

Nano Suspension Drug Delivery System: An Overview

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Abstract

Nano suspensions have gained great interest in the last decade as a formulation tool for poorly soluble drugs. By decreasing particle sizes nano suspensions enhance dissolution rate and bioavailability of the drug. Recently, nanoscale systems have received much interest as a way to resolve solubility issues because of their cost-effectiveness and technical simplicity compared to liposomes and other colloidal drug carriers. They have also been used for drug targeting. Formulation of lipophilic drugs into nano suspensions improves their stability and also enhances their bioavailability significantly. Nano suspensions have unique advantages for which they have been utilized for the production of dosage forms suitable for administration through oral, parenteral, ocular and pulmonary routes. Nano suspensions can be manufactured using the 'Top Down' or 'Bottom's Up' technology and employ a variety of components including surfactants for stability purposes and polymers for sustained release of drug in certain formulations. This paper reviews recent patents, methods of preparation and marketed products with their importance or status, novel researches and characterization implemented till date to overcome the challenges in poorly water soluble drugs.

Keywords: Bioavailability; Controlled Drug delivery; Dissolution Rate; Lipophilic Drugs; Nano suspensions; Patents

Abbreviations: EP: European Patent; US: United States Patent; WO: World Intellectual Property Organization (WIPO)

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Introduction

The formulation of poorly water soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately more than 40% of the new chemical entities being generated through drug discovery programmes are poorly water-soluble. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. A pharmaceutical nano suspension is defined as very finely dispersed solid drug particles in an aqueous vehicle, stabilized by surfactants, for either oral and topical use or parenteral and pulmonary administration, with reduced particle size (Average particle size ranges from 200-600nm), leading to an increased

dissolution rate and therefore improved bioavailability. These can be used to enhance the solubility of drugs that are poorly soluble in aqueous 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. Nano suspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption [1, 2]. Apart from this, nano suspensions have some following advantages: Firstly, drugs no longer need to be in the soluble form. It is effective for those molecules insoluble in oils. Secondly, the high drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose. Thirdly, nano suspensions can increase the physical and chemical stability of drugs as they are actually in the solid state. Finally, nano suspensions can provide the passive targeting. One of the critical problems associated with poorly soluble drugs is too low bioavailability and/or erratic absorption [3]. The problem is even more intense for drugs such as itraconazole and carbamazepine (belonging to Biopharmaceutical Classification Scheme Class II (BCS class II)) as classified by BCS System as they are poorly soluble in both aqueous and organic media, and for those drugs having a log P value of 2. The performance of these drugs is dissolution rate-limited (for Class II and III drugs) and is affected by the fed/fasted state of the patient. There are number of formulation approaches that can be used to resolve the problems associated with the low solubility and low bioavailability of these class II drugs. This review focuses on the various aspects of nano suspensions and their potentials as promising strategy in drug delivery [4, 5].

Advantages of Nano suspension [6, 7]

- It can be applied for the poorly water soluble drugs.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution and tissue targeting can be achieved by IV route of administration.
- Oral administration of nano suspensions provides rapid and improved bioavailability.

- Higher bioavailability and more consistent dosing in case of ocular administration and inhalation delivery.
- Long-term physical stability due to the presence of stabilizers.
- Nano suspensions can be incorporated in tablets, pellets, hydrogels and suppositories.

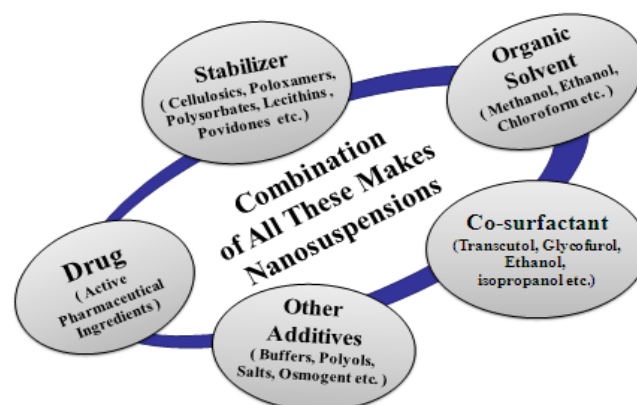


Figure 1: Schematic representation of composition of Nano suspensions

Disadvantages of Nano suspension [6, 7]

- Physical stability, sedimentation and compaction can causes problems.
- It is bulky sufficient care must be taken during handling and transport.
- Uniform and accurate dose cannot be achieved unless suspension.

