostatic stabilization for 6-month stability. El-Shabouri studied the effect of surface charge on bioavailability of cyclosporine-A nanoparticles. The relative bioavailability of positively charged nanoparticles increased, while it decreased for negatively charged nanoparticles.[73] Crystalline State Drug particles of amorphous form are likely to be generated when nanosuspensions are prepared. Hence, it is essential to investigate the extent of amorphous drug particles generated during nanosuspension production. The crystalline status of the nanosuspension can be assessed using differential scanning calorimetry (DSC).[74] This is particularly important when a drug exhibits polymorphic forms, some of which may be toxic. The changes in the physical state of the drug particles as well as the extent of amorphous fraction can be determined by X-ray diffraction analysis [75,76] and can be supplemented by DSC studies.[77] The assessment of the crystalline state and particle morphology together furthers understanding of the polymorphic and morphological changes that a drug undergoes when subjected to nanosizing. Yang et al. studied the effect of supersaturation on bioavailability of inhaled, nebulized aerosols for amorphous versus crystalline nanoparticulate dispersions. Pulmonary delivery of the nanoparticulate amorphous ITZ composition resulted in significantly higher systemic bioavailability than for the nanocrystalline ITZ composition, as a result of the higher supersaturation that increased the permeation.[78] Lai showed that the drug dissolution rate in nanosuspensions is strongly affected by drug solubility and depends on the crystal form.[79] The results of a study by Sigfridsson et al. showed that AZ68 was absorbed at a lower rate for crystalline nanosuspensions compared to amorphous nanosuspensions.[23]

3.3 Saturation solubility

The increase in saturation solubility and consequently an increase in dissolution rate of the compound decide its applications. Although saturation solubility is defined as a Compound-specific, temperature-dependent constant, it also depends on particle size. The increase in saturation solubility can be explained by the Kelvin–Gibbs equation (Eq. 1) and the Ostwald–Freundlich equation (Eq. 2). In the Kelvin–Gibbs equation, the vapor pressure increases with increasing curvature of the droplet of a liquid in gas. If this is extended to a solid, it implies that the dissolution pressure increases with decrease in particle size. According to the Ostwald-Freundlich equation, the increased saturation solubility is due to creation of high-energy surfaces when the

more or less ideal drug microcrystals are disrupted to nanoparticle.[61]

$$In\frac{Pr}{P\infty} = \left(\frac{2yM}{rRT\rho}\right)$$

(1)

$$S = S\infty\left(\frac{2yM}{rRT\rho}\right)$$

(2)

In these equations, Pr is the dissolution pressure of a particle with radius r; P∞ is the dissolution pressure of infinitely large particle; S is saturation solubility of the nanosized drug; S∞ is saturation solubility of an infinitely large drug crystal; γ is the crystal medium interfacial tension; M is the compound molecular weight; r is the particle radius; ρ is the density; R is a gas constant; and T is the temperature. Particle-size reduction of drug particles leads to an increase in surface area, resulting in an increased dissolution rate, according to the Noyes–Whitney equation:

$$\frac{dX}{dT} = \frac{DS}{h}\left(Cs - \frac{Xd}{v}\right)$$

(3)

where dX/dt is dissolution rate, Xd is amount dissolved, D is diffusion coefficient, S is particle surface area, v is volume of fluid available for The equation shows that the dissolution rate of a drug is proportional to the surface area available for dissolution. This principle has been extensively used in the micronization of drug for improving oral bioavailability. Obviously, decrease in particle size to nanometer range will further increase the dissolution rate due to a significant increase in effective particle surface area. According to the Prandtl equation (Eq. 4), Nanosizingresults in the decrease of the diffusion-layer thickness surrounding the particles and an increased concentration gradient between the surface of the particle and bulk solution, which facilitates particle dissolution by increasing dissolution velocity.

$$hH = k.\left(\frac{L\frac{1}{2}}{V\frac{1}{2}}\right)$$

(4)

