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Nanosuspension: A Modern Approach In Drug Delivery System- A Review

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Abstract

The drugs moiety included in Biopharmaceutical Classification System Class II and Class IV has low aqueous solubility and remedy for the solubility problem is nanotechnology techniques. Nanotechnology techniques play an important role at the molecular level and nano length scale size. To increase the dissolution rate of drug moiety which directly lead to increase bioavailability of drug depends on decrease drug particles into nano-scale range. Nanotechnology techniques in the pharmaceutical field include nanosuspension. Nanosuspension is biphasic dosage forms contain colloidal dispersions of nanosized drug particles which are stabilized by surface-active agents. Nanosuspension dosage form increases the stability and bioavailability of low aqueous soluble drugs. Solubility plays a crucial role in the effectiveness of drugs irrespective of the route of administration. Most of the presently investigated drug moieties having lower aqueous solubility and therefore has low bioavailability of drugs. The study is focused on formulation consideration, various methods of preparation along with evaluation parameters of nanosuspension.

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INTRODUCTION

There are certain poorly soluble drugs that do not mix easily with gastric fluids. The stability and bioavailability of such drugs can easily be improved by Nanosuspension technology. Nanosuspensions are drug delivery systems consisting of two phases in which pure drug particles dispersed in an aqueous phase and surfactants are added to make a uniform mixture. Nanosuspensions are comparatively simpler to prepare and have many advantages over other delivery approaches. Nanosuspensions are prepared by various techniques such as wet milling, high-pressure homogenization, emulsification-solvent evaporation, and supercritical fluid extraction. This drug delivery sys-

tem does not have any limitations in the case of administration. It can efficiently be delivered by various routes, including oral, parenteral, pulmonary, and ocular routes.

This study reviews the recent methods used to prepare nanosuspensions and their application in the delivery of dosage form. Nanosuspensions are prepared by colloidal dispersions of nano-sized drug particles in the desired phase and the two immiscible phases are stabilized by surfactants. Nanosuspension consist of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 μm in size. (Mosharraf and Nyström, 1995)

Nanosuspensions are preferred in the preparation of dosage forms in which the drugs are insoluble in the required medium. The minute colloidal particles of the required drugs are dispersed in the medium which is best for administration and stabilized using a palatable surfactant. This, in turn, increases the rate of flooding of the active compound and the required plasma concentration is achieved (oral or intravenous [IV] administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. This technique is used for molecules with poor solubility, poor permeability, or both. Before the development of novel drug delivery systems like this, such drugs caused enormous challenges to the formulators. Such drugs can be administered by Intravenous route only if the size of the drug is in nanometers. Water-insoluble drugs show poor bioavailability, and with recent development and discovery of drugs, a large number of essential drugs are found to be water-insoluble and hence nanosuspensions are found to have a great use these days. It is a very convenient solution to enhance the solubility of hydrophobic drugs.

On industrial scale, nanosuspensions are prepared by media milling and high-pressure homogenization technique. Recently, certain emulsion and microemulsion are used as templates for nano solutions and are administered by parenteral, oral, ocular, and pulmonary routes. Now their application also extended to site-specific delivery. Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion.

Necessity and merits of Nanosuspension

For better drug delivery, required features are contained in nanosuspensions which are as follows. (Vdn and Svn, 2009)

1. Reduced Nano-particle size, extend rate & extent of absorption, fast dissolution rate.
2. More stability when compared to other products.
3. Nanosuspensions can be prepared from drug with High log p-Value, possess enhanced bioavailability.
4. Drugs which are insoluble in water but soluble in oil can be designed as Nanosuspension.
5. Nanosuspension can be administered by a various route like Oral, topical, Pulmonary, Parenterals etc.
6. Nanosuspensions can also be included within tablets, capsules, or even in Suppositories.
7. Passive targeting can be achieved by drug nanosuspension
8. In vivo Performance is enhancing in nanosuspension due to high dissolution rate and solubility of saturation.
9. Uncomplicated manufacturing and unchallenging scale-up during large scale production.
10. In case of target-specific drug delivery Surface medication can be possibly done.
11. In nanosuspension the amount of amorphous portion of the drug is sufficiently increased, which induces high saturation solubility. Potential changes in crystalline structure also occur leading to enhance bioavailability.

