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NANOSUSPENSIONS FOR ENHANCEMENT SOLUBILITY OF POORLY SOLUBLE DRUGS

Kavali Pavan Kumar*[1], Gottemukkula Lakshmi Devi[1], Akkala Govardhan[1], Kasula Arun Goud[1], Kavali Bhavana[1]

[1*]Department of Pharmaceutics, Kummera, Chevella, Rangareddy, Telangana, India.

ABSTRACT

Extremely low bioavailability is a key issue with poorly soluble medicines. For medications like carbamazepine, simvastatin, and itraconazole-which fall within BCS class II of the biopharmaceutical classification system and are poorly soluble in both aqueous and nonaqueous media-the issue is considerably more complicated. To address these issues, formulation as nanosuspension presents a compelling and optimistic substitute. The pure, poorly water-soluble medication in nanosuspension is suspended in a dispersion of no matrix material. Making a nanosuspension is easy and works with any medication that is insoluble in water. A nanosuspension not only addresses the issues of low solubility and bioavailability, but it also modifies the drug's pharmacokinetics, enhancing its safety and effectiveness. The preparation techniques, characterisation and review of this article and applications of the nanosuspension.

KEYWORDS

Solubility, Dissolution, Nano suspensions, Bioavailability and Emulification.

Author for Correspondence:

Kavali Pavan Kumar,

Department of Pharmaceutics,

Kummera, Chevella, Rangareddy,

Telangana, India.

Email: pavanyadav2260@gmail.com

INTRODUCTION

The successful formulation of pharmaceuticals depends on a number of factors, including solubility, stability at room temperature, compatibility with solvent, excipient, and photostability. Over forty percent of the newly created chemical entities resulting from drug development initiatives are lipophilic or weakly water soluble substances as of right now. Drugs with limited solubility and bioavailability can be solved using a variety of formulation techniques. The typical methods include salt production, precipitation, penetration enhancer or cosolvent

usage, micronization, use of fatty solutions, surfactant dispersion method, etc., but their usefulness in improving solubility is still restricted for medications that dissolve badly. Other strategies include vesicular systems like liposomes, solids dispersion, emulsion and microemulsion techniques, and inclusion complexes containing cyclodextrins[1]. These approaches demonstrate promise as drug delivery systems, but a major drawback of these approaches is that they are not universally applicable to all drugs. For pharmacological purposes, nanoparticle engineering has been created and described during the past few decades. In The issues with the several methods previously discussed can be resolved by using nanotechnology. The definition of nanotechnology is the research and engineering done at the 10-9m nanoscale. Techniques like Bottom-Up Technology and Top-Down Technology are used to transfer the drug microparticles/micronized drug powder to drug nanoparticles. Surfactants stabilize submicron colloidal dispersions of medicine particles, which are called nanosuspensions. These can be used to improve the solubility of medications that do not dissolve well in lipid or water-based media. Increased solubility causes the active ingredient to flood at a faster pace, reaching the maximum plasma level more quickly.

This method works well for compounds that are difficult for formulators to work with because they have low permeability, low solubility, or both. Because of the smaller particle size, poorly soluble medications can be administered intravenously without obstructing blood vessels. The suspensions can also be formed into a solid matrix by lyophilization. It also has the benefits of liquid formulations over other formulations in addition to these advantages the benefits, drawbacks and pharmaceutical use of the various preparation techniques as a drug delivery vehicle are the primary topics of this review[2].

BENEFITS OF NANOSUSPENSIONS

Improve a medication's absorption and solubility; suitable for hydrophilic medicines

It is feasible to get higher drug loading;

Dose reduction

Strengthen the medications' chemical and physical stability

Offers a passive method of medication targeting[3]

PREPARATION OF NANOSUSPENSION

As seen in Figure No.1, "Bottom up technology" and "Top down technology" are the two main techniques used to prepare nanosuspensions. Top down technology involves the decomposition of bigger particles into nanoparticles; examples include high-pressure homogenization and milling techniques. Bottom up technology is an assembly approach to generate nanoparticles, such as precipitation, microemulsion, and melt emulsification process.