In this equation, hH is the hydrodynamic boundary layer thickness; k is a constant; V is the relative velocity of the flowing liquid against a flat surface; and L is the length of the surface in the direction of flow. It is clear from Eqs. (3) and (4) that nanosizing is a suitable approach for increasing bioavailability of poorly soluble drugs where dissolution is the rate limiting step in systemic absorption.[80] The theoretical backgrounds of the Kelvin–Gibbs, Ostwald–Freundlich, and Prandtl equations support the fact that below a size of approximately 1–2 μm, the saturation solubility is a function of the particle size. In view of this information, determination of saturation solubility remains an important investigation parameter for nanosuspension because it determines performance. The saturation solubility of the drug in different physiological buffers as well as at different temperature should be assessed using different methods described in literature. For example, saturation solubility can be determined at different temperatures by shaking experiments until equilibrium has been reached. The improvement in dissolution rate of nanosuspension compared to conventional formulations reflects the advantages achieved by nanosizing. Apart from adhesiveness, increased dissolution velocity and increased saturation solubility are the special benefits of nanosuspensions. These two parameters mainly determine the in vivo fate of nanosuspensions. Showing a saturation solubility that was five times greater, improved bioavailability of oral nanocrystals of anthelmintic drug albendazole was observed compared to the raw material.[81] After nanosizing, increase in saturation solubility of nifedipine was observed, resulting in improved dissolution characteristics that resulted in improved bioavailability.[82]

3.4 Surface morphology

Nanoparticles can be directly observed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM), with the former method being better for morphological examinations.[83,84] TEM has a smaller size limit of detection and provides structural information via electron diffraction, but staining is usually required. Researchers must be cognizant of the statistically small sample size and the effect of applied vacuum on the particles during analysis. Very detailed images can be obtained using the freeze–fracture approach in which a cast is made of the original sample.[85] Sample corruption resulting from the extensive sample preparation

is always a possibility, though lower vacuum instrumentation reduces this manipulation, albeit at the loss of some resolution.[86] Atomic force microscopy (AFM) can also be used to confirm the size and shape of nanosized particles. AFM is capable of scanning the surfaces in controlled environmental conditions and is a complementary to SEM imaging.

3.5 Stability

Physical stability is crucial in the formulation of drug nanosuspension. Because nanosuspensions have a mean particle diameter in nanometer range, they are prone to aggregation. The aggregation may be due to Ostwald ripening, which occurs due to different saturation solubilities in the vicinity of very small and larger particles. Nanosizing results in the creation of additional surface area and/or interfaces that lead to a change in free energy and become thermodynamically unstable while tending to minimize the free energy.[3] Hence, stabilizers like surfactants or polymeric macromolecules are required to stabilize the nanoparticles against interparticulate forces and to prevent them from aggregating. Surfactants are used to minimize the free energy and stabilize the system. The stabilization provided by surfactants is by steric or electrostatic processes or a combination of them. Steric stabilization is achieved by adsorbing surfactants/polymers onto the particle surface, while electrostatic stabilization is obtained by adsorbing charged molecules, which can be ionic surfactants or charged polymers, onto the particle surface. Generally, steric stabilization alone is sufficient to provide stability to the nanosized particles, but it is often combined with electrostatic stabilization as an additional measure. Formulation of nanosuspension requires careful selection of stabilizers. The ability of a surfactant to associate with a solid surface is dependent on several factors, including pH, ionic strength, temperature, structure, charge density, and other properties of both the surface and the surfactant.[87, 88] Therefore, selection of appropriate stabilizer for nanosuspension is a challenging task. Also the FDA approval status (GRAS) of the stabilizers must be considered for selection. The most popular surfactants used for stabilization purposes are Polysorbate 80, lecithins, cholic acid derivatives, and sodium lauryl sulfate. The surfactant stabilizers can be non-ionic (polysorbates) or anionic (sodium lauryl sulfate (SLS) and docusate sodium (DOSS). Due to their antiseptic properties, cationic surfactants are typically not used as stabilizers for oral formulation. The polymeric stabilizers most frequently applied are povidones (PVP K 30), poloxamers (F68 and F127), and cellulosics (HPC and HPMC). The molecular weights of these polymers are usually between 50 kDa and 100 kDa, and their chains should be long enough to provide a steric layer but not too large to slow down dissolution. The most popular non-ionic surfactants applied are the poloxamers and Tween 80; while sodium lauryl sulfate is the typical ionic surfactant used for this purpose. To achieve the most stable nanosuspension formulation, the stabilizers can be used alone or in combination. The drug:stabilizer ratios (w/w) in the formulations vary widely, ranging from 1:3 to 50:1. Other stabilizers that were studied for stabilization of drug nanoparticles include cyclodextrins[89] and amphiphilic amino acid copolymers.[88]

