Review Article

Nanosuspension: An approach to enhance solubility of drugs

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Abstract

One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Formulation as nanosuspension is an attractive and promising alternative to solve these problems. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. This review article describes the preparation methods, characterization, and applications of the nanosuspension.

Key words: Bioavailability, colloidal dispersion, drug delivery, nanosuspension, solubility

INTRODUCTION

A range of parameters like solubility, stability at room temperature, compatibility with solvent, excipient, and photostability play a critical role in the successful formulation of drugs. Till date, more than 40% of the new chemical entities being generated through drug discovery programs are lipophilic or poorly water-soluble compounds.[1,2] Many formulation approaches are available to solve the problems of low solubility and low bioavailability of drugs. The conventional approaches include micronization, use of fatty solutions, use of penetration enhancer or cosolvents, surfactant dispersion method, salt formation, precipitation, etc., but still, these techniques having limited utility in solubility enhancement for poorly soluble drugs. Additional approaches are vesicular system like liposomes, dispersion of solids, emulsion and microemulsion methods, and inclusion complexes with cyclodextrins, which show beneficial effect as drug delivery system but major problems of these techniques are lack of universal applicability to all drugs.[3] Over the last decades, nanoparticle engineering has been developed and reported for pharmaceutical applications.[4] Nanotechnology can be used to solve the problems associated with various approaches described earlier. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} m. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology.[5] Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants.[6] Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion.[7] These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is useful for molecules with poor solubility, poor permeability, or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries. The suspensions can also be lyophilized and into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others.[8] In

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the present review, we are mainly focusing on the different methods of preparation associated merits, demerits, and its pharmaceutical application as drug delivery system.

ADVANTAGES OF NANOSUSPENSION[9]

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting

PREPARATION OF NANOSUSPENSION

For the preparation of nanosuspensions, mostly two methods namely "Bottom up technology" and "Top down technology" are used, as shown in Figure 1.[10] Bottom up technology is an assembling method to form nanoparticles like precipitation, microemulsion, melt emulsification method and top down technology involves the disintegration of larger particles into nanoparticles, examples of which are high-pressure homogenization and milling methods. The principles of these methods are described in detail and their merits and demerits are shown in Table 1.[11,12]

Precipitation Method

Precipitation method is a general method used to prepare submicron particles of poorly soluble drugs.[13-15] In this method, drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous

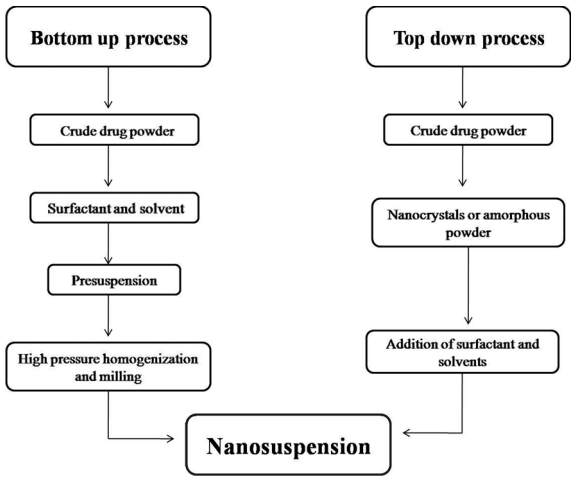

Figure 1: Approaches for preparation of nanosuspension

Table 1: Preparative techniques for nanosuspension with merits and demerits

Technique	Merits	Demerits
Precipitation	Simple process Stable products Low need of energy Low cost of equipment Ease of scale up	Growing of drug crystals needs to be limit by surfactant addition Drug must be soluble at least in one solvent Narrowly applying space, wide size distribution and potential toxicity of nonaqueous solvents
High-pressure homogenization	Simple technique General applicability to most drugs Useful for formation of very dilute as well as highly concentrate nanosuspension Aseptic production possible Low risk of product Contamination ease of scale-up	High number of homogenization cycles Pretreatment of micronized drug particles and presuspending materials before subjecting it to homogenization Possible contamination of product could occur from metal ions coming through wall of the homogenizer
Media milling	High flexibility in handling Very few batch to batch variation in particle size High flexibility in handling large quantities of drugs Ease of scale up	Possible erosion of material from the milling pearls Require milling process for hours to days Prolonged milling may induce the formation of amorphous lead to instability
Dry cogrinding	Easy process Require short grinding time No organic solvent	Generation of residue of milling media
Liquid emulsion/microemulsion template	Simple process Small size particles Stable products Low need of energy High drug solubilization Uniform particle distribution Ease of manufacture	Use of high amount of surfactant and stabilizers Use of hazardous solvent
Melt emulsification	Avoidance of organic solvents compared to the solvent diffusion	Formation of large particles Solvent diffusion

or crystalline drug. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size.[16]

