ejpmr, 2023,10(8), 240-245

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

NANOSUSPENSIONS: A COMPREHENSIVE REVIEW

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Article Received on 13/06/2023 **Article Revised on 03/07/2023** **Article Accepted on 23/07/2023**

ABSTRACT

The study of science, engineering, and technology at the nanoscale, where particle sizes range from 1 to 100 nm, is known as nanotechnology. It is a component of nanotechnology. Drug particles stabilised by surfactants and stabilisers colloidally scatter at submicron sizes in nano-suspensions Drugs that are inefficient in lipidic or aqueous environments may be made more soluble. By using nano-suspensions, which speed up the time it takes for the active ingredient to reach its peak plasma concentration. By addressing the issues of low solubility and bioavailability and changing the pharmacokinetics of the drug, nano-suspensions enhance both its safety and effectiveness. The challenges posed by these traditional methods for improving solubility and bioavailability are overcome by nanotechnology. The field of nanotechnology focuses on tiny particle in the 10- to 9-metre region of the nanoscale. The nano-suspensions are thoroughly explained in the article. In nano-suspensions, pure, insufficiently water-soluble drugs are suspended without any matrix material, are used to increase solubility.

KEYWORDS: Bioavailability, Solubility improvement, Site-specific drug delivery, Nanotechnology, Nano-suspensions, Safety and Efficacy.

INTRODUCTION

The colloidal scattering of drug particles at submicron dimensions is referred to as nano-suspensions, and it is stabilised by surfactants and stabilisers. For diverse drug delivery applications, suitable preparation techniques have been carried out through a variety of routes of administration, including the oral, effective, parenteral, visual, and pulmonary delivery. The appropriate particle size range for nano-suspensions is typically between 200 and 600 nm, which is below one micron. The development of nano-suspensions is better suited for mixtures with higher log P values, melting points, and doses.[1,2]

The difference between nanoparticles and them is that the former are lipid carriers of medications, while the latter are polymeric colloidal carriers of drugs. According to the Nernst, Brunner, and Noye's Whitney equation, as the particle size of drug decreases, surface area increases and a corresponding drop in the rate of dissolution. The Ostwald-Freundlich equation provides a good explanation for how a rise in dissolving pressure during expansion results in smaller particle size and higher saturation solubility.

The Biopharmaceutical Classification System categories that class II and IV drugs can benefit from advancements in nano-suspensions to increase solubility.

Advantages

1. Drugs that are more soluble and bioavailable
2. Fit for medications that are hydrophobic
3. It's possible to attain higher drug loading.
4. It is feasible to lower the dose.
5. Eliminates the problems with drug physical and chemical stability.
6. It offers scale-up for large-scale production and ease of manufacturing.
7. Stabilisers provide long-term stability.
8. Nanosuspensions used orally have a rapid onset and enhanced bioavailability.
9. The intravenous mode of delivery can achieve rapid disintegration and tissue targeting.
10. When administered subcutaneously or intramuscularly, less tissue irritation occurs.
11. A greater bioavailability is obtained with the ocular administration and pulmonary delivery.
12. It is possible to plan nano-suspensions of drugs with larger log P values to boost bioavailability.
13. The high dissociation rate and saturation solubility of medicines contribute to improvements in biological performance.
14. Nano-suspensions can be combined into tablets, pellets, hydrogels, and suppositories, depending on the organisation's needs.[3]

Formulation considerations

The process of making nano-suspensions is laborious,

and numerous parameters must be taken into account.

Temperature

Maintaining the ideal temperature is crucial for creating nano-suspensions. After adding the drug-containing solvent phase to the anti-solvent phase in the emulsion method, homogenization is carried out at a low temperature. Maintaining a low temperature is essential when using organic solvents since, at higher temperatures, the solvents are eliminated more quickly, resulting in uneven particle formation. However, the solvent gradually diffuses out of the system if a lower temperature is maintained during the operation. and circular and uniform nanoparticles are formed[4]

Stabiliser

Nanoscale particles have a high surface energy, which allows them to aggregate or grow in size. The primary goals of the stabiliser are to completely moisten the drug particles in order to establish physical stability and prevent the Ostwald's ripening and aggregation. physical stability of nano-suspension and in-vivo behaviour were controlled by the type and quantity of stabilisers. It may occasionally be essential to mix stabilisers for stable nanosuspensions. The ratio of the drug to the stabiliser may be 1:10 to 20:1. Lecithin is the stabiliser of choice to produce parenterally stable and autoclavable nanosuspensions.[4]

Organic solvents

Organic solvents are used if emulsions or microemulsions are used as the model for creating the nanosuspension. Conventional hazardous solvents like dichloromethane are preferred in the formulation over methanol, ethanol, chloroform, isopropanol, and other pharmaceutically acceptable less perilous water-soluble solvents, as well as partially water-miscible solvents like ethyl acetate, ethyl formate, butyl lactate, triacetin, benzyl alcohol.[5]