Although the number of articles describing nanosuspension formulations is extensive; attempts to evaluate and compare the potential of different stabilizers are limited. A few studies that evaluated the potential of different stabilizers for providing stability to nanosuspensions are reported here. Verma et al. investigated the role of stabilizers (small molecules vs. polymeric) on Ostwald ripening for evaluating physical stability of indomethacin nanosuspension. They observed a lower rate of particle-size increase in small-molecule surfactant at higher concentrations compared to polymeric surfactant.[90] In another study, the ability of povidone (PVP) and hydroxypropyl cellulose (HPC) to obtain nanosuspensions for seven model compounds by wet comminution was evaluated. Results showed that better nanosuspensions were produced when surface energy values of drug and stabilizer were comparable.[91] Lee et al. reported the screening of 5 polymers (i.e., HPC, PVP, Poloxamer 407, polyethylene glycol (PEG) and Poloxamer 188) and 11 model drugs for nanosuspension stabilization. They found that poloxamer 188 was able to stabilize most of the model compounds. They also reported that drugs with lower aqueous

solubility, higher molecular weight, and higher melting points were better candidates for nanosuspension production (i.e., easier to stabilize).[92] Van Eerdenbrugh et al. evaluated nanosuspension production with 13 stabilizers of different classes; each was used in three concentrations for nine structurally different drug compounds. The performance of the surfactant was ranked in the following order: semi-synthetic polymers < linear synthetic < synthetic copolymer. Results showed that the hydrophobicity of the surfaces was decisive for the agglomeration tendency of the particles and hence the ease of nanosuspension stabilization.[93] In another study, the practically water insoluble drug miconazole was nanoground, and the stabilizing effects of a variety of surface active and polymeric excipients were tested. Hydroxypropylcellulose (HPC-LF) in combination with sodium dodecyl sulfate (SDS) were found to be the best stabilizers for the miconazole nanosuspensions. The study showed that excellent wetting of drug particles as well as their electrostatic and steric stabilization by excipients was necessary to produce stable nanosuspensions by nanogrinding.[94] From all of these studies, it can concluded that selection of surfactant is a challenging task important to providing stability to nanosuspensions.

In addition to physical stability (Ostwald ripening), chemical stability of the active content in nanosuspension is affected in some cases by hydrolysis of the compound. The active content of the nanosuspension formulation must be studied, as some drugs have low stability in aqueous media. However, some examples have shown that formulation of nanosuspension prevents hydrolysis of a particular drug compared to solution.[95] Thus, drug content of the formulation must be studied immediately after preparation to verify the chemical stability of the drug. Formation of impurities due to process and formulation parameters must be studied. The impurities can be identified using various techniques such as infrared spectroscopy (IR), high performance liquid chromatography (HPLC), and mass spectroscopy (MS). In addition, impurities related to the process must also be tested, e.g., for the possibility of zirconium content in the formulation if the media-milling method using zirconium oxide beads was used for preparation. The techniques used for characterization of nanoparticulate systems are summarized in Table 1.

Table 1. Methods for Assessing Properties of Nanoparticulate System

Property Relevant Analytical Technique	
Property	**Relevant Analytical Technique**
Particle size Dark field optical microscopy, dynamic light scattering, static light	Dark field optical microscopy, dynamic light scattering, static light, ultrasonic spectroscopy, turbidimetry, NMR, single particle optical sensing
Morphology	TEM, SEM, Atomic force microscopy
Surface charge	Electrophoretic light scattering, U-tube electrophoresis
Surface hydrophobicity	Hydrophobic interaction chromatography
Surface adsorbates	Electrophoresis
Density	Isopycnic centrifugation, sedimentation-FFF
Interior structure	Freeze fracture SEM, DSC, X-ray diffraction, NMR

NMR, nuclear magnetic resonance spectroscopy; TEM, transmission electron microscopy; SEM, scanning electron microscopy; FFF, fast-freezing fixation; DSC, differential scanning calorimetry.