High-Pressure Homogenization

This technique involve the following three steps: First, drug powders are dispersed in a stabilizer solution to form presuspension; after that, presuspension is homogenized by high pressure homogenizer at a low pressure sometimes for premilling; and finally homogenized at a high pressure for 10 to 25 cycles until the nanosuspensions are formed with desired size.[9]

Homogenization in Aqueous Media (Dissocubes)

Dissocubes technology was developed by Muller in 1999. The instrument can be operated at pressure varying from 100 to 1 500 bars (2 800 – 21 300 psi) and up to 2 000 bars with volume capacity of 40 ml (for laboratory scale). For preparation of nanosuspension, it is essential to prepare a presuspension of the micronized drug in a surfactant solution using high-speed stirrer. According to Bernoulli's Law, the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3 cm to 25 μm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this, water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogenizer and homogenization pressure. Preprocessing like micronization of drug and high-cost instruments increases the overall cost of dosage form. Various drugs like Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine And Dexamethasone were prepared as nanosuspensions using this method.[5]

Homogenization in Nonaqueous Media (Nanopure)

Nanopure is suspension homogenized in water-free medium. It is "deep-freeze" homogenization where the drug suspensions in nonaqueous medium are homogenized at 0°C or sometimes below the freezing point. Because of very high boiling point and low vapor pressure of water, oils, and fatty acids, the drop of static pressure is not enough to begin cavitation in nanopure technology.[17] Other homogenization technologies and patents on the homogenization processes are shown in Table 2.[18]

Milling Techniques

Media milling

Liversidge *et al.* had a patent on nanocrystal technology.[19] In this technique, drugs are subjected to media milling for nanoparticle production. Effect of impaction between the milling media and drugs gives essential energy for disintegration of the microparticulate system into nanoparticles. In this process, the chamber of milling is charged with the milling media involving drug, stabilizer, and water or suitable buffer, which is rotated at a very high shear rate to generate suspension. Residues left behind in the finished product is a major problem of this method.[20]

Table 2: Homogenization technologies and patents on the homogenization processes

Technology	Company	Patent number
Dissocubes	SkyePharma	US 5,858,410
Nanopure	PharmaSol	PCT/EP00/0635
Nanocrystal™	Élan Nanosystems	US 5,145,684
Nanomorph™	Soligs/Abbott	D 1963 7517
Nanoedge™	Baxter	US 6,884,436
Hydrosol	Novartis (prev. Sandoz)	GB 22 69 536 GB 22 00 048

Dry cogrinding

Since many years, nanosuspensions are prepared through wet grinding processes by using pearl ball mill. Nowadays, nanosuspensions can be prepared by dry milling methods. Stable nanosuspensions are prepared by using dry grinding of poorly soluble drug with soluble polymers and copolymers after dispersing in liquid medium. Itoh *et al.* have described the colloidal particles formation of many poorly water-soluble drugs like nifedipine, griseofulvin, and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizer.[21-23]

Lipid emulsion/microemulsion template

Nanosuspensions are also obtained by just diluting the emulsion, formed by using a partially water-miscible solvent as the dispersed phase. The emulsion technique is applicable for drugs which are either partially water miscible or soluble in volatile organic solvents. Additionally, microemulsion templates can also produce nanosuspensions. Microemulsions are dispersions of two immiscible liquids like water and oil and stabilized thermodynamically by surfactant or cosurfactant. The drug is either loaded into preformed or internal phase of microemulsion and can be saturated by intimate mixing of drugs.[20] Griseofulvin nanosuspension is prepared by the microemulsion technique by using water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate.[24]

Microprecipitation – High-pressure homogenization (Nanoedge)

Nanoedge is a combination of microprecipitation and high-pressure homogenization techniques. Method includes precipitation of friable materials followed by fragmentation under high shear and/or thermal energy.[25,26] The preparation method of nanoedge is shown in Figure 2.[27]

