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NANOSUSPENSIONS:FORMULATION STRATEGIES AND THERAPEUTIC APPLICATIONS - A REVIEW

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ABSTRACT:
Nano suspension technology has emerged as a pivotal strategy in pharmaceutical formulation, offering solutions to challenges associated with poorly water-soluble specially BCS class II drugs. This review comprehensively explores the preparation methods, evaluation techniques, and diverse applications of Nano suspensions in pharmaceuticals. The review begins by elucidating various preparation techniques employed in the fabrication of Nano suspensions, including high-pressure homogenization, sonication, and wet milling. Moreover, the importance of stabilizers and surfactants in maintaining particle stability and preventing aggregation is highlighted. The article delves into the evaluation parameters crucial for assessing the quality and performance of Nano suspensions. These parameters encompass particle size analysis, zeta potential measurement, morphology characterization, and drug release kinetics. Understanding these evaluation techniques is essential for ensuring the reproducibility and consistency of Nano suspension formulations. The diverse applications like improving the solubility and bioavailability of poorly water-soluble drugs to enhancing targeted drug delivery and sustained release profiles, Nano suspensions offer versatile solutions to pharmaceutical challenges are discussed. In conclusion, this review provides a comprehensive overview of the preparation, evaluation, and applications of Nano suspensions in pharmaceuticals. By synthesizing the latest advancements and insights in this field, it aims to inform and inspire further research and development efforts toward the utilization of Nano suspensions for improved drug delivery and patient care.

INTRODUCTION

Suspensions are pharmaceutical preparation wherein the drug(s) is in suspended form. Based on the solubility of drug, APIs are classified in four different class as per BCS Classifications. The drugs of Class two & Class four have low water solubility. [1] Therein, these drugs tend to have low bioavailability and short shelf-life. Few of the drug belonging to BCS class II are Aceclofenac, Asciminib, Atorvastatin Calcium, Clonazepam, Daclatasvir, Ibrutinib, Rifampicin, Telmisartan and BCS Class IV are sulfamethoxazole, Albendazole, Avacopan Ciprofloxacin HCl, and furosemide. Due to the solubility issue, in the past many technologies have been used to increase the solubility like different pH, buffer systems etc. [2,3] Various techniques have been employed to increase the dissolution of these drugs in the past including to increase the drug surface area by particle size reduction in micro levels, by development of formulation wherein the drug is wetted with specialized excipients causing higher dissolution rate, by lowering the drug diffusion layer forming different dosage forms, by improving apparent solubility of such drugs.[4] Higher bioavailability was obtained by co-excipients combination with drugs, inclusive complex formations, different polymorphic drug structure, nano-lipid based system, derivatives or related salt forms synthesis and particle size reduction.[5]

More than 40% of drug discovery are lipophilic and low solubility drugs comprising a challenge for its bioavailability and drug delivery. Nanotechnology has emerged as one of most widely used tech with different manufacturing process causing increased half-life and less into of drugs. More recent approaches are solid dispersion, microemulsions, liposomes, complex formation etc. In past few years, a lot of focus have been given on nanotechnology, nanoparticles and nano-drug delivery. Nanosuspension [NS] are highly micronized APIs upto nanometer level dispersed in solvents through surfactants. The surfactant forms a matrix with the API in the base causing the API to be in suspended form for long time without change in its physiochemical characteristics.

A novel technology that decreases drug particle size has been developed over the past 20 years to speed up drug breakdown.[6] The Noyes-Whitney equation states that medications with smaller particle sizes have larger surface areas, which increases the rate of dissolution. Drugs' oral bioavailability may also be increased by increasing the dissolution rate and the density gradient between the GI lumen & systemic circulation that results from it.

The PDI (Polydispersity index) of nanosuspension should be typically less than one micron, having range of 200 to 600 nm mean particle size.[7]

The current review is focused in nanosuspension trends for future and its pharmaceutical application specially in anti-diabetic's area.

