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Review on Nanosuspension: A Promising Novel Drug Delivery System

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ABSTRACT

Biopharmaceutical classification system class 2 drugs have low solubility problems. To enhance the solubility of BCS class 2 drugs several methods are introduced by the researchers and formulation scientist. Nanosuspension is a novel drug delivery system which improves the solubility, stability, and bioavailability. In nanosuspension, the particle size of the drug is reduced to 10 to 1000 nm. Nanosuspension is a biphasic system that is stabilized by surfactant, polymer, or combination of both depends on the nature of the drug. Nanosuspension is used in oral, transdermal, injectable, inhalational, pulmonary, ocular, and topical form. Morphology of prepared nanosuspension was evaluated by transmission electron microscopy (TEM), Crystallinity of nanosuspension is confirmed by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). The preparation of nanosuspension in large scale production high-pressure homogenizer and media milling technique is used. In this review cover introduction, method of preparation, application, evaluation, and different drugs used in nanosuspension.

INTRODUCTION:

Now a day's researchers and formulation scientists facing the problem of poor water solubility of drugs. In the successful formulation of drugs, various parameters like solubility, stability at room temperature, compatibility with a solvent, excipient, and photostability play a critical role. Through the drug discovery program, today more than 40% of drug formulation are being generated which are lipophilic or have poor water solubility. To solve the issue of drugs having low solubility and poor bioavailability many formulation approaches are available.[7] The conventional approaches are micronization, incorporation of the fatty solution, addition of penetration enhancer or cosolvent, surfactant dispersion, salt formation, precipitation, etc. But at this technique has limited efficacy insolubility boosting for the drug having low solubility. There are other approaches such as, a vesicular system like liposome, solid dispersion, emulsion, and microemulsion method, which shows the great effect of a drug delivery system. But a lack of universal applicability to all drugs is a major drawback with this technique. Nanoparticle engineering has been advanced and reported for pharmaceutical applications over the last decade. By using the technique like bottom-up and top-down technology, the micronized drug is converted to the nanosuspension. Nanosuspension is a submicron colloidal dispersion of nanosized drug particle-stabilized by surfactant. Nanosuspension is made up of the drug having low water solubility, without any matrix material suspended in dispersion. For the molecules with low solubility, poor permeability, or both which have a considerable challenge for the formulator, this approach is very useful. The suspension can be lyophilized and into a solid matrix. It has also advantaged of liquid formulation over others. [1,7,18,24,29]

ADVANTAGES:[2,12]

1) Enhance drug loading.

2) Reduce the particle size, increasing dissolution rate, increase the rate and extent of absorption.

3) Long term physical and chemical stability.

4) Targeted drug delivery.

5) Ease of manufacture and large-scale production.

6) Drugs having high log p-value can be used for nanosuspension formulation to increase their bioavailability.

7) Nanosuspension can be formulated by compound and soluble on water but exhibit solubility in all.

8) The nanosuspension technology can enhance the amorphous structure in the particle that may lead to a change in solubility and crystalline structure.

9) Nanosuspension delivered through various routes e.g. Oral topical parenteral ocular pulmonary etc and this nanosuspension incorporated in tablet hydrogel suppositories and pellets.

METHOD OF PREPARATION: There are two main techniques involved in the preparation of nanosuspension. [1,3,5,7,14,18]

1) **Top-down method.**[30]

a) **High-pressure homogenizer.**

b) **Nano pure.**

c) **Nano edge.**

d) **Media Milling technique**.

