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NANOSUSPENSIONS - A PROMISING NOVEL DRUG DELIVERY SYSTEM

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Abstract:

In the recent times there has been a tremendous increase in the novel drug delivery systems, hence nanotechnology i.e. use of Nano sized particles has been an emergent drug delivery system to meet the desired needs and efficacy of drug substances. Nano refers to particle size range of 1-1000nm. A nanosuspension can be defined as a very fine colloidal dispersion of drug particles in the aqueous vehicles with certain excipients as stabilizers, co-surfactants, organoleptic agents etc. Solubility is one of the major concerns in the modern drug discoveries hence the basic need for nanosuspension is to create a larger surface area of drug particles and to administer the drugs which are insoluble and increases the bioavailability. These can be administered by oral, parenteral, ocular and pulmonary routes. Nanosuspensions are a very promising strategy for hydrophobic drug substances. Various techniques of their preparation have been patented and applied. This review article describes about the methods of preparation, merits and demerits, application, and evaluation parameters.

Keywords: *Nanosuspensions, Homogenization, Media milling, Formulation, Evaluation*

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INTRODUCTION:

A pharmaceutical suspension may be defined as a heterogenous mixture in which internal phase gets uniformly dispersed in the external phase. It can also be explained as a heterogenous mixture in which insoluble solid particles get uniformly dispersed in the liquid medium. Internal phase of the suspension consists of insoluble particles which are of specific size range and uniformly maintained in the suspending vehicle by a single or a combination of suspending agents. The external phase or suspending medium is generally aqueous in nature. The absorption of the drugs from the intestine mainly depends on the solubility of the drug in the intestinal fluids. Some drugs show poor solubility due to poor dissolution rate which leads to insufficient absorption. About 40% of the new drug molecules that are being generated through drug discovery are either lipophillic compounds or are poorly water-soluble. There are various conventional methods for increasing the solubility of poorly soluble drugs such as micronization, surfactant dispersions, oily solution, salt form, precipitation technique, solubilization using co-solvents and many more but these techniques lack in the universal applicability to all drugs. These techniques are inapplicable for the drugs which are insoluble in aqueous and organic solvents. To overcome this problem different nanosized formulations have been developed. These preparations are favoured for the compounds that are insoluble in water with a high log P value, high doses and high melting point. This technique is also applicable for the compounds that are insoluble in both organic solvents and water. [1-5]

A Nanosuspension may be defined as a colloidal dispersion in which solid drug particles are uniformly dispersed in liquid phase with average particle sizes below 1 μm and are stabilized by the use of surfactants. Nanosuspensions are more advantageous and easy to prepare than other approaches. There are various techniques through which Nanosuspensions are prepared such as high pressure homogenization, super critical fluid, emulsification solvent evaporation and milling. It has an advantage of delivery through various routes like parenteral, ocular, pulmonary and oral.Nanosuspensions are used to increase the solubility of the drugs which are poorly soluble in lipid as well as aqueous media. The reduced size of the particles help in the intravenous administration of the poorly soluble drugs without any blockade in the capillaries.[6-8]

Advantages

1. Suspension has the ability to mask the bitter or unpleasant taste of the drug.
2. Chemical stability of the drugs is improved.
3. Onset of action and duration of the drug can be controlled.
4. Drug in the form of suspension shows a higher rate of bioavailability.
5. They enhance the solubility of drugs.
6. Hydrophilic drugs can be incorporated.
7. Higher drug loading.
8. Dose reduction is possible.
9. Passive drug targeting can be enhanced.
10. Capillary blockade can be avoided, since the particle size in the nanosuspensions is less than the smallest blood capillaries in the body.

Disadvantages

1. Uniformity and accurate dose in the suspensions cannot be achieved.
2. Sedimentation property, compaction behavior and physical stability of the suspensions can cause problems.
3. Suspensions are bulky; therefore special care must be taken during handling and transport.