Precipitation Method

A common technique for creating submicron particles of poorly soluble medications is precipitation. This approach involves dissolving the medication in a solvent, which is subsequently combined with another solvent that contains a surfactant, making the drug insoluble. When a solution is added quickly to a solvent of this type (usually water), the medication quickly becomes supersaturated in the solution, forming ultrafine amorphous or crystalline medication. This process involves the creation of nuclei and the development of crystals, both of which are temperature-dependent. Preparing a stable solution with the smallest possible particle size primarily requires two factors: A high nucleation rate and a low crystal growth rate.

High-Pressure Homogenization

The three phases involved in this technique are as follows: To create presuspension, drug powders are first dispersed in a stabilizing solution. Next, presuspension is homogenized using a high pressure homogenizer at low pressure occasionally for premilling. Finally, high pressure homogenization is performed for 10 to 25 cycles to create nanosuspensions with the desired size[4].

Homogenization in Aqueous Media (Dissocubes)

Muller created the Dissocubes technology in 1999.

With a volume capacity of 40ml (for laboratory scale), the instrument may function at pressures ranging from 100 to 1 500 bars (2 800-21 300 psi) and up to 2000 bars. Using a high-speed stirrer, prepare a presuspension of the micronized medication in a surfactant solution before making the nanosuspension. The liquid flow volume per cross-section in a closed system is constant, according to Bernoulli's Law. Below the boiling point of water at normal temperature, the drop in diameter from 3cm to 25μm results in an increase in dynamic pressure and a decrease in static pressure. As a result, water begins to boil at room temperature and produces gas bubbles that explode when the suspension exits the gap (a process known as cavitation) and the air pressure returns to normal. The number of homogenization cycles, temperature, homogenizer power density and homogenization pressure are the key determinants of the size of drug nanocrystals that can be produced.

Preprocessing, such as medication micronization and the use of expensive equipment, raises the dosage form's overall cost.

Using this technique, numerous medications, including Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine, and Dexamethasone, were made into nanosuspensions.

Homogenization in Nonaqueous Media (Nanopure)

A water-free medium is used to homogenize the suspension of nanopure. This type of homogenization is known as "deep-freeze," in which drug suspensions in a nonaqueous media are combined at room temperature or occasionally even below it. Water, oils, and fatty acids have relatively high boiling points and low vapor pressures, therefore in nanopure technology, the static pressure drop is insufficient to generate cavitation[5].

Milling Techniques

Media milling

A patent for nanocrystal technology was held by Liversidge .This method involves media milling pharmaceuticals to produce nanoparticles. The medications' impaction with the milling media provides the necessary energy for the microparticulate system to break down into nanoparticles. In order to create suspension, the medication, stabilizer, water, or appropriate buffer are added to the milling media inside the chamber, which is then rotated at a very high shear rate. One significant issue with this approach is the residues that are left in the final product.

DRY COGRINDING

Pearl ball mills have been used for wet grinding procedures for many years in the preparation of nanosuspensions. Nanosuspensions can now be made using dry milling techniques.

Dry grinding of weakly soluble drugs with soluble and copolymers following dispersion in liquid media yields stable nanosuspensions. Itoh and colleagues have documented the creation of colloidal particles from a variety of weakly water-soluble medications, including glibenclamide, griseofulvin and nifedipine, when stabilized with sodium dodecyl sulfate and polyvinylpyrrolidone[6].

Lipid emulsion/microemulsion template

Another method for creating nanosuspensions is to simply dilute the emulsion, which is created by employing a partially water-miscible solvent as the dispersed phase. The emulsion approach can be used with medications that are soluble in volatile organic solvents or partially soluble in water. Nanosuspensions can also be made using microemulsion templates.

Microemulsions are dispersions of two immiscible liquids, such as oil and water, that have a cosurfactant or surfactant to stabilize them thermodynamically. Drugs can be intimately mixed to achieve saturation, where the drug is either injected into the internal phase of the microemulsion or the prepared phase. Using the microemulsion process, glisofulvin nanosuspension is made using water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate.

Melt emulsification method

Solid lipid nanoparticles are mainly prepared by melt emulsification method. Kippand 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[7].

Nanojet technology

This method, also known as opposite stream technology, divides a suspension stream into two or more sections within a chamber. High pressure exists between the two streams as they collide. Particle size is reduced as a result of the process's high shear force. Dearns had used the microfluidization method to create atovaquone nanosuspensions. The primary drawback of this method is the high number of passes through the microfluidizer and the comparatively higher fraction of microparticles in the final product.