Stirring speed

The stirring speed is a crucial component in formulation. The particle size is reduced during Homogenization techniques that can be used to mix nano-suspensions together include high-pressure homogenization and high-shear homogenization. A normal pace must be kept throughout the preparation because it has been shown that, on average, increasing the speed of stirring during HSH or the number of cycles during HPH tends to lower particle size. HSH is thought to work best at a speed of 20,000 RPM with five to six cycles. This happens as a result of the suspension producing noticeably more foam due to faster agitation, which causes the solid nanoparticles to separate from the aqueous medium early. Consequently, there may be an inefficient size reduction and a deviation from the nano-sized region.[6]

Surfactants

By reducing the interfacial tension, surfactants are fused into the nano-suspension to increase its stability. They act as wetting or deflocculating agents. For example the most commonly used surfactants such as Tweens and Spans.[7]

Co-surfactants

When creating nano-suspensions using micro-emulsions, the choice of co-surfactant is essential Co-surfactants have the potential to alter phase behaviour; hence, it is important to investigate their effects on drug loading capacity and the internal phase's uptake in a certain micro-emulsion composition Cosurfactants can be used to boost the action of surfactants such as dipotassium glycerrhizinate and bile salts. Several solubilizers may be used as cosurfactants in the production of microemulsions, including transcutol, glycofurol, ethanol, and isopropanol[8]

Strategies for preparation

The bottom-up method is used to prepare nanosuspensions.

Precipitation, microemulsion, and soluble emulsification methods can be used to create nanoparticles.

The top-down approach

Nanoparticles are created via high-pressure homogenization and milling techniques. The term "bottom-up technology" describes the conventional methods of hydrosol precipitation.

A common technique for producing submicron drug particles that are challenging to dissolve is precipitation. This method makes the drug insoluble with the surfactant by dissolving it in a solvent phase before adding it to the solution. The fast addition of solution to the solvent, which is frequently water, results in fast supersaturation and the production of ultrafine drug particles. The process largely entails temperature-dependent crystal growth and nucleus formation. The key criteria for a stable suspension with small particle sizes are higher nucleation rates and lower crystal growth rates. The drug must dissolve in the solvent phase and be miscible with the nonsolvent phase. for the precipitation method to be effective.[9]

Precipitation (Solvent-antisolvent method) method

Submicron particles are created using the precipitation process, notably for drugs that are insoluble. Initial drug dissolution occurs in a dissolvable stage, and the solution is then combined with a miscible antisolvent phase while surfactants are still present. When the solvent phase is poured quickly into the antisolvent phase, the drug becomes supersaturated and develops into ultrafine crystalline or amorphous drug solids.

It is crucial to have a higher nucleation rate and a lower agglomeration rate in order to produce a stable suspension with a small molecular size. The precipitation process is carried out in two stages: crystal growth and nucleus formation. Both are influenced by temperature.

The drug should be soluble with the non-solvent phase of this method and soluble in the solvent phase..[10]

Supercritical fluid process

This technology mainly focuses on solubilization and nanosizing advancements with the use of the supercritical fluid approach for particle size reduction. A non-condensable thick liquid known as a supercritical fluid (SCF) has a critical temperature (Tc) and critical pressure (Tp) that are overshadowed by greater temperatures and pressures. This method results in the micronization of drug particles to submicron size. Nanoparticulate suspensions made of molecules with a size range of 5 to 2000 nm are produced using SCF techniques. The employment of this technology in the pharmaceutical sector is constrained by the low solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure required for these operations. [11]

Solvent evaporation

Emulsions and volatile solvents are used to produce polymeric solutions. Nano-suspensions are created during the evaporation of the continuous phase of the diffused polymeric solution in the emulsion. Conventionally, there are two major methods for creating emulsions: single emulsions, such as oil-in-water (o/w), or double emulsions, such as water-in-oil-in-water (w/o)/w. Following solvent evaporation while being continuously magnetically stirred at ambient temperature or at reduced pressure, high-speed homogenization or ultrasonication is used. After being cleaned with distilled water to remove any other materials, like surfactants, the solidified nanoparticles were then lyophilized. [12]

Melt emulsification method

An emulsion is created by dispersing the drug over the aqueous solution of stabilisers, heating it over the drug's melting point, and homogenising it. The sample holder in this procedure is fastened with a bearing tape equipped with a temperature regulator, and The emulsion is held at a temperature above the drug's melting point. The emulsion is then either placed in an ice bath or gradually cooled to room temperature. [13]

Top-down approach

Top-down method entails the reduction of large particles into micro- and nanosized particles. These are a few of them:

High pressure homogenization

The technique is most frequently employed to create nanosuspensions of various medicines with low aqueous solubility. There are three steps to it.