Method of Preparation

Top-down approaches start from a larger unit of material, slicing or milling this bulk material, to obtain smaller units of the desired shape. Bottom-up approaches arrange smaller sub-units or components (e.g., atoms or molecules) into larger and functionally richer, complex structures. The colloidal dispersion is an example of this method. These manipulations of the size and shape of structures, devices, and systems, produce new structures, devices, and systems with at least one novel or superior characteristic or property from those expressed at

larger scales [8]. The following methods are used to prepare nano suspension [9-13].

1. Bottom Up Technology

Bottom-up technologies are build-up nanoscale particles from molecular solutions.

- Precipitation Method

2. Top Down Technology

- Milling Technique
 - o Media Milling (Nan crystal or Nano systems),
 - o Dry Co-grinding
- High Pressure Homogenization
 - o Homogenization in water (Disso cubes)
 - o Homogenization in nano queous media (Nano pure)

- o Combined precipitation and homogenization (Nano edege)
- o Nano jet technology

3. Melt Emulsification Method

4. Emulsification-Solvent Evaporation Technique

5. Super Critical Fluid (SCF) Method

- Rapid Expansion of Supercritical Solution (RESS)
- Supercritical Antisolvent (SAS)
- Precipitation with Compressed Antisolvent Process (PCA)
- Solution enhanced dispersion by SCF (SEDS)
- Gas Anti Solvent Recrystallization (GAS)

6. Other Methods

- Emulsion as a template
- Micro emulsions as templates
- Hydrosol method

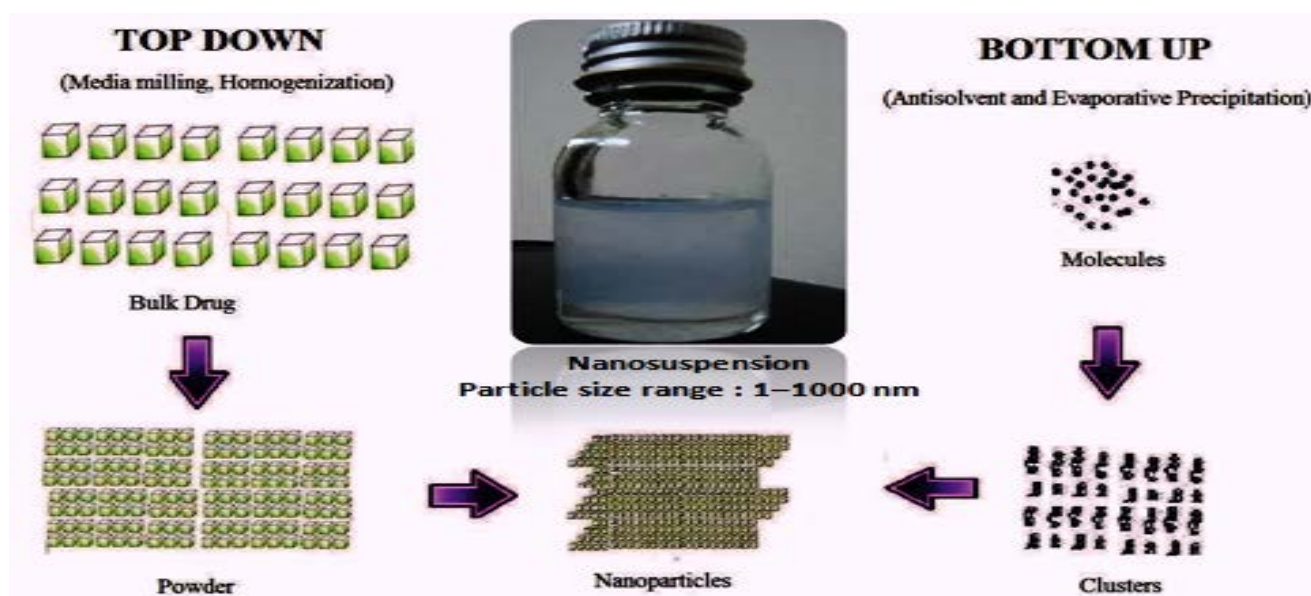


Figure 2: Schematic representation of preparation of Nano suspension.

