REVIEW ARTICLE

Enhancing Medication Solubility Using Nanosuspension: A Method

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Abstract

Its extremely low bioavailability is the main problem with poorly soluble medicines. The presence of medications such as carbamazepine, simvastatin, and itraconazole – which are insoluble in both watery and non-aqueous solutions and belong to the BCS class II of the pharmacological classification system – complicates matters even more. Formulation as nanosuspension is a desirable and feasible answer to these problems. The drug is distributed as a so-called nanosuspension, which is a pure, poorly water-soluble drug without any matrix components. The simple synthesis of nanosuspensions can be advantageous for all drugs that are soluble in water. A nanosuspension changes a drug's pharmacokinetics, boosting safety and efficacy in addition to improving the drug's soluble condition and low bioavailability. The preparation techniques, article description, and review findings.

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

INTRODUCTION

A lot of factors are important for the right pharmaceutical formulation, including the ability to dissolve, toxicity at ambient temperatures, compliance with standards for commercially viable excipients, and photostability. Today, about 40% of newly discovered chemical entities are polar or weakly water-soluble compounds as a result of efforts to develop medications.[1,2] Various formulation techniques can be employed to tackle the restricted accessibility and solubility of pharmaceuticals.

Creating salt, micronizing, using lipid solutions, using cosolvents or permeation enhancers, and other conventional techniques are some of the ways that poorly soluble medications might be made more soluble. However, they are not very effective in this aspect. Neurotrophic factors are naturally occurring compounds that promote brain cell survival, growth, and/or development, making them a great option to halt the progression of neurodegenerative diseases in ways that are currently unattainable with symptomatic therapy, even reversing their trajectory. Treating illnesses of the brain and spinal cord, such as Parkinson's and Alzheimer's, with neurotrophic factors that function as neuroprotective or therapeutic substances has attracted a lot of interest in recent years. Nevertheless, the challenges of delivering these amino acids to the appropriate sites in the brain remain, largely contributing to the lack of therapeutic success. In addition, approaches comprise vesicular systems such as liposomes, solids dispersion, immersion, tiny emulsion methods, and inclusion complexes including cyclodextrins. As drug delivery methods, these approaches show promise, but a significant limitation is that not all drugs can be delivered using them.[3] Nanoparticle-engineered pharmaceutical uses have during the previous few decades, both created and described.[4] The drawbacks of the multiple previously mentioned strategies may be remedied using nanotechnology. Science and engineering in the nanoscale, or roughly 10–9 m, are studied in nanotechnology. Using techniques such as bottom-up and top-down technology, the drug powder is transformed into therapeutic small particles or micronized drug powder.[5] Drug particles stabilized at the nanoscale by surfactants in the form of colloidal dispersions of micron-sized particles are called nanosuspensions.[6] A medication with low water solubility is suspended in a mixture without

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any matrix material to form nanosuspensions.[7] These can be used to increase the solubility of a substance in lipid and aqueous environments, where it may be poorly soluble. Because of its increased solubility, the active substance floods the body more quickly and reaches its maximal plasma level more quickly. Compounds with poor flexibility, low solubility, or both make them challenging for makers to work with, yet this approach works well for them. It is possible to inject poorly soluble drugs without blocking blood arteries because of the reduced particle size. Transporting enzymes or gene therapy vectors to the head's nerve cells has proven challenging due to the blood–brain barrier, which generally blocks all but the smallest (<0.5 kDa), lipophilic compounds from accessing the cerebral cortex in the bloodstream after systemic treatment. The passage of the blood–brain barrier has sometimes required highly intrusive surgical approaches to inject vectors or peptides for genetic treatment into the neural parenchyma or cerebrospinal fluid.[8] It is possible to target C components in the mind and spinal cord using non-invasive techniques, which is very important, particularly for chronic conditions when repeated dosing may be needed over time. This review focuses on the many preparation methods, their advantages and disadvantages, and their possible use in health as a drug system for administration.[9-11]

ADVANTAGES OF NANOSUSPENSIONS

1. Increase a medication's solubility and bioavailability
2. Appropriate for hydrophilic medications
3. One can attain a higher drug-loading
4. It is feasible to lower the dosage
5. Increase the pharmacological and physical stability
6. Offers a pharmacological targeting that is passive.