Supercritical fluid methods

Nanoparticles are produced using a variety of techniques, including the precipitation with compressed antisolvent (PCA) process, the supercritical antisolvent process and the rapid expansion of supercritical solution (RESS) process. The RESS technique involves expanding a drug solution through a nozzle into a supercritical fluid, which causes the drug to precipitate as small particles due to the supercritical fluid's lack of solvent power. Young *et al*. Synthesized 400-700nm-diameter cyclosporine nanoparticles by the RESS technique. The medication solution is atomized into the pressurized CO2 chamber in the PCA procedure. The solution becomes supersaturated as the solvent is removed, leading to precipitation in the end. When a drug solution is injected into a supercritical fluid, the solvent is removed and the drug solution turns into a supercritical antisolvent[8].

CHARACTERIZATION TECHNIQUES

The solid state of nanoparticles also modifies the dissolution performance and has an impact on the particle size, dispersion, and zeta potential that affect the stability, safety, and efficacy of nanodrug delivery systems. To predict the in vitro and in vivo efficacy of nanodrug delivery systems, therefore, nanoparticle characterisation is crucial. The crystalline state, particle shape, particle size and distribution, and particle charge (zeta potential) all have a significant impact on the in vivo pharmacokinetic performance and biological function of nanosuspension.

Mean Particle Size and Particle Size Distribution

The in vivo performance of nanosuspensions, physical stability, dissolution rate, and saturation solubility are all impacted by the mean and distribution sizes of the particles. The polydispersity index (PI), which measures the range of the particle size distribution, can be found using coulter counters, laser diffraction (LD), photon correlation spectroscopy, and microscopes.

The physical stability of nanosuspensions is determined by PI, which should be as low as feasible to ensure long-term stability. A reasonably tight size distribution is indicated by a PI value between 0.1 and 0.25, and a very broad distribution is indicated by a PI value greater than 0.5[32] LD is able to identify and measure the drug microparticles while they are being produced. In addition, it provides a volume size distribution and can quantify particles with sizes ranging from 0.05 to 2000µm[9].

Crystalline State and Particle Morphology

By evaluating the crystalline state and particle morphology, polymorphic or morphological changes of nanosized particles can be verified Since high-pressure homogenization is necessary for nanosuspension, the formulation's crystalline structure changes and can take on amorphous or other polymorphic forms[31]. X-ray diffraction analysis is used to assess changes in the drug particles' solid state and the size of the amorphous component. It is complemented by differential scanning calorimetry analysis[10].

Surface Charge (Zeta Potential)

Zeta potential is used to investigate the surface charge characteristics of the nanosuspensions. The stability of nanosuspensions at the macroscopic level is indicated by the value of the particle surface charge. For electrostatically stabilized nanosuspensions, a zeta potential of at least ±30mV and ±20mV for steric stabilization are needed, respectively[35-37] Values for the zeta potential are frequently computed by first figuring out how mobile the particle is electrophoretically, and then converting that mobility zeta potential in reach. In the fields of material sciences, the electroacoustic approach is also employed to determine the zeta potential[11].

PHARMACEUTICAL APPLICATION OF NANOSUSPENSION

Post production processing is used to prepare nanosuspensions into different dosage forms. Because of its bigger surface area and smaller particle size, nanosuspension accelerates the pace at which drugs dissolve and are absorbed. Table No.1 lists the pharmaceuticals that are now on the market as nanosuspensions along with their modes of administration[12].

Parental Drug Delivery

These days, parental delivery can be achieved using vesicular systems like liposomes and niosomes, cosolvent solubilization, salt creation, cyclodextrin complexation, and micellar solutions. Yet, these techniques have drawbacks, such as low parental acceptance, high manufacturing costs, and low solubilization capability. Utilizing nanosuspension technology, the aforementioned issues are resolved. An intraarticular, intraperitoneal, intravenous and other parenteral route can be used to give nanosuspensions. Drugs delivered parenterally are also more effective when formulated in nanosuspensions. In terms of lowering the median tumor burden, paclitaxel nanosuspension was found to be superior. In Mycobacterium avium-infected female mice, clofazimine nanosuspension demonstrated superior stability and efficacy compared to liposomal clofazimine). In according to Rainbow *et al*, rats' antifungal activity was more effective when itraconazole was suspended intravenously than when the solution was used[13].