Methods of Preparation of Nano Suspensions:

The basic techniques that can be employed for the preparation of Nano suspensions are: Generally two methods of preparation of Nanosuspensions are employed. The conventional method includes precipitation technique and is called 'Bottom up technology'. In this technique the drug is dissolved in a solvent, then added to non-solvent and crystals are precipitated. The 'Top Down Technologies' include Media Milling, High Pressure Homogenization, and combination of Precipitation and High-Pressure Homogenization etc.[9-20]

1) Homogenization
2) Media milling
3) Emulsification
4) Precipitation
5) Supercritical fluid process
6) Nano jet Technology
7) Dry co-grinding

The above various methods of preparation of nanosuspension are discussed below:

Homogenization

It is one of the widely used methods for the preparation of nanosuspensions. Primarily, the drug powders are dispersed in a stabilizer solution to form a pre-suspension. Then this involves the forcing of the prepared suspension under pressure through a valve having a narrow aperture than pre-suspension at a low pressure for several times and is finally homogenized at a high pressure for 10-20 cycles until the nanosuspensions with the desired size are obtained. A Nanosuspension with a higher concentration of solids can be prepared by using very

fine drug particles are required, which can be obtained by pre-milling. APV micron LAB 40(APV Deutschland GmbH, Lubeck, Germany) is the most commonly used homogenizer for the preparation of nanosuspensions. DissoCubes technology is an example of this technique.

Advantages
- Erosion of processed materials is not seen.
- Both dilute and concentrated products can be prepared by handling 1mg/ml to 400mg/ml drug quantity.
- It is applicable to the drugs that are poorly soluble in both aqueous and organic media.
- General applicability to most drugs.
- It is a Simple technique.
- Aseptic production of nanosuspension is possible.

Disadvantages
- Preprocessing of the drug is required.
- High cost instruments are involved thus increases the cost of dosage form.
- High number of homogenization cycles may be required.

Media milling

It is an example of Top-Down technology. In this, nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with media, water, drug and stabilizer rotates at very high shear rate at controlled temperatures. Generally the medium is of glass, highly cross-linked polystyrene resin and zirconium oxide. The particles get nano sized due to the high amount of shear acting on them inside the mill. Equipment like planetary ball mills can be used for this purpose.

Advantages
- Involves a simple technology.
- Low-cost process.
- Large-scale production can be made possible.

Disadvantages
- Product contamination due to erosion may occur.
- Duration of the process is not production friendly.
- Growth of germs in the water phase if milled for a long time.

Emulsification

It is the technique that involves the preparation the of drug solution by emulsifying it in another liquid that is non-solvent. Then the solvent is evaporated which concentrates the product. Evaporation of the solvent leads to precipitations of the drug. Sometimes crystal growth and particle aggregation occurs that can be controlled by creating high shear force using a high velocity stirrer. Few other emulsifying techniques include Melt emulsification method, Micro-Emulsion template etc.

Advantages
- Specialized equipment is not necessary.
- Particle size can easily be controlled.

Disadvantages
- Poorly soluble drugs both in aqueous and organic media cannot be formulated by this technique.
- High amount of surfactant/stabilizer is required as compared to other production techniques

Precipitation

The most common method used is anti-solvent addition method in which the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti solvent. Mixing processes vary considerably. Precipitation has also been coupled with high shear processing. This process involves two phases, 1) Nuclei formation and 2) Crystal growth. In the preparation of a stable suspension with minimum particle size, a high nucleation rate and low growth rate is necessary. Both of these are dependent on temperature, the optimum temperature for nucleation might be below that for crystal growth, which permits the temperature optimization that is stabilized by an interfacial film of surfactant.

Advantages
- Simple process
- Low cost equipment
- Ease of scale up

Disadvantages
- Drugs have to soluble at least in one solvent and this solvent needs to be miscible with a non-solvent which is not always easy.
- Growing of drug crystals needs has to be controlled by addition of surfactants.

Supercritical fluid process

It is a nano-sizing and solubilization technique whose application has increased particle size reduction by supercritical fluid processes. Supercritical fluid can be defined as a dense non condensable fluid whose temperature and pressure are greater than its critical temperature and pressure. This process allows micronization of drug particles. Current processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm. Sometimes poor solubility of the surfactants and drugs in the supercritical fluids and the requirement high pressure for these processes reduces its utility.