PREPARATIONS OF NANOSUSPENSIONS

The two primary methods for producing nanosuspensions –"Bottom up technology" and "Top down technology" – are shown in Figure 1. Tenth Reference Whereas bottom-up technology employs construction processes such as the process of precipitation microemulsion, and melting the emulsion to make nanoparticles, top-down technology involves transforming larger particles into nanoparticles using procedures such as homogenization under extreme pressure and milling. The specific principles of several methods are described, as well as the benefits and drawbacks of each.

PRECIPITATION METHOD

One common use for the method of precipitation process is the preparation of minute pieces of poorly soluble medications.[12-15] This process renders the drug insoluble by dissolving the medication in a solvent and mixing it with another solution that contains a surfactant. When the solution is rapidly diluted with such a solvent, the drug in it becomes supersaturated very quickly, generating a nanoamorphous or crystallized drug (typically water). This method largely relies on temperature for the formation of crystals and the synthesis of nuclei. A high rate of germination combined with a low crystallized growth rate is the prerequisite for generating a stable solution with the smallest feasible particle size.[16]

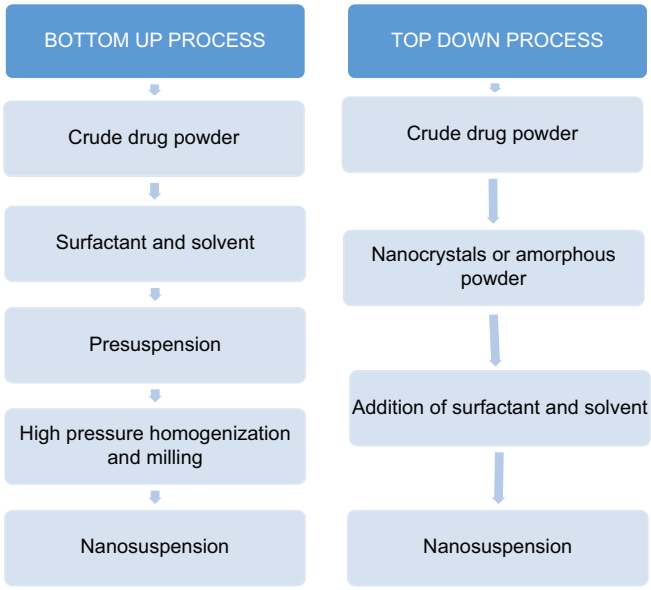

Figure 1: Techniques for making a nanosuspension

ELEVATED-PRESSURE AMPLIFICATION

This approach comprises the following three phases: To make pre-suspension, medication granules are first dispersed in a stabilizing solution. Subsequently, the presuspension undergoes homogenization at high tension for 10–25 cycles to generate nanosuspensions of the required size. This is done by intermittently pre-milling it at low pressure using high levels of pressure homogenizer.[17]

Topic: Homogenization of Aqueous Media Muller developed Dissocubes technology in 1999. Operating pressure ranges for the device include 100–1500 bars (2800–21,300 psi) or up to 2000 bars (for laboratory scale). The gadget has a 40 mL volume capacity. The pre-suspension containing the micronized drug in the presence of detergent needs to be made using a high-speed stirrer before the nanosuspension can be made. In an enclosed system, Bernoulli's Law states that the amount of liquid flowing through each area is constant. Both the dynamic and static pressures increase and decrease with a reduction in width of 3 cm–25 μm, and they are both below the boiling point of water at room temperature. Since the gas suspension leaves the space and the air movement returns to its normal level, water thus begins to boil at ambient temperatures and causes what is known as cavitation or the bursting of gas bubbles. A mixer's power density,

homogenized pressure, number of homogenous cycles, and humidity are the main variables that determine how large a drug nanotechnology may be created. Dosage form cost is increased by pre-processing techniques such as medicine micronization and expensive equipment. Amphotericin B, buparvaquone, prednisolone, carbamazepine, fenofibrate, thiomersal, and dexamethasone were among the drugs that were made into nanosuspensions using this method.