In addition to characterization of the properties mentioned, additional characterization of the nanosuspension is required if surface modification of particles is performed. The parameters for which surface-modified nanosuspensions are evaluated include adhesion properties, surface hydrophilicity/ hydrophobicity, and interaction with body proteins. The adhesiveness of the drug nanoparticles is considered to be a major factor that contributes to increased bioavailability and reduced variability of absorption. Surface hydrophobicity determines the interaction with

the cells prior to phagocytosis and is a relevant parameter for adsorption of plasma proteins. This is considered to be an important parameter affecting in vivo organ distribution after intravenous injection. Separation by hydrophobic interaction chromatography (HIC) depends on the reversible adsorption of biomolecules according to their hydrophobicity, and HIC is widely used for the separation and purification of proteins in their native states.[96] The HIC technique is used for determining surface hydrophilicity/ hydrophobicity; hydrophilic particles pass through the column faster, and elution of hydrophobic particles is retarded.[97]

4. CONVERSION OF NANOSUSPENSION TO SOLID STATE

Nano sizing is now a well-established technique for enhancing the dissolution rate of drugs with low water solubility by increasing the surface area of particles. Despite their advantages, the stability of nanosuspension is a critical aspect that defines the safety and efficacy of the drug product. Stability issues related to nanosuspension include sedimentation or creaming, agglomeration, and crystal growth. The transformation of a nanosuspension into a solid product is often required for physical stability and/or patient convenience.[30] Particle growth may occur in a nanosuspension during manufacturing, storage, or shipping. To maintain particle size, surfactants are often used but they might not be able to maintain the particle size for the required period. Therefore, conversion of a nanosuspension to a solid form becomes essential if stable nanosuspension is unattainable. Solid dosage forms are convenient with regard to marketing. Thus, there is a current need to develop an efficient technique for converting nanosuspensions to solid forms while maintaining their performance characteristics. Various methods are available for this purpose. The acceptability of the method generally depends on its effectiveness in preserving particle size after processing. Methods that are commonly used for conversion of nanosuspension to dry state include spray drying, freeze drying (lyophilization), pelletization, and granulation.[95] The most common processes are freeze-drying and spray-drying.[22] Spray drying is widely used due to its simplicity and cost-effectiveness; it is generally preferred over lyophilization by the pharmaceutical industry to transform liquid nanosuspensions to dry products because it is faster and consumes less energy. In spray drying, nanoparticulate dispersion is atomized to fine droplets that evaporate in a warm air current to form dry particles. The driving force for drying is controlled by the liquid content and the difference between the inlet and outlet temperatures of the drying air. Chemical degradation of the drug due to heating is the foremost concern in spray drying. Nanosuspension of drugs like celecoxib and itraconazole successfully convert into nanocrystals by spray drying.[98, 99] Freeze drying is another convenient method of converting nanosuspension to a solid powder.[100] Freeze drying involves the nucleation and propagation of ice crystals (freezing) and a following sublimation process. When nanoparticulate dispersion is freeze dried, a temperature gradient inevitably develops, and nucleation begins in the area at the lowest temperature. After nucleation, the temperature gradient leads more liquid water molecules to rearrange themselves into the open structure of a solid lattice, resulting in the propagation of the freezing interface. While fast freezing results in polycrystalline structures that sometimes have defects, slow freezing allows water molecules to exclude foreign particles and eventually causes them to aggregate.[101] The freezing step is more important than the subsequent sublimation step, as the steric stabilization of polymers becomes inactive when nanocrystal dispersions are freeze dried. In the freeze-drying process, a cryoprotectant can be used to prevent aggregation. Lee and Cheng found that freezing rate is a critical factor in freeze drying and that it depends on the API concentration of the dispersion.[102] For a conversion of nanosuspension of drugs like 2-methoxyestradiol, naproxen, and loviride in its dry form Freeze drying is successfully used.[103-105]

To improve patient convenience, the powder can be filled in capsules or converted to tablets. A few reports are available on the conversion of nanosuspension into tablets.[97, 98, 106, 107] These studies have shown that the tablet formulations containing nanosized drug particles dissolve faster than the unmilled drugs. This suggests that

the conversion of a nanosuspension does not affect the properties of the drug. Although conversion to a dry state may provide the advantages of stability and/or patient convenience, it should not adversely affect the dissolution properties of the nanosuspension. Generally, various matrix formers are used in the process of converting a nanosuspension to a solid state. The selection of these matrix formers determines the utility of this approach. Thus, due consideration must be given to the excipients and processes which are used to enhance the stability of the nanosuspension formulation.