2) **Bottom-up technique**

a) **Supercritical fluid process.**

b) **Solvent - Antisolvent precipitation method.**

c) **Emulsification solvent evaporation.**

d) **Lipid- emulsion/ Micro-emulsion.**

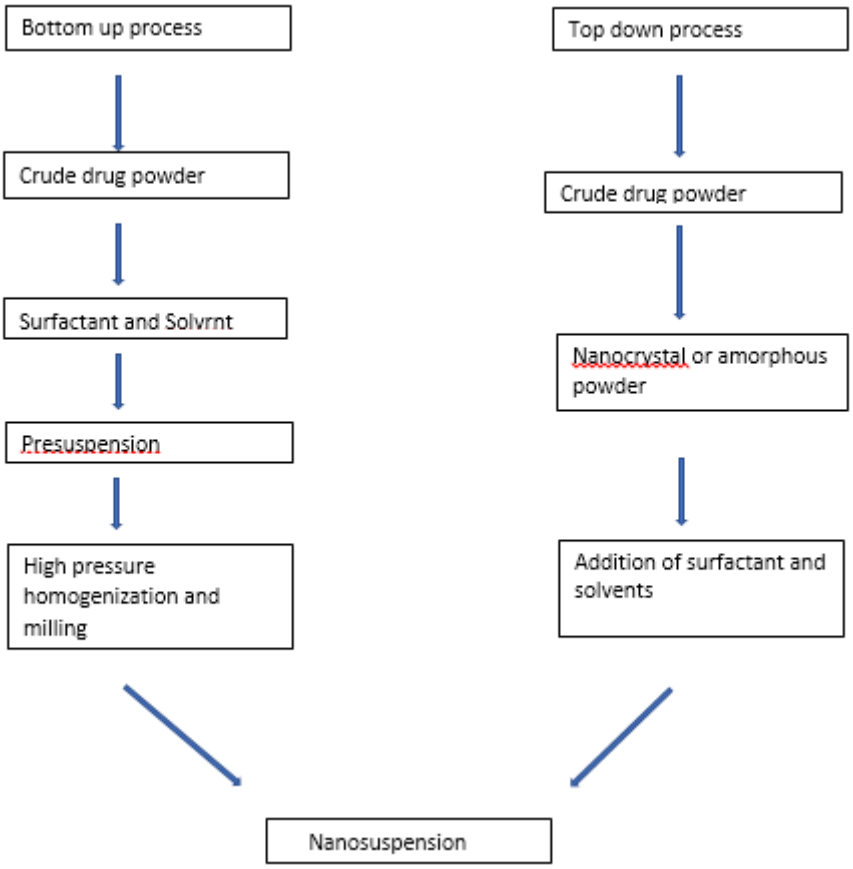

Figure No. 1: Techniques of preparation of Nanosuspension.

1) Top-down method: Top-down method includes the reduction of solid particles which are coarse size than that of the desired nanosized particle.

a) High-pressure homogenizer: High-pressure homogenizer is a mostly used top-down approach for the preparation of nanosuspension. The high-pressure homogenizer is a simple technique and it applies to the wide range of drugs. This technique can be used for very dilute and highly concentrated nanosuspension. Aseptic production can be possible. But there are some drawbacks. A high number of homogenization cycles. There is a possibility of contamination of products due to metal ion from the wall of the homogeniser. [20]

There are two principles involved:

The First Micro fluidization process involved jet stream principle and have two types of specialized geometric chamber Z type and Y type. The core suspension contains drugs and stabilizers. There is specially design interaction chamber through which the dispersion

medium is passed at high velocity. When the dispersion medium passes through specially design chamber the suspension is separated into two streams. When forces like turbulence cavitation impaction and shear force coming contact the direction gets change. The forces maintained above and attrition between the particle and against the wall of chamber result into particle size reduction. In micro fluidization there are some critical parameters such as micro fluidization pressure, milling time, stabilizer type, and concentrations, processing temperature should be optimized to get the desired nanosuspension. This technique is widely used in the preparation of liposomes, emulsion, and microcapsule. In this technique, some drawbacks like time-consuming methods, require intensive energy input. [27]

Second Piston-gap homogenizer for the production of large scale nanosuspension the high-pressure homogenization will be an excellent choice in large scale production high-pressure homogenizer is preferred. Under the high velocity and high pressure, the suspension including drug and stabilizer is forced to pass a very tiny gap approximately 4-20 micrometers. According to Bernoulli's law when the suspension is passing the narrow gap the dynamic pressure of suspension increases rapidly with a reduction in static pressure. For the conversion of particles into nanosized crystals, collisions are enough. Homogenization of drug particles can be performed in nonaqueous media or water-miscible liquid. [27]

b) Nano pure: Nano pure is nothing but a suspension which is homogenized in water-free media. The drug suspension in the nonaqueous medium is homogenized at 0^0C or in some cases even below the freezing point, therefore it is called deep freeze homogenization. [19]

c) Nano edge: A combination of microprecipitation and high-pressure homogenization technique is called the nano edge. This method includes precipitation of friable material followed by fragmentation under high shear and/or thermal energy. [5]

d) Media milling technique: In this technique drugs are given to the media milling for the production of the nanoparticle. The consequence of impaction between the milling media and drug use the imperative energy for the disintegration of the microparticulate system into nanoparticles. In this process, the chamber of milling media is charged as well as the milling media containing a drug, stabilizer, and water or suitable buffer which is rotated at a high shear rate to induce the suspension. This method having a major problem like residue left behind in the finished product. [4,18]