Furthermore, there are advantages to nano-suspension like

- Easy manufacturing and faster scale up
- Physical stability with co-excipients
- Nanosuspension when taken orally, faster absorption and release
- Easy IV route of administration
- Supports subcutaneous and intramuscular route of administrations
- APIs having greater log p value can be made to nanosuspension and administered easily
- High dissolution rate for all forms of dosage form
- Higher bioavailability compared to respective market preparations
- High saturation solubility
- With high solubility, lower drug concentration required
- Cheaper drug with lower dose of drug in formulation point of view

Preparation of Nanosuspensions [8-9]

Widely, there are two techniques for manufacturing of Nanosuspension i.e. Bottom up technique (where a stable formulation is prepared using different excipients and drug is added at the end to form nanoparticle, method include precipitations, microemulsion, melt emulsification) and Top down technique (breaking and decreasing drug particle size to nano level and adding the same in formulation for form a stable nanosuspension wherein the method includes high shear homogenization, milling etc.)

Bottom up Nanosuspension:

Raw drug → Formulation development with excipients → Stable Suspension → High Shear Homogenization or milling of formulation as is → Nanosuspension

Top bottom Nanosuspension:

Raw Drug or API → Reduce particle size by different techniques → Nano sized drug in crystal of amorphous form → Addition in formulation → Nanosuspension

Different Techniques of nanosuspension preparation are:

Precipitation Method

This is a drug supersaturation technique in which appropriate solvent is used to dissolve a drug. With the help of syringe solution containing drug is added in a second solvent in which the drug is insoluble, drop wise causing instant supersaturations making nanocrystals or an

amorphous nano sized drug particle. [10,11] This method has two stages i.e., nuclei formation and later crystal growth. For this formulation process a high nucleation rate with lower growth is necessary, only then a stable formulation can be prepared. As per literature, both are dependent on temperature. Both the solvent used in the technique have to miscible and drug must be soluble in minimum one solvent.[12]

Melt Emulsification Technique

As the name suggest is to melt the drug in a aqueous phase wherein the drug is insoluble. Add weighed quantity of drug to a solution comprising known stabilizer. Now, heat the aqueous phase at a temperature more than API's melting point so as to melt the drug completely. This phase is homogenized to form an emulsion and then cooled to 25˚C gradually otherwise use an ice pack. Precipitation of drug occurs during the cooling phase wherein the drug particle size is in nanometers therefore increasing the drug surface area. Few parameters are critical using this technique like drug concentration (more drug can cause supersaturation), stability used needs to be compatible with the drug, melting temperature of drug (if very high, can cause drug degradation also) and homogenization time and cycle. [13]

High Pressure Homogenization

Use solution containing stabilizer to disperse the drug. The phase is homogenized as low speed initially causing the drug to get wet completely following high speed homogenization for at least 15 to 20 cycles until desired drug particle size achieved. This is a very general technique and most widely used. Longer time homogenization can cause increase in temperature and also changes in rheological properties of the phase. [6]

Nanopure – Homogenization in Nonaqueous medium

In a water-free media, nanopure is homogenized in suspension. When this suspensions in water-free liquid get homogenized below freezing temperature like 0˚C, it is known as "deep-freeze" homogenization. Because aqueous and non-aqueous liquids have very high boiling points & low vapor pressures, the static pressure drop required to start cavitation with nanopure technology is insufficient.

Nanoedge

Nanoedge technology combines precipitation and homogenization and hence obeys its basic principle. Use of nanoedge overcomes crystalline nature and extended stability. Major advantage of using nanoedge is that great stability and lower particle size can be achieved in brief time.

Techniques including Milling

i) Media Grinding

This technique is developed and Patented by Liversidge in 1992.[14] Here, drugs are exposed to high shear mill to form nano-sized particles. In procedure, the grinding chamber contains grinding media, API, water & stabilizer. This grinding chamber gets spined at maximum shear rate at monitored and maintained thermal conditions for 2-7 days.[15] As a result of impaction between milling media and drug an essential energy gets produced, which disintegrate microparticle into nanoparticles.

ii) Dried co-grinding

The NS is prepared by dried grinding methods. This technique does not require any organic solvent, hence is cost-effective. In this method, poorly soluble drugs are dry grinded with soluble polymers and copolymers to form stable nanosuspension after dispersing in liquid medium. [16]