5. APPLICATIONS OF NANOSUSPENSIONS

Nanosuspensions are used to advantage in diverse dosages forms. Their small size and increased surface area leads to increased dissolution rates and increased bioavailability. In contrast, particulate nature of nanosuspension can result in targeting of monocyte phagocytic systems (MPSs), with unusual pharmacokinetic significances. Nanosuspensions can play a critical role as an enabling technology for molecules of low water solubility or permeability having significant activity as observed in in vitro studies. These molecules may pose problems at one or both of the following stages during new drug development processes:

- Formulation of an intravenously injectable product for preclinical in vivo evaluation to measure its toxicity and other pharmacokinetic characteristics.
- Improving absorption of the drug candidate from the gastrointestinal tract (GIT) which showed poor bioavailability during preclinical as well as clinical development studies.

As the particle size of nanosuspension is the range of 1–1000 nm, these formulations are suitable for application through various routes of administration like parenteral, oral, topical, pulmonary, and other targeted drug-delivery systems.

Oral

A route most which is most widely favored for drug administration is Oral drug delivery. But some drugs shows very limited bioavailability due to their poor solubility and absorption, and which eventually lowers their efficacy. For such cases, nanosuspension is most suitable option as it helps to improve the dissolution rate and absorption due to enhanced surface area and improved adhesiveness. Nanosuspension can make possible increased mucoadhesion, which may improve gastrointestinal transit time and cause increased bioavailability. When administration with the conversion of atovaquone micronized drug in atovaquone as a nanosuspension resulted in a 2.5 fold increase in oral bioavailability. The improvement in oral bioavailability can be accredited to the adhesiveness of the drug nanosuspension, increased surface area and saturation solubility.[108] Taste masking of a particulate system in oral delivery is also easy. Administration of the nanosuspension has been reported to enhance oral bioavailability of BMS-488043 in dogs compared to the conventional formulation containing the micronized crystalline drug substance.[109] Nanosuspension formulation also helps to avoid the effect of food on absorption, as observed for Emend (aprepitant) formulation in another study.[110]

Parenteral

A nanosuspension is an approach by which one can convert poorly soluble non-injectable drugs into a formulation suitable for IV administration. Although the production of nanosuspension for parenteral use is very precarious, recent developments in nanosuspension technology have proven its usefulness for injectable formulations. Nowadays techniques for preparation of nanosuspensions are now accurately controlled and have a capacity to develop uniform particles with greater control over maximum particle size. Injectable formulation of nimodipine nanosuspension proved better than commercial product (ethanol based) in terms of local irritation and phlebitis risks.[111] Lou et al. demonstrated that when formulated as a nanosuspension, oridonin showed stronger antitumor activity in mice compared to the free oridonin solution.[112] Zakir et al. demonstrated that the pharmacokinetic profiles of Amp B, when given in the nanosuspension formulation, were different compared to the corresponding raw drug.[113]

Ocular Delivery

Nanosuspension approach is a beneficial for drugs which shows very low solubility in lachrymal fluids. Nanosuspension is an ideal approach for ocular delivery of hydrophobic drugs due to their characteristic ability to improve saturation solubility of drugs. Kassem et al. developed a nanosuspension delivery system for certain glucocorticoid drugs.28 Gupta et al. designed a study to improve the bioavailability of forskolin via the influence of precorneal residence time and dissolution characteristics. They proved that the pH and thermoreversible polymeric in situ gel-forming nanosuspension with controlled drug release exhibited a greater potential for glaucoma therapy than the original formulation of the drug.[114] Ali et al. assessed ocular bioavailability of hydrocortisone nanosuspensions in albino rabbits using hydrocortisone solution as a control. Significantly higher bioavailability of hydrocortisone nanosuspensions was observed compared to the hydrocortisone solution. A sustained drug action was maintained for up to 9 h with the nanosuspensions compared to 5 h with the drug solution.[115]

Table 2. Reported Examples of Various Routes for Nanosuspension Technology.

Active	Route	Method Used	Used References
Amphotericin	Oral	High-pressure homogenization	[124]
Fenofibrate	Oral	High-pressure homogenization	[125]
1,3-dicyclohexylurea	Oral	Wet milling	[126]
AC88 and BA99	Oral	Wet milling	[124]
Nitrendipine	Oral	Precipitation-Ultrasonication	[127]
Hydroxycamptothecin I	Intravenous	Precipitation combined high pressure homogenization	[128]
Curcumin	Intravenous	High-pressure homogenization	[129]
Asulacrine (ASL)	Intravenous	High-pressure homogenization	[130]
Ornidone	Injectable	High-pressure homogenization	[131]
Fluticasone	Pulmonary	Wet milling	[116]
Budesonide	Pulmonary	High-pressure homogenization	[132]
Forskolin	Ocular	Wet crushing of crystals using a highperformance disperser	[114]
Amphotericin A	Ocular	Solvent displacement process	[133]
Hydrocotison	Ocular	Microfluidic nanoprecipitation and Wet milling	[115]
Diclofenec sodium	Transdermal	Homogenization followed by freeze-drying and ultrasonication	[134]
Hesperetin	Dermal	High-pressure homogenization	[135]