2) Bottom-up method

a) Supercritical fluid process: In this technique, the supercritical fluid is used for the production of nanosuspension. All supercritical fluid methods are based on gas antisolvent recrystallization and rapid expansion of the supercritical fluid. In RESS lipophilic drug is dissolved in SCF solvent after which pressure is quickly decreased, precipitating the drug from SCF. An organic solution of the lipophilic drug is made to saturate supercritical fluid, which leads to decreasing solubility of the drug in the solvent a consequently causes the drug precipitate efficiency of the organic solution into the supercritical solvent is a parameter in achieving ultrafine and uniform particle. Commonly used SC solvent like CO2, nitrous oxide, ethylene, propylene, propane, ammonia, water, ethanol, and n-pentane. [5]

b) Antisolvent precipitation method: Antisolvent precipitation is an impressive way to prepare micro or nanosized drug particle. In this method firstly the drug is dissolved in a solvent and quickly followed by the introduction of drug solution into the antisolvent. Result in precipitation due to the rapid dissolution of the drug. In this method stabilizers such as polymer and surfactant are commonly used as antisolvent in aqueous solutions. Antisolvent precipitation technique has some basic problem i.e. after the precipitation difficulty into the main size of the particle, usually with a fast growth rate, and therefore they are bigger and have a broad particle size distribution. [.14]

c) Emulsification solvent evaporation: The emulsion is prepared by first dissolved the drug in organic solvents and cosolvent accordingly dispersed in an aqueous phase containing a surfactant, it acts as a stabiliser. Fast evaporation of the solvent under the decreased pressure immediately produce nanosuspension. In the emulsification method, the globule size and concentration stabilizers should be the key factors. [5.18]

d) Lipid emulsion: In this method, the drug was dissolved in a suitable organic solvent, and then it is emulsified in an aqueous phase by using a suitable surfactant. The organic solvent was slowly evaporated under the decrease of the pressure to form drug particle precipitating the aqueous phase forming the aqueous suspension in required particle size. This suspension diluted to nanosuspension. The drawback of this technique is vastly used stabilizer and surfactant. Use of hazardous solvent. [5]

Table No. 1: Drug in the form of nanosuspension with there therapeutic class and method of preparation

Drug	Therapeutic class	Method of preparation
Albendazole	Anti-helmintic	High-pressure homogenization
Artemisinin	Antimalarial	Anti- precipitation
Azithromycin	Macrolide antibiotics	Solvent/ Antisolvent precipitation
Bufadienolide	Anti-arrhythmic	Weight milling
Carbamazepine	Psycholytic	High-pressure homogenization, Precipitation
Carvedilol	Alpha beta-receptor blocker	Antisolvent
Cefdinir	Cephalosporine antibiotic	Media milling
Cilostazole	Vasodilator, antiplatelet	Precipitation
Clarithromycin	Macrolide antibiotic	Sono-precipitation
Cyclosporine	Immunosuppressant	Media milling
Diclofenac	NAIDS	Nano precipitation
Dihydro Artemisinin	Anti-malarial	Anti-precipitation method
Diosmin	Hemorrhoids	Anti-solvent precipitation
Etodolac	NAIDS	Media milling
Everolimus	Anti-neoplastic, a kinase inhibitor	Micro fluidization
Febuxostat	Xanthine oxidase inhibitor	Media milling
Flurbiprofen	NAIDS	Micro fluidization
Furosemide	DIURETIC	Anti-solvent/ solvent precipitation
Griseofulvin	Antifungal	Micro-emulsion
Glimepiride	Anti-diabetic	Ultrasonication assisted precipitation
Glyburide	Hypoglycaemic	Media milling
Indomethacin	NAIDS	Aqueous eight bead milling
Isradipine	Calcium channel blocker	ANTI-SOLVENT MICROPRECIPITATION
Ketoprofen	Analgesic	Media milling
Lacidipine	Calcium channel blocker	Anti-solvent precipitation
Loratadine	Antihistaminic	Ultrasonic assisted precipitation
Megestrol acetate	Steroid hormone	Media milling
Methotrexate	Antimetabolite	Antisolvent precipitation
Mitotane	Adrenal cortex hormone	Media milling
Myricetin	Anticancer	Ultrasonic -Antisolvent precipitation
Nifedipine	Calcium channel blocker	Nanoprecipitation
Nitrendipine	Calcium channel blocker	Precipitation ultrasonication
Olmesartan medxomil	Angiotensin receptor blocker	Media milling
Paliperidone palmitate	Antischizoprenia	Media milling
Prednisolone	Glucocorticoid	Sono–precipitation
Rebamipide	Gastric ulcer	Micro fluidization
Resveratrol	Stilbenoid	Anti-solvent precipitation
Ritonavir	Anti-HIV protease	Micro fluidization
Simvastatin	Hmg-coa reductase inhibitor	High-pressure homogenization
Tacrolimus	Eczema	Nanoamorphism method

FORMULATION OF NANOSUSPENSION:

The formulation of nanosuspension required proper solvent system, stabilizer or surfactant, and other ingredients for its preparation.