Lipid emulsion or Micro-emulsion

The majority of pharmaceuticals that are soluble in organic solvents that evaporate easily or solvents that are only partly miscible with water are processed using this approach. In this method, the medication is first dissolved in an organic solvent that is appropriate for the procedure, and then, once dissolved, it is emulsified in an aqueous phase using surfactants that are appropriate for the procedure. Under conditions of decreased pressure, the organic solvent that is used is allowed to evaporate, which results in particles of drug precipitating in the aqueous phase to create the aqueous suspension of the drug in the requisite particle size. Because this suspension may be appropriately diluted to produce the desired nanosuspension, it is an essential step in the production of the medication. In addition to this, microemulsion templates have the ability to create nanosuspensions. Microemulsions are defined as dispersions that include two immiscible liquids and are then stabilised thermodynamically by a surfactant or a cosurfactant. Either the medication is placed into a prepared phase of the microemulsion or an internal phase, and the microemulsion is able to be saturated by the intimate mixing of medicines. [17]

Supercritical Fluid Process

Solubilization and Nanosizing technologies through Supercritical fluid process are used to achieve particle size reduction. When the processing temperature and pressure conditions are higher than the critical point, the supercritical state is reached. Numerous methods, including

the precipitation with compressed antisolvent process (PCA), the supercritical antisolvent process (SAPS), and the supercritical solution process (RESS), can be applied. When using the supercritical solution process method, the drug solution is expanded within the supercritical fluid using a nozzle. This causes the supercritical fluid to lose its ability to act as a solvent, which in turn precipitates the medication as small particles. Recent developments in the SCF method have enabled the production of nanoparticulate suspensions with particle sizes ranging from 5 to 2000 nm in diameter [18]. In PCA, the medication CO2 filled compartment is used to atomize solution. After solvent exclusion, it gets supersaturates and precipitates.

Solvent Vaporization

This technique involves preparation of polymer solutions in low boiling point solvents & emulsions. In previous years, dichloromethane and chloroform were utilized, however they have since been substituted by ethyl acetate due to their improved toxicological characteristics. Upon the evaporation of the solvent for the polymer, the emulsion undergoes a transformation into a suspension of nanoparticles. This process enables the diffusion of the polymer through the continuous phase of the emulsion**.** It also involves high-speed homogenization or ultrasonication, followed by solvent evaporation through magnetic stirring at room temperature or decreased pressure. Ultracentrifugation collects solidified nanoparticles, which are cleaned with purified water to eliminate additives. Concentration of polymer, speed of homogenizer and quantity of stabilizers affects particle size.

Requirements for formulation:

Stabilizers

The primary function of stabilizer in formulation of nanosuspension is to ensure proper moistening of drug particles and prevention of Ostwald's ripening and agglomeration for better stability**.** Ionic or Steric barriers are used to maintain the physical stability of the solution. Tween poloxamers, cellulosics, polysorbate, povidones, span series, lecithins are some common examples of stabilizers used in preparation of Nanosuspensions. [19]

Co-surfactants

Phase behavior of microemulsions can be highly influenced by co-surfactant, so the selection of co-surfactant has affected the drug loading capacity. Most common co-surfactant like Bile salt used in the formulation of microemulsions with various solubilizers like glycofurol, isopropanol, ethanol and Transcutol. [20]

Organic Solvents

When preparing microemulsions or Nano emulsions with the Microemulsion template approach, organic solvents may be necessary for the formulation of the microemulsions or Nano emulsions. There are organic solvents that can be harmful to both people's bodies and the environment. Therefore, it is recommended to use some less hazardous water-miscible solvents such as alcohol and partially water-miscible solvents such as benzyl alcohol in place of dichloromethane, which is reported to be a conventionally hazardous solvent.

Different substances added

Based on the formulation and characteristics of the nanosuspension formulation, other materials or reagents can be added to attain stable and better results. These may be some salts, polyols, preservatives, buffers and cryoprotectants.