Pulmonary

Nanosuspensions have confirmed beneficial for delivering drugs that exhibit low solubility in pulmonary secretion. Nowadays , available tactics for pulmonary delivery such as aerosols or dry powder inhalers holds some drawbacks, such as incomplete diffusion at required site, less residence time, etc., That all problems can be overcome by nanosuspensions. Success formulation which overcome aforementioned problem of pulmonary delivery is Fluticasone and budesonide.[116] Po-Chang Chiang et al. evaluated aerosol delivery of fluticasone nanosuspension for pre-clinical pulmonary delivery. Results showed that the aerosol delivery of fluticasone with

nanosuspension was as effective as intranasal (IN) dosing and was able to attain dose-dependent lung deposition. Using lipopolysaccharide model, Po-Chang Chiang et al. demonstrated pulmonary-targeted preclinical efficacy and differentiated the side effects after intratracheal administration of nanosuspensions of inhaled corticosteroids. However, it was only suitable at sub maximum efficacy levels.[117]

Dermal

The nanocrystalline form shows enhanced saturation solubility, resulting in improved diffusion of the drug into the skin. With the properties, such as increased penetration into a membrane, enhanced permeation, and bio adhesiveness, this might be very suitable for dermal application. Pio et al. showed increased permeability of Diclofenec sodium nanosuspension across the skin compared to the control for transdermal delivery.[118] Kobierski et al. developed nanosuspensions of the anti-oxidant resveratrol for dermal application.[119] Pardeike and Muller studied dermal application of PX-18 and PX-13 nanosuspension for psoriasis treatment. The results of the EPISKIN test indicated that the nanosuspension was not irritating to the skin.[120]

Targeting

The particle size is main factor on which uptake of drug nanoparticles depends. By changing the surface properties of nanoparticles, there in vivo behavior can be altered; thus they may use in targeted delivery systems. With the preparing stealth of nanocrystals or by preparing smartcrystals (i.e., drug particles less than 100 nm) We can solved a problem of phagocytotic uptake of nanocrystals. Due to the simplicity of these methods, nanosuspension is a commercially viable option for targeted drug delivery. Mucoadhesive nanosuspension has been reported for targeting Cryptosporidium parvum.[121] Surface properties of particle e.g., surface hydrophobicity, surface charge, presence, and concentration of certain functional groups are responsible for their structure distribution. Thus, nanocrystals coated with Tween 80 can be used for brain targeting. Atovaquone nanocrystals coated with Tween 80 were used to treat toxoplasmosis, and the parasites were efficiently eradicated in brain.[122] Shegaonkar and Singh reported using nevirapine nanosuspension for HIV reservoir targeting. Macrophage uptake studies have confirmed enhanced cellular uptake for nanosized nevirapine with no added cytotoxicity, while gamma scintigraphy studies have shown that nanosuspensions can be used to target the spleen, thymus and lungs, which represent anatomical viral reservoirs.[123] In addition to these examples, clinical applications of nanocrystal technology have been summarized in an excellent review by Junghanns and Muller.[136] Applications of nanosuspensions have been reported for many routes of administration, and a few examples are summarized in Table 2.

6. CONCLUSION

Nanosuspensions looking to be a exclusive and yet commercially viable approach to opposing problems such as poor bioavailability which are mainly connected with the delivery of hydrophobic drugs, including those which are poorly soluble in aqueous as well as organic media. Developing techniques such as media milling and high-pressure homogenization have been successfully employed for large-scale production of nanosuspensions. The advances in developing techniques using emulsions or microemulsions as templates have provided still simpler approaches for production but with limitations. Additional investigation in this regard is still required. Some attractive features have widened the applications of nanosuspensions for various routes, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing. The applications of nanosuspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been become conscious. However, their applications in buccal, nasal and topical delivery are still awaiting exploration. The development of stealth nanosuspensions fastened with functionalized surface coatings capable of eliciting passive or active targeting as per the requirement can be regarded as the future step in nanosuspension research.

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