Organic solvent- In preparation pf nanosuspension generally organic solvents are used. In physiologic and environmental means this solvent is very hazardous but some less hazardous water-miscible solvents like chloroform, ethanol, methanol, isopropanol, and partially water-miscible like butyl lactate, benzyl alcohol, triacetyl ethyl acetate, ethyl formate are used over the reported conventional hazardous solvent.

Stabilizers- Stabiliser provides high physical stability by weighting the surface of the solute or drug particle and retard the Ostwald ripening and agglomeration. Commonly used stabilizers povidone, cellulosic, polysorbate(tween or span series), oligomers, and lecithin.

Other additives- use of other additives depends on the route of administration or physical properties of the drug. Commonly used additives are buffers, polyols, salts, cryoprotectants, and osmogene. [5,18]

EVALUATION AND CHARACTERISATION OF NANOSUSPENSION: [6,7,24,25]

1) Particle size distribution: Particle size and size distribution are important characteristics of nanosuspension. To analyze the mean particle size photon correlation spectroscopy (TCS) or dynamic light scattering (DLS) and coulter counter multisizer are used. To achieve volume distribution of data, laser diffractometry (LD) is employed and it is used to check micron size particle which is important in the case of nanosuspension made for parenteral and pulmonary delivery. The nanosuspension prepared for iv delivery can be analyzed for the particle size by coulter counter analysis. [5,11,30]

2) Scanning electron microscopy (SEM): Scanning electron microscope is used to determine is especially for morphology or surface characterization of particles for scanning electron characterization the nanoparticles of nanosuspension are converted into a dry form. Modern SEM generates data in digital form. This equipment has the risk of radiation exposure. [9]

3) Surface charge / Zeta potential: Zeta potential gives an idea about the surface charge property as well as the long-term physical stability of nanosuspension. For suspension stabilize only by electrostatic repulsion require minimum zeta potential +- 30mV is essential. If combine electrostatic and steric stabilizer use, a zeta potential of +-20mV would be enough. [5]

4) Crystalline state and particle morphology: To get the polymorphic or morphological changes that the drug may undergo while nanosizing, evaluation of the crystalline state and particle morphology can help. Because of high-pressure homogenization, nanosuspension can change the crystalline structure, which may be a polymorphic form or two other amorphous forms. X-ray diffraction analysis and supplemented by DSC are used to determine the change in the solid-state of the drug particle and extent of the amorphous fraction but particle morphology evaluation scanning electron microscopy is preferred. [5]

5) Dynamic light scattering: It is generally known as photon correlation spectroscopy. John Tyndall introduced the earliest light scattering is an experiment that evaluated light scattering from colloidal suspension. The limitation related to the DLS instrument is that any sample the quantification of the aggregate present. [12]

6) Differential scanning colorimetry: This technique is based on the Exothermic and Endothermic mechanism. A thermal analytical technique measures the difference to the extent of heat which is essential to increase the temperature of reference and sample. DSC temperature is identical throughout the experiment. The sample holder temperature increases linearly. In DSC less amount of sample is required. [15,28]

7) Fourier transform infrared spectroscopy (FTIR) – FTIR generally used to analyze the small particle and molecule. This technique is used for three-dimensional data of structure derived from the x-ray diffraction. In FTIR vibration frequencies of a given compound which is predicted to be in a particular region which is based on the type of chemical bond as well as the type of atom present in it. This technique is used for the characterization of biomolecule and microbial samples. The major limitation of these techniques is FTIR measures interferogram and does not measure spectra, which makes it difficult to interpret without performing FTIR initially to produce a spectrum. The equipment has high initial cost and maintenance issues. [1,3]

CONCLUSION:

One of the major problems with poorly soluble drugs has very low bioavailability. Nanosuspension technology is able enough to bring enormous immediate benefit. Preparation of nanosuspension not only solve the problems for poor solubility and bioavailability but also improve drug safety and efficacy. For large scale production of nanosuspension high-pressure homogenization technology and media, milling has been successfully used.

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