Consistency in the non-aqueous medium is attained (Nanopure). A dry environment causes the nanoparticle suspension to become uniform. Medicine formulations in a non-aqueous media are combined at 0°C, or occasionally even below freezing, in the course of a homogenization procedure known as "deep-freeze." The decrease in static pressure required to initiate cavitation in the nanopore approach is insufficient due to the high temperature of boiling and low vapor pressures associated with oils, water, and omega-3 fatty acids. Additional homogenization technologies and process-related patents are covered in.[18]

GRINDING METHODS

Milling media

There was a patent on nanocrystal technology.[19,20] To create nanoparticles, this approach requires media-milling medicines. The impingement effect between the medications and the milling media helps the microparticulate systems break down into nanoscale. During this process, the milling media is rotated at a very high shear frequency to produce suspension. The drug, stabilizer, and saltwater or adequate buffering are all added to the media. The residues that remain in the finished product after using this procedure are one of its key problems.[21]

Dry cogrinding

For many years, wet grinding techniques have been employed to create nanosuspensions using pearl ball mills. Making nanosuspensions can now be accomplished with the use of dry milling processes. To make stable nanosuspensions, weakly soluble medicines are dry ground with hydrophilic polymer and copolymers, then dispersed in a liquid medium. Itoh *et al*. have described producing colloidal particles from a range of weakly water-soluble drugs, such as glibenclamide, griseofulvin, and nifedipine, by stabilizing the mixture with polyethylene glycol and the sulfate of sodium dodecyl.[22,23]

Lipid emulsion/microemulsion template

By merely diluting an insufficiently water-miscible solution used to create the dispersed state, an emulsion can also be created as nanosuspensions. Drugs that are soluble in organic solvents containing volatile chemicals or marginally miscible in water can be administered using the emulsion method. In addition, nanoemulsion templates can be used to create nanosuspensions. The thermodynamic stability of a microemulsion is achieved by a surfactant or cosurfactant. Two immiscible fluids, such as water and oil, are dispersed to create microemulsions. By closely combining the drugs, the drugs can be saturated and added to the microemulsion's prepared phase or internal phase. The ingredients for grenaflour nanosuspension are sodium taurodeoxycholate, water in a container butyl lactic acid, lecithin, and the microemulsion method.[24]

Microprecipitation – high-pressure homogenization (Nanoedge)

Nanoedge works by combining microprecipitation and high-pressure homogenization processes. The formation of precipitates of friable materials is followed by a high-stress and/or thermally driven disintegration stage.[25,26]

The melt emulsification process

To produce solid lipid nanoparticles, melt emulsification is the principal method. Initially, Kipp *et al*. used the emulsion approach to melt the ibuprofen to create nanosuspensions. To accomplish this, four steps are needed. An initial step involves combining the medication with a stabilizer-infused water-based solution.[27] Once heated above the melting point of the drug, the fluid is homogenized with a high-speed mixer to form an emulsion. The medication's temperature is kept constant during the entire process. Finally, the emulsion is cooled to precipitate the particles. The kind and quantity of stabilizers, the cooling temperature, the homogenization process, and the drug concentration are the main variables that influence the size of the small particles.[28,29]

Technology using nanojets

This technique, also called opposing stream technology, makes use of a vessel that divides a suspension stream into two or more pieces. The two torrents are crashing together with enormous pressure. The process's intense shear force results in smaller particle sizes. Dearns produced atovaquone nanosuspensions by means of the microfluidization process. This method has a lot of disadvantages because it requires a lot of microfluidizer cycles and produces a product with a significantly higher percentage of microscopic particles.[29]

Supercritical fluid techniques

Many methods are used to produce nanoparticles: The super antisolvent process, the rapid expansion of supercritical solution (RESS) deceit, and the precipitation method using the compressed antisolvent (PCA) process. The RESS method expands the drug solution and is injected through a nozzle into

the supercritical solution, causing the medication to precipitate as minute particles; Young *et al*.[30] produced cyclosporine nanoparticles with a diameter of 400–700 nm using the RESS technique; the medication water is added to the CO_2 pressurized chamber after being atomized using the PCA procedure; precipitation occurs when the solution eventually reaches supersaturation and the solvent is removed. After the medication is added to the supercritical fluid, the solvent is extracted in the supercharged antisolvent technique.