Pulmonary Drug Delivery

Mechanical or ultrasonic nebulizers can be used to nebulize nanosuspensions for pulmonary administration. All aerosol droplets include drug nanoparticles because of the abundance of tiny particles. The preparation of budesonide corticosteroid as a nanosuspension for pulmonary administration has been accomplished with success. Because the drug's particles are so minute, aqueous solutions can be delivered by pulmonary route and easily nebulized. Nebulizers come in a variety of forms and can be used to provide liquid formulas.

Budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc. are a few of the medications that have been effectively tried with the lung route[14].

Ocular Drug Delivery

Drugs are delivered to the eyes via nanosuspensions for a prolonged release. Using Eudragit, Liang and colleagues made a cloricromene nanosuspension for ocular administration. The drug's availability in the rabbit eye's aqueous humor was higher, according to the experiment. Therefore, the use of nanosuspension formulation presents a viable means of enhancing the medication's bioavailability and shelf life following ophthalmic application.

Targeted Drug Delivery

The surface characteristics of nanosuspensions make them appropriate for targeting certain organs. Furthermore, using a different stabilizer makes it simple to modify *in vivo* behavior. Deliveries of the medicine to specified regions are made possible by the mononuclear phagocytic system. If the infections continue to live inside cells, this can be utilized to target macrophages with antifungal, antimycobacterial, or antileishmanial medications.

To enhance the drug's targeting to Leishmania-infected macrophages, Kayser created an aphidicolin nanosuspension solution. The drug's EC50 in nanosuspension form was 0.003µg/ml,

according to him, while the drug's EC50 in conventional form was 0.16µg/ml.

Atovquone nanosuspension therapy for toxoplasmic encephalitis was reported by Scholer *et al*, to have improved medication targeting to the brain[15].

Nanosuspensions along with their modes 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	Lovride	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 Prednisolone Hexadecadrol	Glucocorticoid	M. A. Kassem
Pulmonary	Budesonide Fluticasone	Asthma	Jerry Z. Yang
Intrathecal	Busulfan	Anticancer	SkyePharma
Topical	Silver	Eczema	Nucryst

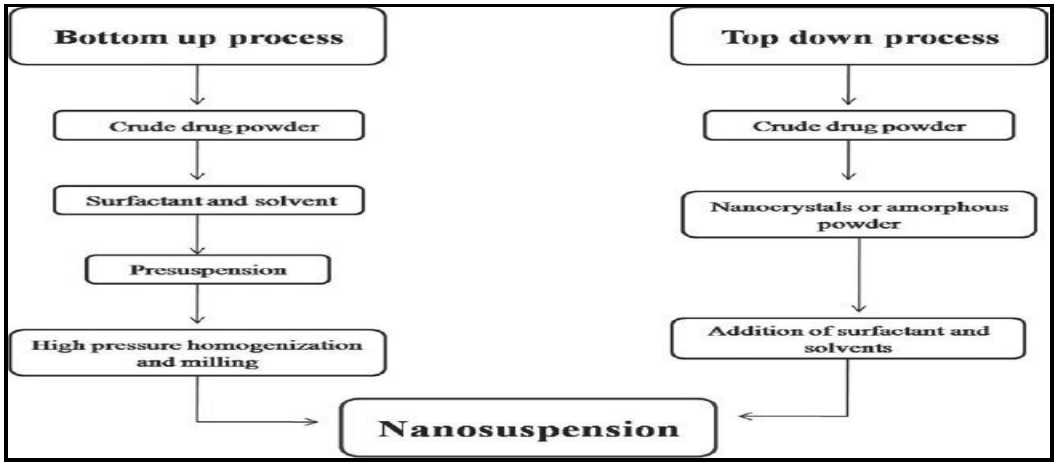

Figure No.1: Approaches for preparation of nanosuspension

CONCLUSION

A unique and practically viable method for addressing the issues associated with hydrophobic drugs, such as low solubility and low bioavailability, is the use of nanosuspensions. High-pressure homogenization technology and media milling have been effectively applied for the large-scale manufacturing of nanosuspensions. Remarkable properties such as enhanced solubility at saturation, enhanced bioadhesivity, variety in surface modification, and simplicity in postproduction processing have expanded the uses of nanosuspensions for different delivery systems. Although applications in pulmonary and ocular distribution still need to be assessed, the uses of nanosuspensions in oral and parental routes have been well established. But there is still work to be done on their buccal, nasal and topical administration.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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