Evaluation of Nanosuspension

The nanosuspension can be evaluated for various parameters, as given below:

Color, Odor, Taste

Mainly Orally administered nanosuspensions are examined for its color, odor and taste. Change in color, odor and taste indicates chemical instability as it may result in change in dissolution and size of the particle and crystalline nature. [21]

Specific Gravity

It is a critical parameter in evaluation of nanosuspension, so, to measure Density using instruments like Precision hydrometer well mixed uniform formulation should be used. [22] As inference, the lower the specific gravity the presence of entrapped air within formulation structure is higher.

pH Value

The pH value of the aqueous formulation should be measured at a certain temperature and after the settling equilibrium has been established in order to reduce "pH drift" and electrode surface coating with suspended particles. To stabilize the pH, avoid adding electrolyte to the formulation's exterior phase.[22]

Globule Size

The size of the droplet distribution of the micro emulsion vesicles may be determined by the use of either the light scattering method or electron microscopy. A dynamic light scattering spectrophotometer employs the usage of a neon laser with a wavelength of 632 nm. [23]

Mean Particle Size

Mean particle size and particle size distribution have an effect on the in vivo performance of the nanosuspension, as well as saturation solubility, dissolving rate, and physical stability.[6] Laser diffraction (LD), the microscope, coulter plate spectroscopy, and spectroscopy using photon correlation are all viable methods for calculating the polydispersity index (PI).[24]Because the PI is crucial for the physical integrity of the nanosuspension, it is recommended that the PI be decreased in order to achieve prolonged stability. A PI Value that is more than 0.5 suggests a very broad distribution, while a value in the range of 0.1 to 0.25 indicates a size distribution that is reasonably restricted. [24] LD may be used to estimate the quantity of medication microparticles, as well as their volume size distribution and detection throughout the production process. Particles ranging in size from 0.5 micrometers to 2,000 micrometers. [25] Coulter count may be used to determine the actual quantity of particles per volume for the various size classes. This method is more important than LD for quantifying contamination of nanosuspension. [26]

Crystalline State and Particle Morphology

Crystalline state and particle shape can both be evaluated in order to examine whether nanosized particles have undergone polymorphic or morphological changes.[27] When the formulation's crystalline structure is altered and the nanosuspension is homogenized under high pressure, the nanosuspension can transform into amorphous or other polymorphic forms.[28] Analysis of differential scanning calorimetry and X-ray diffraction can be used together to evaluate the degree to which drug particles have changed throughout their transition from a liquid to a solid state [29].

Zeta Potential

It is necessary to calculate the Zeta Potential in order to examine the surface charge characteristics of the nanosuspension. The value of the particle's surface charge can be used as an indicator of the nanosuspension's stability at the macroscopic level. It is necessary to have a zeta potential of at least 30 mV for an electrostatically stabilized nanosuspension [30], and it is necessary to have a zeta potential of at least 20 mV for steric stabilization [31]. The values of zeta potential are typically determined by first calculating the electrophoretic mobility of the particle and then translating the electrophoretic mobility to the zeta potential [32]. The electroacoustic method is one that may be utilized while doing research in the field of material sciences for the purpose of zeta potential determination. [33,34]

Dissolution Velocity and Saturation Solubility

These two characteristics are measured in a wide variety of nanosuspensions and physiological solutions. For the purpose of evaluating the formulation's performance in vitro. There is also the possibility of using dissolution stability and saturation solubility. According to the findings of Bohm and colleagues, there was a decrease in the size of the particles to the nanometer range when there was also an increase in the dissolving pressure and dissolution velocity. As a result, the size reduction causes an increase in the dissolution pressure. [35]

Viscosity Measurement

A rotational Brookfield type viscometer may be utilized for the purpose of determining the viscosity of lipid-based formulations of various compositions when subjected to varying temperatures and shear rates. The temperature of the sample room, which is part of the equipment, has to be kept at 37 degrees Celsius using a thermo bath, and the samples need to be submerged in it.[36]