Nano jet Technology

It is also called as opposite stream technology. In this technique a stream of suspension is divided in two or more parts then passed with high pressure and made to colloid with each other. And due to these high shear forces produced during the process the reduction of particle size occurs.

Dry co-grinding

Nanosuspensions can be obtained by dry milling techniques by dry-grinding of the poorly soluble drugs with soluble polymers and copolymers after dispersing them in a liquid media. Many soluble polymers and co-polymers such as polyethylene glycol (PEG), PVP, HPMC and cyclodextrin derivatives can be used. The poor solubility of the drugs can be improved by the addition of surfactants and co-surfactants. It is also an economic process and the use of organic solvents can be prevented.

Table-1: Patented/ Marketed products of Nanotechnology

Product Name	Active Ingredient	Phamacological Use
TriCor®	Fenofibrate	hypercholesterolemia
EMEND®	Aprepitant	Antiemetic
RAPAMUNE®	Sirolimus	Immunosuppressant
Triglide™	Fenofibrate	hypercholesterolemia
MEGACE® ES	Megestrol acetate	Appetite stimulant

Formulation of Nanosuspensions:

There are four basic parameters involved in the formulation of a nanosuspension. They are discussed below:[21-27]

1. Active Principles
2. Stabilizers
3. Organic solvents
4. Co-surfactants
5. Other

Important part of the nanosuspension in other words can also be called as the heart of the suspension. It is the active pharmaceutical ingredient (API) itself. The preparation may contain one or more active ingredients designed to gain the required action.

Stabilizers

These are added to the formulation for stabilizing the nanosuspension for a longer half-life and better quality product. This basically works by wetting the surface of the particles and prevents agglomeration of the suspension. Generally used stabilizers are poloxomers, polysorbate, cellulosics, povidones, and lecithins.

Lecithins is a choice when the preparation is meant for parenteral route.

Organic solvents

These are used in the formulation when emulsions are used as a template. Less hazardous solvents that are miscible in water like methanol, additives

Active Principles

This is the most chloroform, ispropanol, ethanol, and partially water miscible solvents ethyl acetate, ethyl formate, triacetin, propylene carbonate, butyl lactate, benzyl alcohol, are preferent in the formulation over the conventional solvents, such as dichloromethane.

Co-Surfactants

Selection co-surfactant is critical when using micro emulsions in the formulation of Nanosuspensions. Co-surfactants can greatly influence phase behaviour, the effect of it on the uptake of the internal phase for selected micro emulsion composition and on drug loading hs to be investigated. Although numerous literature describes the use of bile salts and dipotassium glycerrhizinate as cosurfactants, various solubilizers, such as Transcutol, isopropanol, glycofurol, ethanol can be safely used as co-surfactants in the formulation of nanosuspensions.

Other additives

Many ingredients such as buffers, pH modifiers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moietyto ensure the desired safety and efficacy of the product.

Evaluation of Nanosuspensions

Nanosuspensions are evaluated as same as conventional suspensions such as appearance, colour, odour, assay, related impurities etc. Along with these the other parameters like particle size, zeta potential, morphology, dissolution study; in-vivo studies are also performed.[28-37]

According toNoyes-Whitney equation, which is based on Fick's first law of diffusion, decreasing particle size causes an increase in particle surface area that in turn increases drug solubility in aqueous media contributing to an enhanced dissolution rate , this can be given by an equation:

$$dM/dt=DA/h\ (C\text{Bulk} - C\text{Eq})$$

In the above equation, dM/dt is the rate of dissolution, D is the average diffusion coefficient, A is the surface area of the solid, CBulk is the concentration of drug in the bulk solution, CEq is the concentration of drug in the diffusion layer surrounding the drug, and h is the diffusion layer thickness.

Increased solubility with reduction of particles size is also demonstrated by Ostwald-Freundlich equation:

$$(r) = C(\infty) \exp (2\gamma M/r\rho RT)$$

In the above equation, (r), $C(\infty)$ are the solubilities of a particle of radius r and infinite size,$M$is the molecular weight, ρ is the density of the particle, γ is the interfacial tension, r is the particle radius, R is the gas constant, and T is the temperature.