1) To create pre-suspension, drug powders are mixed with the stabiliser solution.
2) To reduce size, A low-pressure, high-pressure homogenizer is used to homogenise the pre-suspension.
3) Preparation is done using a variety of techniques, including Disso blocks, Nano Pure, Nano Edge, and Nano Jet.[14]

Homogenization in aqueous media (DissoCubes)

R.H. Muller created the method in 1999 using a piston-gap-style high-pressure homogenizer. A high-pressure homogenizer's nanosized aperture valve is used to propel a suspension comprising the medicine, stabilisers, and surfactants through the homogenizer.[15]

Principle

The underlying idea is cavitation. A cylindrical device with a 3 cm diameter and dispersion is suddenly passed over a 25 m-wide space. According to Bernoulli's theorem, a closed system's liquid flow rate per cross section is constant. As a result of decrease in cylinder diameter from 3 cm to 25 mm, the dynamic pressure rises and At room temperature, the static pressure is lower than the boiling point of water. Then, as soon as the water reaches its boiling point at room temperature, gas bubbles begin to form and eventually burst inside the liquid, a process known as cavitation. Particles have a powerful and adequate cavitation force.[16,17]

Nanopure

The mixing of suspensions in water or in water-free media like PEG 400 or PEG 1000 is known as the "nanopure" method. At 0 degrees, the freezing point, or even at room temperature, the temperature is maintained. This is why it is called "deep freeze homogenization. suitable for thermolabile materials in more temperate conditions. In this method, the drug nanocrystals are diffuse in liquid polyethylene glycol or other oils, which may be used to make drug solutions for HPMC capsules or gelatin.[18]

Nanoedge

In this method, the drug solubilises in an organic solvent before being combined with a miscible antisolvent to carry out precipitation. Due to the limited solubility of the water-solvent mixture, precipitation occurs. Rapid precipitation and high-pressure homogenization are combined with high shear preparation to form precipitation.[19]

Advantage:

1) Nanoedge innovation prevents crystal development and ensures long-term stability.
2) Better absorption is accounted for by increased particle surface area.

Nanojet

It is sometimes referred to as "opposite stream technology and entails dividing a suspension stream into two or more sections inside a chamber. In this chamber, the particles clash at high pressures of up to 4000 bar and a high speed of 1000 m/s. It causes the production of strong shear pressures and has a tendency to reduce particle size.[20]

Limitations

1) The presence of tiny particles alters the homogeneity.
2) Takes a lot of time.

A high-shear media mill is used to formulate the product.

Milling techniques

a) Media milling

A high-shear media mill is used to formulate the product. The milling chamber contains milling media, water, drug, and a stabiliser. It is rotated at a very high shear rate for at least 2 to 7 days while being kept at a controlled temperature. The drug's microparticles break down into nanoparticles as a result of the collision that occurs between the milling media and the drug, producing significant shear rates. Glass or strongly cross-linked polystyrene resin make up the milling media. Zirconium oxide is another option. You have the option of running the procedure in batch mode or recirculation mode.[21,22]

b) Dry-Co-grinding

The process of dry co-grinding is relatively simple and affordable. Without organic solvents, it can be carried out Due to the drug's transformation during co-grinding from crystalline to amorphous,, the physicochemical characteristics and dissolving rate of pharmaceuticals that are weakly water-soluble can be enhanced.[23]

Nano-suspension characterization

A) In vitro evaluations

Average particle Size and Distribution.

The stability, rate of dissolution , physical stability, and biological performance of nano-suspensions are all governed by the average particle size and the width of the particle size distribution, which are crucial characterization characteristics. Mueller & Peters (1998) noted that the drug's changing particle size causes a significant fluctuation in the drug's saturation solubility and dissolution speed.[24]

Zeta potential

Zeta potential plays a role in the stability of nano-suspensions. stabilising agent as well as the drug itself determine it. To stabilise a nano-suspension, the zeta potential must be at least 30 mV, and it must be at least 20 Mv to stabilise both the steric and electrostatic forces.[25]

Crystalline State and Morphology of particle

Amorphous or other polymorphic forms of the nano-suspensions crystalline structure may result from high-pressure homogenization. Understanding the drug's polymorphism or morphological alterations depends on the particle morphology and crystalline state. To assess the amount of the amorphous fraction and changes in the solid state of drug particles, X-ray diffraction and DSC analyses are used. To comprehend particle morphology, (SEM) is used.[26]

Saturation Solubility and Dissolution rate

Determination of the formulation's in vitro behaviour benefits from the evaluation of the saturation solubility and dissolution velocity. It can be enhanced by nano-suspensions.