Stability of Nanosuspension

Tiny particle sizes in nanosuspension have high surface energies, which leads drug crystals to aggregate. By producing a steric or ionic barrier, stabilizers moisten the drug particles, avoiding agglomeration and Ostwald ripening, which gives physically stability to the solution. [37]

In-vivo biological performance

Evaluation in vivo should be done so that the effectiveness of the medicine may be tracked while it is being used in the body. It is crucial in the context of intravenously given nanosuspensions due to the fact that the organ distribution is dependent on the various drug's surface characteristics, which in turn are dependent on the behavior of the drug in vivo. This makes the concept of surface hydrophobicity particularly important. [38] It is generally agreed upon that size and the kind of protein absorption pattern that is observed following intravenous injection of nanoparticles are key elements that influence organ distribution. This notion has gained widespread acceptance in recent years. In order to comprehend the behavior that occurs in vivo, it is essential to make use of the appropriate techniques to analyses the surface characteristics and protein interactions.[39] Hydrophobic interaction chromatography is one approach that may be used to evaluate surface hydrophobicity. Two-dimensional polyacrylamide gel electrophoresis is another method that can be used to measure and evaluate the adsorption of protein in animals following intravenous administration of the test substance. [40]

Application of Nanosuspension [41-50]

Oral Drug Delivery

For many medications, taking them by mouth is both an increasingly common and preferred method of administration. Both its bioavailability and its solubility will rise once it has been reduced to nanoscale size. Increased saturation solubility leads to a rise in concentration gradient between the lumen of the gastrointestinal tract and blood, which in turn leads to an increase in the dissolution velocity of the medication. Adherence of drug nanoparticles to the mucosa suggests that bioavailability has been enhanced.

Ocular drug delivery

The nanosuspension technique is effective for administering medications that have a low solubility in lachrymal fluids. When it comes to the topical administration of hydrophobic medications, nanosuspension is the method of choice since it allows for saturation solubility in the lacrimal fluid. The nanoparticles of the drug had demonstrated an extended residual period in the cul-de-sac, which resulted in a sustained release of the drug.

Pulmonary

When it comes to the delivery of medications that have a low solubility in pulmonary secretions, nanosuspension can be an effective method. At the moment, inhalers are used to administer these medications as aerosols or dry powder. While these methods are effective, they do have a few drawbacks, including restricted diffusion at the needed location and a shorter residence period. These issues can be circumvented by utilizing nanosuspensions, however. Nebulization of nanosuspensions is an option for pulmonary administration, and it may be accomplished using either mechanical or ultrasonic nebulizers. Direct transport of the medicine to the site of action, which results in lower dosages and fewer adverse effects, is one of the benefits of pulmonary drug delivery in comparison to oral and parenteral drug administration.

Mucoadhesion of the nanoparticles

Due to small particle size nanoparticles can adhere to the mucosa. Prior to particle absorption, nanoparticles adhere to surface. Mucoadhesive polymers are used to formulate hydrogels in order to increase the adhesive time of nanosuspension. This will to improve the bioavailability and the targeting of GIT parasites.

Dermal application

The nanocrystalline form of drugs can enhance saturation solubility to improve the penetration of the drug. As this nanosuspension have the improved permeability, higher membrane penetration and adhesiveness makes it more reliable for cutaneous application.

Targeted drug delivery

As the nanosuspension has small particle size they are appropriate for aiming any specific organs. As of improved surface characteristics of the nanoparticles, it turned easy to modify their in-vivo actions to target particular organ of interest. The phagocytic system uptakes nanoparticles to allow region specific delivery. Various drugs like antifungal, antimycobacterium, leishmanial in nanosuspension form can be used to act on the pathogen intracellularly.

Parenteral Administration

Parenteral administration became first choice when it comes to anaphylactic shock and cardiac arrest, as Parenteral administration includes subcutaneous, i.e. intramuscular, and intra-arterial methods administration. Higher bioavailability, reliable doses and avoidance of first pass metabolism are some of the advantages of this type of administration. Nanosuspension used for this administration possess more regulation over dose & rate which allows more expectable pharmacokinetic & pharmacodynamics profile. Oridonin nanosuspension were investigated on mice for prevention of tumor growth and it results in decreasing weight and volume of tumor by 60.23% on the other hand conventional form inhibited the growth upto 42.49%. Hence, it is proven that nanosuspension improves therapeutic efficiency reduces the cost of therapy.

