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Review Article

Nanosuspension: A Novel Approach for The Treatment of Hyperlipidaemia

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ABSTRACT

Hyperlipidaemia is a condition characterized by increased levels of lipids in the bloodstream, which can lead to cardiovascular diseases such as stroke. The medications used to treat hyperlipidemia include statins, fibrates, and cholesterol absorption inhibitors, all of which have low water solubility, dissolution, and bioavailability. To address the issue of poor aqueous solubility, these BCS class II drugs often undergo nanosuspension formulation. Nanosuspensions, which are colloidal dispersions of nanosized drug particles, present a promising method for enhancing the pharmacokinetic characteristics of poorly water-soluble drugs. By reducing particle size to between 100 and 600 nm or converting the crystalline form of the drug into an amorphous form, nanosuspensions exhibit a high dissolution rate. During the preparation of nanosuspensions, stabilizers play a crucial role in reducing particle size and preventing the aggregation of drug particles.

INTRODUCTION

Hyperlipidaemia is a medical condition characterised by elevated levels of lipoproteins (LDL, VLDL) and triglycerides, along with decreased levels of HDL (High-density lipoprotein), commonly referred to as good cholesterol. As lipoprotein levels increase, plaque

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forms in the blood vessels. A significant accumulation of plaque can disrupt blood flow and potentially lead to a stroke. The oral route of drug administration exhibits high patient compliance. BCS class II drugs demonstrate low bioavailability due to their low aqueous solubility. To enhance the solubility and bioavailability of BCS class II drugs, nanotechnology has transformed drug delivery and research. Within nanoparticles, there are nanosuspensions, polymeric nanoparticles, and lipid nanoparticles. Nanosuspension refers to the colloidal dispersion of solid drug particles in an aqueous phase, with a particle size ranging from 100 to 600 nm. In the nanosuspension, there are pure drug or API and stabilisers or surfactants. The pathophysiology of hyperlipidaemia is based on the increasing levels of lipoproteins except HDL. Lipoproteins are HDL (high-density lipoprotein), LDL (low-density lipoprotein), VLDL (very low-density lipoprotein), Triglycerides (TG), and Chylomicrons (CH)

Current treatment and limitations of treatment

In the current treatment of hyperlipidaemia, there are

- ✓ Statins
- ✓ Fibrates
- ✓ Bile acid sequestrants
- ✓ Lipolysis
- ✓ Sterols

Table No. 1: MOA & Limitations of treatment of hyperlipidaemia

Drug class	Examples	Daily dose (mg) [1]	MOA [2]	Limitations [1]
Statins (HMG-CoA reductase inhibitors)	Lovastatin Simvastatin Pitavastatin Rosuvastatin Atorvastatin Provastatin	10-80 5-40 10-80 5-20 10-80 40-80	By blocking HMG-CoA reductase, reducing hepatic cholesterol synthesis, and boosting the removal of LDL cholesterol from the bloodstream	Hepatotoxicity, Myopathy, and the safety of statins during pregnancy have not been established
Fibrates (Fibric acid derivatives)	Gemfibrozil Bezafibrate Fenofibrate	1200 600 200	Fibrates activate the PPAR-α receptors, which increase the lipoprotein lipase, leading to lower TG and decreasing VLDL in the liver.	Myalgia, Rashes, Eosinophilia, Blurred vision and Myopathy is uncommon
Niacin	Nicotinic acid	2k-6k	Because niacin inhibits hormone-sensitive lipase, TGs are broken down into free fatty acids less frequently. Hepatic TG synthesis is decreased when fewer FFAs enter the liver, which lowers the VLDL.	It acts as vasodilator at high doses, Dyspesia, Dryness and Hyperpigmentation, Gout and should not use in the diabetics
Cholesterol absorption inhibitors	Ezetimibe	10	By inhibiting the NPC1L1 transporter in the small intestine, cholesterol absorption inhibitors like EZ reduce blood cholesterol levels by preventing the absorption of dietary and biliary cholesterol. As a result liver receives less cholesterolwhich causes it to increase LDL receptors. This improves the liver's ability to remove LDL.	No specific Adverse effect except reversible hepatic dysfunction and rarely mytosis noted

Comparison between conventional & nanosuspension [7]

The comparison table between the conventional dosage and the Nanosuspension dosage forms for easy understanding

Table no:2 Comparison of Conventional and Nanosuspension

Parameters	Conventional dose	Nanosuspension
Solubility	Low for BCS II	High due to Low particle size
Bioavailabiliy	Low for poorly soluble drugs like BCS II	High due to the Large surface area
Onset of action	Slow	Faster
Dose required	The dose requirement is high	The dose requirement is low
Formulation Complexity	Simple formulation	Complex formulation
Stability	Highly stable	Unstable because of particle agglomeration
Administration	Mostly Oral	Suitable for Oral, Ophthalmic, and Topical
Patient Compliance	Moderate	Better for lower doses
Cost	Low	High

Preparation methods of nanosuspensions; [4,5]

In the preparation methods of Nanosuspensions, there are Bottom-Up technology, Top-Down technology, and Combination Technology.

- **Bottom-Up technology;** In this approach drug is dissolved in a solvent phase (Methanol, Ethanol, Acetone, etc) and then precipitated as nanoparticles in the presence of an anti-solvent (water). In Bottom-Up techniques, there are Solvent-Anti-Solvent, Supercritical fluid, and Lipid emulsion methods.

- **Top-Down technology;** In this approach drug will become nanosized from large particles using mechanical forces. In the Top-down technique, there are Media milling method, High-pressure homogenization, nanoedge, and Nanopure methods.