Stability

Particle size plays a crucial role in determining stability. As the particle size of the Nano-suspensions increases it leads to an increase in surface area and higher dissolution rate The particle's surface energy rises with increasing particle size, which also increases the likelihood of agglomeration. By acting as a steric or ionic barrier, stabilisers have the dual purpose of reducing the likelihood of Ostwald ripening and improving the stability of the suspension. In the majority of cases, the nano-suspensions use stabilisers like cellulosic, poloxamers, PVA, polysorbates, HPMC, lecithin, polyoleate, and povidones. The stability is examined under various stress conditions, including varying temperatures (15, 25, 35, and 45°C), thermal cycling, mechanical shaking, and changes in the mean particle size that can be monitored for three months. Drug content, pH, and osmolarity are additional in vitro evaluation criteria.[27]

B) In-Vivo Pharmacokinetic correlation

The drug and administration route are important factors in the in vivo assessment of the nanosuspensions. The formulation can be administered via the necessary route, and HPLC-UV visible spectrophotometry was used to estimate the plasma drug levels. Other factors that are typically assessed in vivo include surface hydrophilicity, adhesion characteristics, and interactions with body proteins.

Applications

Oral drug delivery

For drugs that must be taken orally, such as antibiotics, atovaquone, and bupravaquone, the oral route is the most practical and recommended one. Due to the enhanced saturation solubility and increased gradient between the gastrointestinal tract lumen and blood, as well as the increased drug dissolving velocity, the nanosizing approach can significantly boost oral absorption and enhance bioavailability. By maintaining stable blood levels in the plasma, oral administration of the high pressure homogenised Amphotherin B Nano-suspensions efficiently lowers parasite counts.[28]

Parenteral drug delivery

Patients who experience vasospasm due to subarachnoid haemorrhage are prescribed nimodipine. Nimodipine has a limited bioavailability when administered orally because the liver has a high rate of first-pass metabolism. An alternative to oral treatment that may offer improved absorption is intravenous injection. Compared to Nimodipine nano-suspensions taken orally, Nimodipine nano-suspensions given intravenously cause less local irritation.

Pulmonary drug delivery
Nano-suspensions can be created for drugs that are not well soluble in pulmonary secretions. The drugs are administered either as dry powders for dry powder inhalers or as suspension aerosols. Ultrasonic or mechanical nebulizers are used to achieve nebulization.

Ocular drug delivery
Drugs with low lachrymal fluid solubility greatly benefit from nanosuspensions. The nano-sizing technology accounts for increased solubility, a higher dissolution rate, higher bioadhesion, corneal penetration, and resident length in a cul-de-sac while avoiding the high tonicity produced by water-soluble medications. The effectiveness of an ocular treatment will rise if the particle diameter is decreased to less than 10 m because it will lessen particle irritants to the eye and decrease weeping. It was demonstrated, for instance, that the nano-suspensions of hydrocortisone, prednisolone, and dexamethasone improve the rate of dissolution, the volume of ocular drug absorption, and the potency of therapeutic action.[29]

Target drug delivery
As their surface characteristics and in vivo behaviour may be changed by modifying the stabilisers and surfactants, nano-suspensions can be employed for targeted drug delivery. By utilising various surface coating techniques for active or passive targeting of the optimum place, sheath nano-suspensions were designed.

Bioavailability enhancement
A nano-suspension uses stabilisers and surfactants to solve the issue of inadequate bioavailability. Oleanic acid's poor solubility is overcome through a nano-suspension formulation. When lyophilized nano-suspensions powder was compared to the dissolution of conventional dosage forms, the lyophilized nano-suspensions powder disintegrated 90% faster in 20 minutes, considerably improving the therapeutic impact.

Topical formulations
The saturation solubility of the drug in the topical dosage form increases when the drug's nanocrystalline form is added to creams and water-free ointments. This increases the drug's diffusion into the skin, increasing its bioavailability and permeability.

Mucoadhesion of the nanoparticles
Orally administered nanoparticles that are in suspension permeate into the fluid medium and soon penetrate the mucosal surface. Due to bioadhesion, the particles are immobilised at the intestinal surface.

Following this, the concentrated suspension serves as a particle reservoir, and an adsorption process occurs very quickly. The bio-adhesive phase occurs before the particle is absorbed. The nano-suspensions' adhesiveness, according to Ghobad Mohammadi, enhances the bioavailability and targeting of the parasites still present in the GIT.[30]

CONCLUSION
Nano-suspensions offer a novel yet commercially viable solution to the problems of poor bioavailability and solubility. Large-scale manufacture of nanosuspensions has been accomplished with the use of methods like media milling and high-pressure homogenization. The most intriguing characteristics of nanosuspension are its higher bioavailability, increased saturation solubility, and increased dissolving rate. One of the biggest problems formulation scientists encounter is poor aqueous solubility. Any method of drug administration can benefit from the therapeutic performance enhancement provided by nanocrystal formation.

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