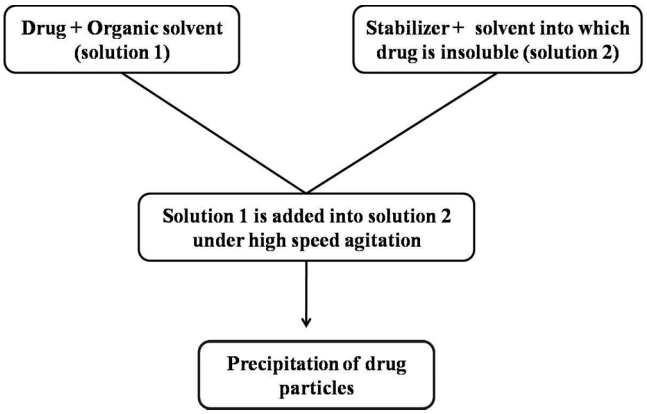

Figure 2: Method for preparation of nanoedge

Melt emulsification method

Solid lipid nanoparticles are mainly prepared by melt emulsification method. Kipp and co workers firstly prepare nanosuspensions of ibuprofen by using melt emulsification method. It is a four-step procedure. Drug is first added to aqueous solution having stabilizer. The solution is heated at temperature higher than the melting point of the drug and then homogenized by high-speed homogenizer for the formation of emulsion. The temperature is maintained above the melting point of the drug during overall process. Finally, the emulsion is cooled to precipitate the particles. The particle size of nanosuspension mainly depends on parameters like drug concentration, concentration and type of stabilizers used, cooling temperature, and homogenization process.[28]

Nanojet technology

This technique is also called opposite stream technology, uses a chamber where a stream of suspension is divided into two or more parts. Both streams are colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Dearns had prepared nanosuspensions of atovaquone using the microfluidization process. The major disadvantage of this technique is the high number of passes through the microfluidizer and that the product obtained contains a relatively larger fraction of microparticles.[29]

Supercritical fluid methods

Various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process are used to produce nanoparticles. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. By using RESS method, Young *et al.* prepared cyclosporine nanoparticles having diameter of 400 to 700 nm. In the PCA method, the drug solution is atomized into the CO_2 compressed chamber. As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution becomes supersaturated.[30]

CHARACTERIZATION TECHNIQUES

The particle size, particle size distribution, and zeta potential affect the safety, efficacy, and stability of nanodrug delivery systems as well as dissolution performance is also altered by solid state of nanoparticles. Thus, characterization of nanoparticles plays a great role in forecasting *in vitro* and *in vivo* performance of nanodrug delivery systems. *In vivo* pharmacokinetic performance and biological function of nanosuspension strongly depends on its particle size and distribution, particle charge (zeta potential), crystalline state, and particle morphology.

Mean Particle Size and Particle Size Distribution

The mean particle size and particle size distribution affects saturation solubility, dissolution rate, physical stability, and *in vivo* performance of nanosuspensions.[9] The particle size distribution and its range named polydispersity index (PI) can be determined by laser diffraction (LD), photon correlation spectroscopy, microscope, and coulter counter.[31] PI gives the physical stability of nanosuspensions and should be as lower as possible for the long-time stability of nanosuspensions. A PI value of 0.1 to 0.25 shows a fairly narrow size distribution, and PI value more than 0.5 indicates a very broad distribution.[32] LD can detect and quantify the drug microparticles during the production process. It also gives a volume size distribution and can be used to measure particles ranging from 0.05 up to 2 000 μm.[33] The coulter counter gives the absolute number of particles per volume for the different size classes. It is more efficient and suitable than LD to quantify the contamination of nanosuspensions.[30]

Crystalline State and Particle Morphology

Polymorphic or morphological changes of nanosized particles can be checked by assessing the crystalline state and particle morphology.[30] As nanosuspension requires high-pressure homogenization, change in crystalline structure of formulation occurs which may be converted to either amorphous or other polymorphic forms.[31] Alteration in the solid state of the drug particles and the extent of the amorphous portion is determined by X-ray diffraction analysis[34] and supplemented by differential scanning calorimetry analysis.[30]

Surface Charge (Zeta Potential)

Surface charge properties of the nanosuspensions are studied through zeta potential. The value of particle surface charge indicates the stability of nanosuspensions at the macroscopic level. A minimum zeta potential of ±30 mV is required for electrostatically stabilized

nanosuspensions[35,36] and a minimum of ±20 mV for steric stabilization.[37] The zeta potential values are commonly calculated by determining the particle's electrophoretic mobility and then converting the electrophoretic mobility to the zeta potential.[38] Electroacoustic technique is also used for the determination of the zeta potential in the areas of material sciences.[39]

PHARMACEUTICAL APPLICATION OF NANOSUSPENSION

By using postproduction processing, nanosuspensions are prepared into various dosage forms. Nanosuspension increases dissolution rate and absorption of drug due to smaller particle size and larger surface area. The available marketed drugs in the form of nanosuspensions along with their routes of administration are mentioned in Table 3.[12]