Demerits of Nanosuspensions

1. Like conventional suspensions Physical instability, sedimentation, and compaction are the major problems in Nanosuspensions.
2. Nanosuspensions are bulky hence utmost care should be taken during transportation.
3. Uniform and accurate dose cannot be achieved unless suspensions are in the proper dose. (Krishna and Prabhakar, 2011a)

Basis of Drug selection for nanosuspension

Drugs should possess the following properties for formulating as nanosuspension

1. Drug or API with high log P value i.e. insoluble in water but dissolve in oil or immiscible in both water and oils.
2. Drug with a highly effective dose amount.

3. Crystalline API which tends to remain not dissolved irrespective of solvent. Yadav *et al.*

Formulation consideration of nanosuspension

Stabilizers

To avoid agglomeration and aggregation of drug particles in nanosuspension a proper stabilizer is very much needed. This is the major cause of physical instability in nanosuspensions, hence stabilizers are essential to be incorporated for stable nanosuspension. E g. Polysorbates. (Jaiswal *et al.*, 2016)

Solvents

Organic solvents were used in nanosuspension when microemulsions were taken as templates. As organic solvents are hazardous, less hazardous solvents like ethanol, methanol is selected for use and ensure their removal from the formulation. (Shah *et al.*, 2015)

Surfactants

Surfactants are used to reduce interfacial surface tension, improve the wettability of drug particles in nanosuspension. Also used as a deflocculating agent e.g. Tweens and spans. (Vedaga *et al.*, 2019)

Co-surfactant

Selection of Co-surfactant is crucial when Nanosuspention Formulated by taking microemulsion as a template. It affects the Phase operation. Hence the effect of c0-surfactant on the internal phase of microemulsion should be inspected. E.g. Ethanol, iso-propanol, glycofurol. (Geetha *et al.*, 2014)

Other ingredients

Additives used in nanosuspensions are buffers, polyols, osmogents, cryoprotectants. Other additives used to depend on the physicochemical properties of the API or administration route. (Sahu and Das, 2014)

Method of preparation of nanosuspension

Two opposite action methods are used for making nanosuspensions, those are Bottom up and Top-down Technology.

Bottom-up Technologies

Antisolvent precipitation

This method can be used efficaciously for the preparation of nano-size drug particles. In this method firstly drug was dissolved in a solvent, this mixture is then immediately added into antisolvent. The solution made to supersaturate, which further results in precipitation of crystals for the better stability of nanosuspension, the stabilizer used should have empathy for particle surface. Also, it should have high diffusivity for covering of precipitate matter surface. Quantity of stabilizer should be such as it should cover the Particle surface. (Krishna and Prabhakar, 2011b) E.g. all-trans retinoic acid nanosuspension prepared using this technology. This method involves simple and low-cost equipment. The advantage of this method is it achieves higher saturation solubility which is not done in other methods for the preparation of nanosuspension. This method has certain demerits like, it is not applicable to poorly soluble drugs both in aqueous as well as non-aqueous solvents. (Zhang *et al.*, 2006)

Top-down Technologies

Media milling (nanocrystals or nanosystems)

In this technique, high shear media mills or pearl mills are used for the preparation of nanosuspension. The media mill comprises of milling and recirculation chamber with a Shaft. The milling medium is enclosed of glass, zirconium oxide, or cross-linked polystyrene resin. The milling chamber is inflicting with milling medium and drug stabilizer which is rotated at a very high shear rate. It is done under the controlled condition of temperature & humidity. Impaction of milling media with drug produces high energy and shear forces. This energy is utilized for the size reduction of the drug from micro to nano-sized. The distribution profile of single-mode and mean diameter of <200 is required within 30-60 min. Once the method optimized batch to batch variation can be done to improve the quality of dispersion. Naproxen nanosuspension was prepared by a pearl milling technique with a particle size of 300-600 nm. (Ain-Ai and Gupta, 2008)