- **Combination technique**; It integrates both Bottom-Up (Precipitation) and Top-down (High pressure homogenisation) approaches

Bottom-up technique; [4]

Solvent-anti-solvent Method- This method comes under the Precipitation method. In this method, the drug is dissolved in an organic solvent phase and the stabilizer is dissolved in the aqueous phase. After dissolving the boh phases solven phase is added to the aqueous phase in a drop-by-drop manner with continuous stirring. After the stirring, the formulation undergo sonication for reducing the particle size.

Table No. 3: Advantages and Disadvantages of solvent Solvent-Solvent Method

Advantages	Disadvantages
Simple and easy process	Drug loading is low.
Low energy and no heat generation	Particle aggregation is high.

Top-down technique; [5]

Media milling method: This method works on the high shear media mill. The chamber contains water, Drug, stabilizer, and milling media (glass + zirconium oxide + resins). This chamber rotates at

high speed for 2 to 5 days to break down the particle size. Her some of the advantages and disadvantages of the media milling method

Table No. 4: Advantages and Disadvantages of Media Milling

Adavantages	Disadavantages
By this method, we can prepare very dilute as well as very concentrated formulations.	It is a time-consuming process.
Easy method to perform	Some fragments can be in the micro-sized

High pressure homogenization method; In this method, there are mainly 3 steps. In the 1st step, the drug is dispersed into stabilizer solution, and this solution is homogenized in high pressure and finally homogenized at high pressure for 15 to 25 cycles until to get the desired nano-sized particles and. In this method, there are Homogenization in Aqueous media, in Non-aqueous media, and Nanoedge. Here are some of the advantages and disadvantages of the HPH method

Table No. 5: Advantages and Disadvantages of the HPH Method

Advantages	Disadvantages
The major advantage is no ned for Organic solvents	Possibility of contamination
Having high stability and uniform particle size	High energy input for these lads to high a cost

Combined techniques; [5]

Emulsion diffusion method; The Drug and stabilizer are dissolved in a suitable solvent, and the stabilizer is dissolved a water. Add the solvent phase into to aqueous phase with continuous phase under ultrasonication for reducing the droplet size. Add a large amount of water and let the solvent evaporate in the solution.

Table No. 6: Advantages and Disadvantages of Emulsion Diffusion

Advantages	Disadvantages
No need for high shear	Having stability issues
Having a good encapsulation Efficiency	Low drug compatibility

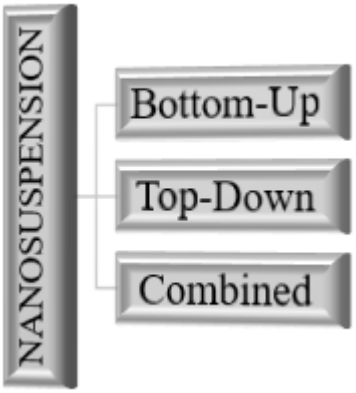

Figure 1: Flow chart of the preparation of nanosuspension

Excipients in the preparation of nanosuspension [6]

Table no 7 Excipients in Nanosuspensions

Category	Function and example
Stabilizers	In stabilisers, there are polymers (poloxamer 188) and Surfactants (SLS) which are helpful in stabilization and to prevent the nanoparticle aggregation.
Solvents	These are used in the precipitation method to dissolve the drug and to provide steric stabilization. Examples are Methanol, Ethanol, Acetone
Anti-solvents	It helps in the formation of the precipitate of the drug in the solvent. Examples are water and suitable pH buffers.
Other additives	Other additives are Tonicity adjusters (Sodium chloride) to maintain isotonicity in the parenteral dosage forms.

Evaluation parameters of nanosuspensions;

The evaluation parameters of nanosuspension are

- ✓ Particle size and Poly dispersity Index
- ✓ Zeta potential
- ✓ Drug content
- ✓ Drug entrapment efficiency
- ✓ Saturation solubility
- ✓ Scanning Electron Microscopy
- ✓ Transmission electron microscopy
- ✓ In vitro or Dissolution studies
- ✓ In vivo studies

Particle size analysis [5,6]: Particle size affects the Physicochemical properties like solubility and dissolution rate. To analyse the particle size of the formulation Particle size analyser (Zetasizer) is used, and the particle size should be in the 100 to 600nm range.

PDI [4]; Poly Dispersity Index is to know the uniform particle sizes, and it should be <0.1 to get the monodisperse particles, and the Dynamic Light Scattering evaluates it

Zeta Potential[7]; It is to know the stability of the suspension and to know the electrostatic forces between the dispersed particles, and the minimum zeta value is 30 mV

Drug Content: The weighed amount of the formulation is subjected to high-speed centrifugation to separate drug-loaded nanoparticles. After collecting the supernatant liquid, add a suitable solvent and sonicate the mixture. Then, filter the solution and measure the absorbance using UV-visible spectrophotometry, comparing it with the calibration curve.

Drug content (%) = (amount of drug estimated/Theoretical drug content) X 100

Drug Entrapment Efficiency: Centrifuge the formulation at high speed to separate the free drug. Collect the supernatant liquid and filter it. After filtration, measure the absorbance by UV-visible spectrophotometry and compare it with a calibration curve.

EE = Total drug- Free drug/Total drug

Saturation Solubility[4, 5]**;** It is necessary to evaluate the drug's saturation solubility in various physiological buffers and at various temperatures, utilizing techniques outlined in the literature. Assessment of saturation solubility helps in figuring out the formulation's in vitro behaviour

SEM: Scanning Electron Microscopy; It is used to determine the shape and morphological structures of the suspended particles

In Vitro Studies; It is performed in a basket or paddle type dissolution apparatus with a suitable buffer and at a temperature of 37 degrees Centigrade with paddle speed 50 rpm.

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