USE OF NANOSUSPENSION IN PHARMACOLOGY

For nanosuspensions, post-production processing enables the development of several dosage forms. Nanosuspension's larger surface area and tiny particles speed up the rate at which medication dissolves and absorbs. The medications and delivery systems that are currently on the market in the form of nanosuspensions.

Drug delivery orally

The main issues with administering medications orally are poor dissolution, partial dissolution, and insufficient effectiveness. Oral small suspensions, with their much higher surface-to-volume ratio and lesser particle size, are specifically used to increase the accessibility and effectiveness of weakly soluble medications.[31] It was found that after 5 h, around 65% of azithromycin nanosuspensions dissolved, compared to only 20% in micronized medications.[32] Among the benefits of nanosuspension are enhanced oral intake, less intersubject variability, and dosage proportionality. Administering drug nanosuspensions into capsule, pill, and fast-melt dosage forms is made simple using standard production techniques. Ketoprofen small particles were successfully incorporated into pellets for a 24-h duration of the drug's extended release.

Delivery of drugs to parents

These days, vesicular systems such as liposomes and niosomes, cosolvent solubilization, micellar solutions, cyclodextrin complexation, and salt creation are used to achieve parental distribution. Nonetheless, there are drawbacks to these techniques, including low solubilization capacity, high manufacturing costs, and restricted parental approval. The nanosuspension method is used to solve the challenges listed above. Numerous methods, including intra-articular, intraperitoneal, infusion, etc., can be used to deliver nanosuspensions. Furthermore, medications that are supplied parenterally perform better when they are prepared as nanosuspensions. Paclitaxel nanosuspension has been shown to more successfully decrease the median weight of tumors.[33] In female mice infected with *Mycobacterium avium*, clofazimine nanosuspension was found to be more stable and effective than liposomal clofazimine.[34]

Administration of medicines to the pulmonary system

Nanosuspensions for pulmonary delivery can be nebulized using mechanical or ultrasonic nebulizers. Because aerosol droplets are composed of so many little particles, drug nanoparticles can be found in every single one of them. One efficient way to produce budesonide, a corticosteroid, for pulmonary administration is as a nanosuspension. With regard to[35] the microscopic particles in the water suspension are readily crushed and administered through the lungs. Nebulizers are offered in several varieties for the delivery of liquid substances. Lung cancer can be effectively treated using a variety of medications, such as budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, and others.[36]

Delivery of drugs through the eyes

Medicine is delivered with a sustained release using ocular nanosuspensions. Eudragit was used by Liang and Binner to manufacture cloricromene particles for intramuscular usage in the eyes. The watery humor of the rabbit's eye showed an increase in drug supply during the trial. Consequently, making nanosuspensions is a workable plan for increasing the medication's bioavailability and extending its shelf life following ocular delivery.[37]

Personalized medicine administration

Nanosuspensions are suitable for organ-specific focus because of their surface properties. Moreover, in real-life situations can be readily altered by modifying the stabilizer. The neutrophil phagocytic mechanism enables the delivery of the drug to particular areas. Antimicrobial in nature antimycobacterial, or antileishmanial drugs can be used to target macrophages if the infections persist inside the cells.[38] Kayser developed an aphidicolin nanosuspension to more effectively target the medication to macrophages infected with *Leishmania*. As per his statement, the drug's EC_{50} in nanotechnology form was 0.003 µg/mL, whereas the traditional version was 0.16 µg/mL. An enhanced drug delivery system for toxoplasmic encephalitis that uses an atovaquone nanosuspension to target the brain.[39]

CONCLUSION

The new and commercially viable technique of nanosuspensions can address the low solubility and limited absorption of hydrophobic medications. Homogenization at a high-temperature technique and intermediate milling has been utilized to efficiently produce nanosuspensions on a large scale. Due to its remarkable properties, such as improved bioadhesive, enhanced solubility at saturation, variety in surface modification, and ease of post-production processing, applications of small halted the implementation

for diverse delivery systems have grown. The application of small amounts in oral and familial routes is well-established, but there is still much to learn about their use in being able to breathe and ocular transport. The effort to give them directly on the skin, nasally, or buccally has not yet been completed.

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