Organoleptic Characters

These characters can also be called as the organoleptic characters of the preparation. They are especially important in orally administered formulation. The variation in taste, can often be attributed to changes in particle size, crystal habit and subsequent\ particle dissolution. Changes in color, odor and taste can also indicate chemical instability.

Particle charge (zeta potential)

The calculation of zeta potential of a nanosuspension is important as it gives the physical stability parameters of the product. The electric potential at the shear plane is known as the zeta potential. It is governed by the stabilizer and the drug itself. For an electrostatically stabilized nanosuspension the minimum zeta potential of 30mV is required. In the case of a combined electrostatic or steric stabilizer, a zeta potential of 20 mv would be required or be sufficient.

Crystalline state and particle morphology

This has to be done to characterize the polymorphic changes due to impact of high-pressure homogenization on the crystal structure of the particles, for these techniques like X-ray diffraction in combination with differential scanning calorimetry or differential thermal analysis can be employed. The preparation may undergo a change in crystalline structure, that may be to an amorphous form or to other polymorphic forms because of the various production process employed.

Droplet Size

The droplet size can be determined by either light scattering technique or electron microscopy. The instrument called Dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm can be used for the evaluation test.

***In-Vivo* Biological Performance**

It is generally done in case of intravenous Nanosuspensions since the in-vivo behavior of the drug depends on the organ distribution, that in turn depends on its surface properties, like surface hydrophobicity and interactions with plasma proteins, Techniques such as hydrophobic interaction chromatography can be employed to determine the in vivo performances of the drug or the preparation.

Stability of Nanosuspension

The high surface energy of the particles causes agglomeration of the drug crystals. The stabilizer is to used wet the drug particles efficiently to prevent Ostwald ripening and agglomeration of the preparation and form a physically stable formulation. Examples of stabilizers include cellulosics, polysorbates, lecithin, poloxamer, polyoleate and povidones. According to Stoke's law, decreasing particle size, reducing the density difference of solid phase, and increasing the viscosity of the medium decrease the precipitation velocity

$$V = 2r2\ (\rho\ 1 - \rho\ 2)\ g/(9\eta)$$

Here, V is the precipitation velocity, r is the particle size, ρ 1 is themass density of particles, ρ 2 is the mass density of fluid, g is the gravitational acceleration, and η is the viscosity of the medium.

Applications

Nanosuspens have been proven to be very useful and efficient for various desired actions. A few of them are listed below: [38-42]

1. Nanosuspensions are formulated as drug in order to increase the dissolution rate, bioavailability of drug and saturable concentration.
2. Nanosuspensions are applicable in various routes of administration such as ophthalmic, topical, mucoadhesive, oral, parenteral, targeted drug delivery as well as pulmonary.
3. Nanosuspensions are also applicable for ocular drug delivery. Nanosuspensions are considered to be a boon for those drugs that shows poor solubility in lachrymal fluids.
4. Nanosizing of the drugs can lead to an increase in their bioavailabilty and oral absorption.
5. Intravenous administration of nanosuspensions is one of the most important aspect of this technology. Parenteral administration can lead to several advantages like improvement of the therapeutic effect of the drug which is available as conventional oral formulation, etc.

6. Saturation solubility increases in the nanocrystalline form which results in increased drug diffusion in the skin.
7. A nanoparticle can show an ability by which it can adhere to the mucosal surface due to small size of the particles. To increase the time of adhesiveness nanosuspensions are formulated with hydrogels which are made from mucoadhesive polymers.
8. Nanosuspensions can also be administered to Central Nervous System.
9. Drugs that undergo extensive first pass metabolism can be administered intravenously as nanosuspensions.

CONCLUSION:

Nanosuspension technology has proved to be a boon for the drugs that are poorly soluble in aqueous and organic solvents. The problem of poor bioavailability of the drugs which are hydrophobic in nature has been resolved to an extent by the implication of various techniques of Nanosuspensions. This technology can be combined with traditional dosage forms like tablets, capsules, pellets, for parenteral products which would eventually improve the performance and action of the drug substance. Transformation of any drug to nanoparticles leads to an increase in the saturation, solubility, dissolution, and providing the general feature of an increased adhesiveness to surfaces and increased bioavailability is one of the most important achievements.

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