Oral Drug Delivery

Poor solubility, incomplete dissolution, and insufficient efficacy are the major problem of oral drug administration. Due to smaller particle size and much larger surface to volume ratio, oral nanosuspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs.[40] In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugs.[41] The nanosuspension have advantages like improved oral absorption, dose proportionality, and low intersubject variability. By using standard manufacturing techniques, drug nanosuspensions can be simply incorporated into various dosage forms like tablets, capsules, and fast melts. The nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over the period of 24 hours.[42]

Table 3: Available marketed drugs in the form of nanosuspension with their route of administration

Route	Drugs	Therapeutic class	Company/author
Oral route	Carbamazepine	Psycholytic	D. Douroumis
	Megestrol acetate	Steroid hormone	Par Pharmaceuticals
	Paliperidone palmitate	Anti schizophrenia	Johnson and Johnson
	Insulin	Diabetes	BioSante
	Ketoprofen	Analgesic	Remon J. P.
	Azithromycin	Antimicrobial	Dianrui Zhang
	Albendazole	Anthelmintic drug	Mittapalli P. K.
	Tarazepide	Selective CCKa-antagonist	C. Jacobs
	Griseofulvin	Antifungal	Boris Y. Shekunov
	Mitotane	Adrenal Cortex Hormones	Michele Trotta
	Cilostazol	cagent	Jun-ichi Jinno
	Aphidicolin	Antileishmanial	O. Kayser
	Buparvaquone	Antibiotic	Müller R. H.
	Fenofibrate	Lipid lowering	SkyePharma
	Cytokine inhibitor	Crohn's disease	Elan Nanosystems
	Emend	Anti-emetic	Elan Nanosystems
	Rapamune	Immunosuppressant	Elan Nanosystems
	Probucol	Lipid lowering	Jyutaro Shudo
	Danazol	Hormone	Rogers T. L.
Parental	Naproxen	Anti-inflammatory	Anchalee Ain-Ai
Intravenous	Loviride	Antivirotic	B. Van Eerdenbrugh
	Clofazimine	Antimycobacterials	K. Peters
	Oridonin	Anticancer	Lei Gao
	Ascorbyl palmitate	Antioxidant	Veerawat T.
	Dihydroartemisinin	Antimalarial	Jiraporn C.
	Omeprazole	Proton pump inhibitor	Jan Möschwitzer
	Thymectacin	Anticancer	Elan Nanosystems
	Paclitaxel	Anticancer	American Bioscience
Ophthalmic	Hydrocortisone	Glucocorticoid	M. A. Kassem
	Prednisolone		
	Hexadecadrol		
Pulmonary	Budesonide	Asthma	Jerry Z. Yang
	Fluticasone		
Intrathecal	Busulfan	Anticancer	SkyePharma
Topical	Silver	Eczema	Nucryst

Parental Drug Delivery

The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc. To solve the above problems, the nanosuspension technology is used. Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden.[43] Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal clofazimine in *Mycobacterium avium*-infected female mice.[44] Rainbow *et al.* showed that intravenous nanosuspension of itraconazole enhanced efficacy of antifungal activity in rats relative to the solution formulation.[45]

Pulmonary Drug Delivery

For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid has been successfully prepared in the form of nanosuspension for pulmonary delivery.[46] Aqueous suspensions of the drug can be easily nebulized and given by pulmonary route as the particle size is very small. Different types of nebulizers are available for the administration of liquid formulations. Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc.[47]

Ocular Drug Delivery

Nanosuspensions are used in ocular delivery of the drugs for sustained release. Liang and co-workers prepared cloricromene nanosuspension for ocular delivery using Eudragit. Experiment showed higher availability of drug in aqueous humor of rabbit eye. Thus, nanosuspension formulation offers a promising way of improving the shelf-life and bioavailability of drug after ophthalmic application.[37]

Targeted Drug Delivery

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter *in vivo* behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly.[48] Kayser formulated an aphidicolin nanosuspension that improved the drug targeting to macrophages which were Leishmania infected. He stated that the drug in the form of nanosuspension had EC_{50} of 0.003 μg/ml, whereas the conventional form had 0.16 μg/ml.[49] Scholer *et al.* described an enhanced drug targeting to brain in the treatment of toxoplasmic encephalitis using an atovaquone nanosuspension.[50]

CONCLUSION

Nanosuspensions are distinctive and commercially feasible approach to solve the problems of hydrophobic drug such as poor solubility and poor bioavailability. For large-scale production of nanosuspensions, media milling and high-pressure homogenization technology have been successfully used. Striking characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of postproduction processing, have widened the applications of nanosuspensions for various routes of administration. The applications of nanosuspensions in oral and parental routes have been very well established, although applications in pulmonary and ocular delivery have to be evaluated. However, their delivery through buccal, nasal, and topical delivery is yet to be done.

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