Patents on Nano Suspension

From these patents it is clear that nano suspensions have tremendous potential for delivery of all compounds with low water solubility. Some of these patents are very informative and disclose background on the formulation, clinical data and

review of controlled drug delivery as summarized in Table 1. A review of the patent literature by santus describes the patent controlled nano suspensions drug delivery design from 1950 to 2000. Summary of granted patents based on Nano suspension drug delivery systems given in Table 1 [14-30].

Table 1: List of Various Patents on Nano Suspension

Patent No.	Contents	Ref.
US5726164 (1998)	A pharmaceutical nanosuspensions composition for the intravenous administration of the sparingly soluble composed of N-benzyol staurosporin derivative, Poloxamer, ethanol, water, lecithin, glycerol and sorbitol.	[14]
EP0734955 (1998)	A Resuspension optimization method for storing nanoparticulate suspensions of photographically useful chemical substance in the form of solid particle dispersion.	[15]
US5858410 (1999)	Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution, prepared by ultrasonication, pearl milling and ball milling techniques.	[16]
US0170311 (2003)	A microfluidization process of manufacturing a stable controlled-release nanosuspension for delivery of a biologically active agent into the bloodstream of a subject is disclosed.	[17]
US0096000 (2003)	Sustained release of hydrophobic agents may be achieved by incorporation of the agents into liposomes and microspheres. The encapsulation nanosuspension may be used as the aqueous solution in the formation of the liposomes and microspheres.	[18]
US0202094 2005	A nanosuspension provides compositions comprising dispersions of anti-retroviral agents for increased CNS delivery.	[19]
US0280761 (2006)	A method of manufacturing a stable nanosuspension for delivery of a biologically active agent, particularly vitamin B-12 or nanofluidized b-12, into the bloodstream of a subject is disclosed and process for treating pernicious anemia.	[20]
US0003487 (2007)	A pharmaceutical composition, constituting a spray suspension includes at least one liquid excipient and at least one solid excipient substantially insoluble in the liquid excipient, and at least one pharmaceutical active ingredient. A method of preparing porous suspension particles includes wet or dry-milling, spray drying and aggregating.	[21]
US0107736 (2008)	A nanosuspension is directed at a pharmaceutically active nanoparticles suspension that may be optically clear.	[22]
US0293796 (2008)	Parenteral and oral nanosuspension formulations of benzimidazoles	[23]
US0294357 (2009)	A method for concentrating a nanosuspension including nanopowder particles suspended in a liquid and controlling the dispersion of the nanopowder particles in the liquid.	[24]
US0047297 (2010)	Provided are cosmetic preparations for topical application, containing nanocrystals of cosmetic actives leading to an increased bioactivity of the molecules in the skin and methods of making the cosmetic preparations produced by a combination process of low-energy pearl milling.	[25]
US0190245 (2011)	Itraconazole nanosuspension with antifungal medication to be administered via inhalation with improved impurity profile and safety.	[26]
US0124702 (2011)	Oral nanosuspension of a poorly soluble drug via microfluidization process	[27]

WO080148 (2011)	An aqueous intravenous amiodarone nanosuspension with markedly decreased adverse effects.	[28]
WO151418 (2011)	A nanosuspension formulation comprising particles of at least one functional ingredient dispersed in a hydrophobic phase comprising a polydimethylsiloxane phase that can be used, e.g., in the pharmaceutical, cosmetics and food industry, in agriculture as well as for technical applications.	[29]
US0155802 (2013)	Compositions and methods for preparing nanoformulations (e.g., nanosuspension, nanoemulsion or another small particle system) and systems for nano-delivery using focused ultrasonic acoustics.	[30]

Recent Advance Novel Researches in Nano Suspension

Some of these articles are very informative and disclose background on the formulation, clinical data and review of controlled nano suspensions drug delivery. These articles further provide an insight into various commercial platform technologies for oral controlled drug delivery.

Kocbek P et al. had investigated nano suspensions for enhancing the dissolution of poorly soluble drugs, ibuprofen were prepared by melt emulsification method where usage of organic solvents in the preparation of suspension are avoided, and using tween80 and PVP K25 as stabilizers in combination yields smallest average particle size and increased dissolution rate more than 65% compared to micronized drug [31].