Literature Review

Table 1: Literatures on Nanosuspensions

Sr. No	Method of preparation	Drug Name	Polymers used	Reference
1	Precipitation-Ultrasonication method	Glimepiride	Hydroxypropyl methylcellulose, polyvinylpyrrolidone K30 and Sodium Lauryl Sulphate	51
2	Microfluidization method	Ritonavir	Hydroxypropyl methylcellulose and Sodium Dodecyl Sulphate	52

3	Nanoprecipitation technique	Furosemide	Poloxamer 188, Polyvinylpyrrolidone K-30	53
4	High shear homogenization technique.	Glimepiride	Hydroxypropyl methylcellulose E15	54
5	Solvent evaporation technique	Cefdinir	Polyvinylpyrrolidone K-30	55
6	Solvent & anti-solvent precipitation method.	Lafutidine	Polyvinylpyrrolidone K-90	56
7	Nanoprecipitation technique	Valsartan	Hydroxyl propyl methyl cellulose E50, Polyvinyl Pyrrolidone k-30, Polyethene Glycol 6000	57
8	High-pressure homogenization method	Naringenin	Hydroxypropyl methyl cellulose (HPMC)	58
9	Solvent-antisolvent precipitation method	Azilsartan Medoxomil	Polyvinylpyrrolidone K-30	59
10	Nanoprecipitation method	Silybum marianum, Elettaria cardamomum and Coriandrum sativum)	Polyvinyl Alcohol	60
11	Precipitation method	Irbesartan	Polyvinylpyrrolidone K-15	61

12	High-pressure homogenization method and H96 approach	Aprepitant	tween 80 and poloxamer 188,	62
13	Emulsification – Solvent – Method.	Pioglitazone	Eudragit L100 and Eudragit S100	63
14	Pearl milling process	Valsartan	poloxamer 407 (Lutrol F 127)	64
15	Wet media milling technique	Soluplus	Hydroxypropyl methyl cellulose (HPMC)	65
16	Wet ball milling	Sucrose ester	Sucrose monolaurate (SEL) and Sucrose monopalmitate (SEP)	66
17	Nanoprecipitation method	Zaltoprofen	Hydroxypropyl methyl cellulose (HPMC) and Pluronic F68	67
18	Solvent-antisolvent precipitation technique	Amorphous ezetimibe	Tween 80	68
19	Nanoprecipitation method.	Celecoxib	Lbabrafil 1944 CS	69
20	Precipitation process	Pitavastatin	Polysorbate 80, PVP and urea.	70
21	Wet media milling	Dispersing agent	0.5% hydroxypropyl methylcellulose (HPMC) and 0.5% Tween 80	71
22	Precipitation-ultra sonication method	Felodipine	Hydroxypropyl methylcellulose (HPMC)	72
23	Media milling technique	Olmesartan medoxomil	Mannitol	73

CONCLUSION

This article gives an overview of the recent advancements that have been made in the production of therapeutic nanosuspensions by a variety of methods including high pressure homogenization, media milling, and emulsification. However, although the research is still in its initial stages, multiple studies have clearly demonstrated promise of these drug delivery vehicles in various modes of administration. These administration routes need not only a regulated release but also a suitable bio adhesion. The investigation of nanosuspensions as delivery systems for drugs is only getting started. However, these systems provide the flexibility and potential for additional tweaking of particles and surface features to improve in vivo responses. Additionally, the invention of novel therapeutic techniques for treating a variety of illnesses (including heart disease, cancer, diabetes, Parkinson's disease, and Alzheimer's disease, among others) is necessary. Considering that the absorption of nanoparticles is proportional to their size, focusing on the optimization of the size of drug nanosuspensions can assist us in the preparation of a suitable nanosuspension formulation that has improved diffusion rate. In addition, one potential next step in nanosuspension research is the attachment of polymers to the surface of the particles and their decrease in size.

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