High-pressure Homogenization (DissoCubes)

As the name indicates high pressure, 100-1500 bars are involved. At this pressure particles easily converted to nano-size. Particles of micron size i.e. <25 μm are required for that drug should pass through the jet mill. This method can be used for batch as well as continuous processing. Equipment capacity is 40 ml-1000 L. we have to prepare the presuspension form by jet milling. (Sutradhar *et al.*, 2013)

Emulsion as Template

Drugs that have partially solubility in water and complete insolubility in organic solvents are selected for the preparation of nanosuspension by this method. Organic solvents used were methylene chloride and chloroform. Due to the hazardous nature of organic solvents, their use is restricted nowadays in the manufacturing of nanosuspension. Ethyl formate and ethyl acetate are still taken into consideration for use, as they are relatively

safer. (Rabinow, 2004)

Microemulsion Template

The microemulsion was thermodynamically stable. The microemulsion is clear suspension of oil and water which made miscible by the use of surfactants and co-surfactants. Drug nanosuspension was prepared by dilution of the microemulsion. Drugs can be included within the internal phase of the microemulsion, or microemulsion was saturated with drugs by inward mixing. Eg. Griseofulvin nanosuspension is prepared by microemulsion technique using water butyl lactate, lecithin, and the sodium salt of taurodeoxycholate. (Chingunpituk, 2011)

Combination Technologies

This method involves a pretreatment step followed by a high energy step. The NANODGTM technology uses this precipitation process first and followed by an annealing step with high energy. Annealing is a process in which thermodynamically unstable substances made more stable by application of high energy, with subsequent thermal relaxation. According to Patent claim, the annealing process prevents the growth of precipitated nanocrystals. This energy lowering can be done by converting the solid form to the ordered lattice structure. This minimum energy stabilization achieved by rearranging surfactants at the interface of two immiscible phases. (Shegokar and Müller, 2010)

Evaluation parameters

Dose uniformity

10 ml of each formulation was withdrawn and add in 10 mL of isotonic solution and kept it for 12-14 hrs. 10 mg of drug used in nanosuspension was measured and diluted to the strength of 1010μg/mL. The dilutions were filtered and analyzed for dose uniformity utilizing UV-spectrophotometer. The λ_{max} was set at 245 nm.

Absorbance of formulation was measured. The concentration of drug in formulation can be calculated from absorbance of known standard solution. (Mudgil *et al.*, 2012)

pH

Nanosuspension pH can be measured using digital pH meter at temperature 25$\pm$1 $\circ$C. The electrode of pH meter was a dip into the formulation and allowed to equilibrate for 1 min. Three observations were recorded and the mean was calculated with standard deviation. (Yadav and Singh, 2012)

Particle shape and Size

Particle shape and size of the nanosuspension can be evaluated by utilizing Scanning Electron Microscopy. (Kolaib and Sharma, 2013)

In vitro drug release

In-Vitro drug release studies were performed in the dissolution apparatus using the paddle method with a rotation speed of 50 rpm. The dissolution medium used was 900 mL maintained at a temperature of 37.0$\pm$0.2 $^\circ$C. Samples were withdrawn at fixed time intervals, filtered and the assay was performed. The assay of samples was done by UV absorption determination at 245 nm using the Shimadzu UV spectrophotometer. (Prasanta, 2012)

CONCLUSIONS

The nanosuspension has been proved out to be a game-changer for the administration of low aqueous soluble drugs, and hence the issue of low bioavailability of drugs can easily be encountered. There are a few other formulation approaches which help to resolve the problems of low solubility and low bioavailability but Nanosuspension not only solves the problems of low solubility and bioavailability but also alters the pharmacokinetics of the drug and thus improves drug safety and efficacy. Most of the presently investigated drug moieties having lower aqueous solubility and therefore has low bioavailability of drugs. Apart from increasing the solubility and bioavailability of the drug, the administration of a certain drug in nanosuspension technology provides certain special characteristics to the drugs, such as the enhanced dissolution rate and saturation solubility. This review study is focused on formulation consideration, various methods of preparation along with evaluation parameters of nanosuspension.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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