Ali HS et al. researched on hydrocortisone nano suspensions for ophthalmic delivery by micro fluidic nano precipitation method and wet milling methods respectively, which are characterised for particle size, shape, and zeta potential. Crystallinity was studied using x-ray diffraction, Differential Scanning Calorimetry (DSC). Sustained action was shown by nano suspension compared to drug solution when checked for ocular bioavailability by measuring intra ocular pressure [32].

Dengning X et al. prepared and characterize stable nitrendipine nano suspensions using the precipitation-ultrasonication method for enhancement of dissolution and oral bioavailability. The effects of five important process parameters includes (i) the concentration of PVA in the anti-solvent (ii) the concentration of nitrendipine in the organic phase (iii) the precipitation temperature (iv) the power input and the time length of

ultrasonication on the particle size of nano suspensions were investigated systematically and (v) the optimal values were 0.15%, 30 mg/ml, below 3°C, 400W and 15 min, respectively. The particle size and zeta potential of nano crystals were 209nm (± 9 nm) and -13.9 mV (± 1.9 mV), respectively. The morphology of nano crystals was found to be flaky in shape by Scanning Electron Microscopy (SEM) observation. The X-ray powder diffraction and Differential Scanning Calorimetry (DSC) analysis indicated that there was no substantial crystalline change in the nano crystals compared with raw crystals. The in vitro drug release rate of nitrendipine was significantly increased by reducing the particle size. The in vivo test demonstrated that the Cmax and AUC0→12 values of nano suspension in rats were approximately 6.1-fold and 5.0-fold greater than that of commercial tablets, respectively [33].

Francesco L et al. prepare Diclofenac nano suspensions. The role of crystalline form and preparation procedure in nano suspension formulation to optimize dissolution properties of Lipophilic, poorly soluble drugs was performed on diclofenac which exist in different crystalline and characterized for particle size, size distribution, morphology, and thermal behavior of different formulations studied using Scanning Electron Microscopy (SEM), X-ray diffraction, Differential Scanning Calorimetry (DSC) and proved drug dissolution rate majorly enhanced by drug solubility in physiological fluids of body which depend on crystal form of drug [34].

Thakkar HP et al. prepare nano suspensions of olmesartan medoxomil for bioavailability enhancement by using media milling methods followed by its lyophilization using mannitol

as a cryoprotectant. Characterization of the prepared nano suspension was done with respect to particle size, zeta potential, saturation solubility, dissolution rate, morphology study, in-vitro and ex-vivo drug diffusion study etc [35].

Mou D et al. invented potent dried drug nano suspensions for oral bioavailability enhancement of poorly soluble drugs,

itraconazole with pH-dependent solubility by using spray drying methods, and characterization of suspension was done by Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), X-ray diffraction studies. Stability of suspension was checked using different stabilizers like HPMC [36].

Table 2: Recent advance marketed nano suspensions formulations reported and marketed by now

Drugs	Therapeutic use / Class	Author/ Pharma company	Routes	Marketed Status
Danazol	Hormone	Rogers T. L	Oral	Reported
Cilostazol	Anti-platelet agent	Jun-ichi Jinno	Oral	Reported
Calcium phosphate	Mucosal vaccine adjuvant for herpes	BioSant	Oral	Phase I
Morphine sulfate	Psychostimulant drug	King Pharmaceuticals	Oral	Marketed
Griseofulvin	Antifungal	Boris Y. Shekunov	Oral	Reported
Aprepitant	Anti-emetics	Elan Nanosystem	Oral	Marketed
Cytokine Inhibitor	Crohn's disease	Elan Nanosystem	Oral	Phase II
Sirolimus	Immunosuppressant	Elan Nanosystem	Oral	Marketed
Panzem NCD	Recurrent glioblastoma	EntreMed	Oral	Phase II
Ketoprofen	Analgesics	Remon J. P.	Oral	Reported
Buparvaquone	Antibiotics	Mullar R. H.	Oral	Reported
Tricor	Lipid lowering	Skypharma	Oral	Marketed
Paliperidone palmitate	Anti-schizophrenia	Johnson and Johnson	Oral	Phase III
Silver	Eczema	Nucryst	Topical	Phase III
Budesonide	Asthma	Jerry Z. Yang	Pulmonary	Reported
Busalfen	Anticancer	Skypharma	Intrathecal	Phase I
Naproxen	Anti-inflammatory	Anchalee Ain-Ai	Oral/parenteral (I.P)	Reported
Omeprazole	Proton pump inhibitors (PPIs)	Jan Moschwitzter	Parental (I.V)	Reported
Ascorbyl palmitate	Ascorbyl palmitate	Veerawat T.	Parental (I.V)	Reported
Oridonin	Leukemia (Anticancer)	Lei Gao	Parental (I.V)	Reported
Dihydro-artemisinin	Antimalarial	Jiraporn C.	Parental (I.V)	Reported
Diagnostic agent	Imaging agent	Elan Nanosystem	Parental (I.V)	Phase VII
Loviride	Antiviral	B.Van Eerdenbrugh	Parental (I.V)	Reported
Paclitaxel	Leukemia (Anticancer)	American Bioscience	Parental (I.V)	Marketed
Clofazimine	Antimycobacterium	K. Peters	Parental (I.V)	Reported
Thymectacine	Leukemia	Elan Nanosystem	Parental (I.V)	Undisclosed
Hydrocortisone	Glucocorticoid	M. A. Kassem	Ophthalmic	Reported
Prednisolone	Glucocorticoid	M. A. Kassem	Ophthalmic	Reported

Characterization of Nano suspensions

Essential characterization parameters for nano suspensions are in-vitro and in-vivo or clinical procedures. A number of techniques have been used to characterize nano suspensions and determine the various feasibility or flexibility of their formulation process [37-42].

1. In-Vitro Evaluations

- Size and size distribution
- Particle charge (zeta potential)
- Crystalline state and Particle Morphology
- Dissolution velocity and saturation solubility
- Stability of Nano suspensions

2. In-Vitro Evaluations

The in vivo evaluation of the nano suspensions is specific to drug and route of administration. Most commonly the formulation was given by required route of administration and the plasma drug levels were estimated using HPLC-UV visible spectrophotometry.

- Adhesion properties (in case of mucoadhesive particles)
- Surface hydrophilicity/hydrophobicity (determines interaction with cells prior to phagocytosis)
- Interaction with body proteins
- Sterility and Pyrogenicity

Applications of Nano Suspension Formulations

1. Parenteral Administration

The parenteral route of administration provides a quick onset of action, rapid targeting and reduced dosage of the drug. It is the preferred route for drugs undergoing first-pass metabolism and those that are not absorbed in the GIT or degraded in the GIT. One of the important applications of nano suspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic cosolvents, improving the therapeutic effect of the drug available as conventional oral formulations

and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages.

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). Nano suspensions 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 nano suspension formulation. The therapeutic effect was significantly enhanced, which indicated higher bioavailability. This was due to the faster dissolution (90% in 20 min) of the lyophilized nano suspension powder when compared with the dissolution from a coarse powder (15% in 20 min).

3. Pulmonary Administration

Aqueous nano suspensions 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. They also increase adhesiveness and thus cause a prolonged residence time. Budesonide drug nano particles were successfully nebulized using an ultrasonic nebulizer [43-44].

4. Ocular Drug Delivery

Nano suspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids as it governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. One example of a nano suspension intended for ophthalmic controlled delivery was developed as a polymeric nano suspension of Ibuprofen. This nano suspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nano suspensions of

glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone enhance rate, drug absorption and increase the duration of drug action.

5. Targeted Drug Delivery

Nano suspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the in vivo behavior. The drug will be up taken by the mononuclear phagocytic system to allow regional-specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly.

6. Mucoadhesion of the Nano Particles.

Nano particles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. 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 nano suspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT [45-46].

Conclusion

The nano suspensions technology can be successfully utilized for overcoming problems associated with poorly soluble drugs or lipophilic drugs insoluble in both organic and aqueous media, and enhance the bioavailability of several drugs. Altered pharmacokinetic profiles of drugs caused by nano suspensions have become appreciable insofar as they improve safety and efficacy. So the study on in-vivo biological performance is extremely important, and the establishment of an in-vitro/in-vivo relationship will become a hot research field in the further study of nano suspensions. Thus, nanotechnology can play a vital role in drug discovery programs to increase aqueous solubility as well as bioavailability of poorly soluble drugs. In future more research work can be carried out for further developments in nano suspension oral control drug delivery

systems. This patent review article provides an updated bird's eye view various account on the publications and patents of different novel nano suspensions delivery approaches for use in both oral and non-oral applications. I hope that my effort is going to find new applications in near future.

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