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Nano Suspension Drug Delivery System: An Approach to Enhance Solubility of Drug

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ABSTRACT

Nanotechnology is the science that distributes with the process that occurs at the molecular level and of Nano length scale size. The particle size of Nano suspension range from 1-1000 nm. The major problems associated with poorly soluble drugs are very low bioavailability[1]. Formulation of the Nano suspension is an attractive and encouraging alternative to solve these problems. A pharmaceutical Nano suspension is defined as very finely colloid, biphasic, dispersed solid drug particles in an aqueous vehicle, there are sizes below 1 µm stabilized by surfactants and polymers prepared by using suitable methods of drug delivery application[2]. Nano suspension is a liquid dosage form for the formulation and delivery of hydrophobic drugs. There are different techniques used in improved the solubility of poorly water-soluble drugs. Nano suspension contains nanoparticles that enhance the drug aqueous solubility and bioavailability by increasing surface area of bioavailability by increase surface area of particles and by increasing dissolution rate possible by particle size by reducing into submicron range[3]. This review article describes the method of preparation of Nano suspension using in the different techniques and applications of nanosuspension[4, 5].

INTRODUCTION:

Nanotechnology is an appearing field in all areas of science, engineering, and technology. A range of the parameters like solubility, compatibility with the solvent, stability at room temperature, excipient, and photostability play an important role in the successful drug formulation[6]. Nowadays, more than 40% of the new chemical entities being created through drug discovery programs are lipophilic or poorly water-soluble compounds. Many changes of Nano suspension existing to solve the problems of low solubility and low bioavailability of drugs[7].There are many standard methods such as micronization, surfactant dispersion solubilization used in co-solvents and precipitation method has been developed for changing solubility of poorly water-soluble drugs. But these are the techniques used that show more limitation to the drugs, not soluble[8]. Nano suspension is defined as a biphasic system consisting of solid drug particles dispersed in an aqueous vehicle. The diameter of the particle is less than 1 µm in size with an average particle size ranging between 200 and 600 nm. These formulations are not only solved the problems like poor solubility and bioavailability but also change in pharmacokinetics properties of the drugs[9]. Nano suspension is defined as the science and engineering carried out in the Nanoscale that is 10^{-9}m. The microparticles of the drug are shifted to drug nanoparticles by using techniques like Bottom-Up and Top-Down technology[10]. Nano suspension includes the poorly water-soluble drugs across any matrix material suspended in dispersion. They are also used to enhance the solubility of poorly water-soluble drugs as well as lipid[11, 12]. In nanotechnology, the drug is continued in the required crystalline state with decrease particle size leading to an increased rate of dissolution and therefore improved bioavailability of drugs. Nano suspensions are several pharmaceutical applications like oral, parenteral, pulmonary, and ocular drug delivery system[13, 14].

- **Selection criteria for a drug used in Nano suspension:**

Nano suspension can be prepared for using an active pharmaceutical ingredient that is having each of the following characteristics[15].

➢ This drug compound is water-insoluble but soluble in oil. The water-insoluble drug which soluble in oil is prepared as liposomes. API is insoluble in both water and oils[16].

➢ Using the drug compound whose API with a very large dose, melting point, and log p-value is high[17].

➢ Drugs with the lower tendency of the crystal to dissolve, regardless of the high[18].

- **Advantages of Nano suspension:**

✓ It can be used for poorly water-soluble drugs.

✓ Easy to manufacture.

✓ Most cost-effective.

✓ Improved dose frequency.

✓ Physically more stable than liposomes.

✓ Reduced the tissue irritation.

✓ Orally absorption will be increased.

✓ Increase the solubility and dissolution rate.

✓ It can be given by any route[19, 20].

- **Formulation of Nano suspension:**

Table No. 1: Excipient and their function and example[21, 22]

Sr. No	Excipients	Function	Example
1.	Stabilizer	Wet the drug particles thoroughly, prevent Ostwald's ripening and agglomeration of nanosuspension, providing a steric or ionic barrier.	Lecithin, Poloxamers, Polysorbate, Cellulosic, Povidones.
2.	Co-surfactants	Influence phase behavior when microemulsions are used to formulate nanosuspensions.	Bile salts, Dipotassium-Glycyrrhizinate, Transcutol, Glycofurol, Ethanol, Isopropanol.
3.	Organic solvent	Pharmaceutically acceptable less hazardous solvent for preparation of formulation.	Ethanol, Methanol, Chloroform, Isopropanol, Ethyl acetate, Butyl lactate, Triacetin, Propylene carbonate benzyl alcohol.
4.	Other additives	According to the requirement of the route of administration or the properties of the drug moiety.	Buffer, Salts, Polyols, Osmogens, Cryoprotectan.

- **Preparation method/ Techniques of Nano suspension:**

1. Bottom-up technology

✓ Precipitation (Hydrosol)

2. Top-down technology

- Media milling (Nanocrystal)
- High-pressure homogenization (HPH)

✓ HPH in water (Disso Cubes)

✓ HPH in nonaqueous media (Nano pure)

✓ Combination of precipitation and HPH (Nano edge)

3. Microemulsion as template

4. Emulsion as template

For the preparation of Nano suspension, there are two covers methods "Bottom-Up Technology "And "Top-Down Technology"[23,24].

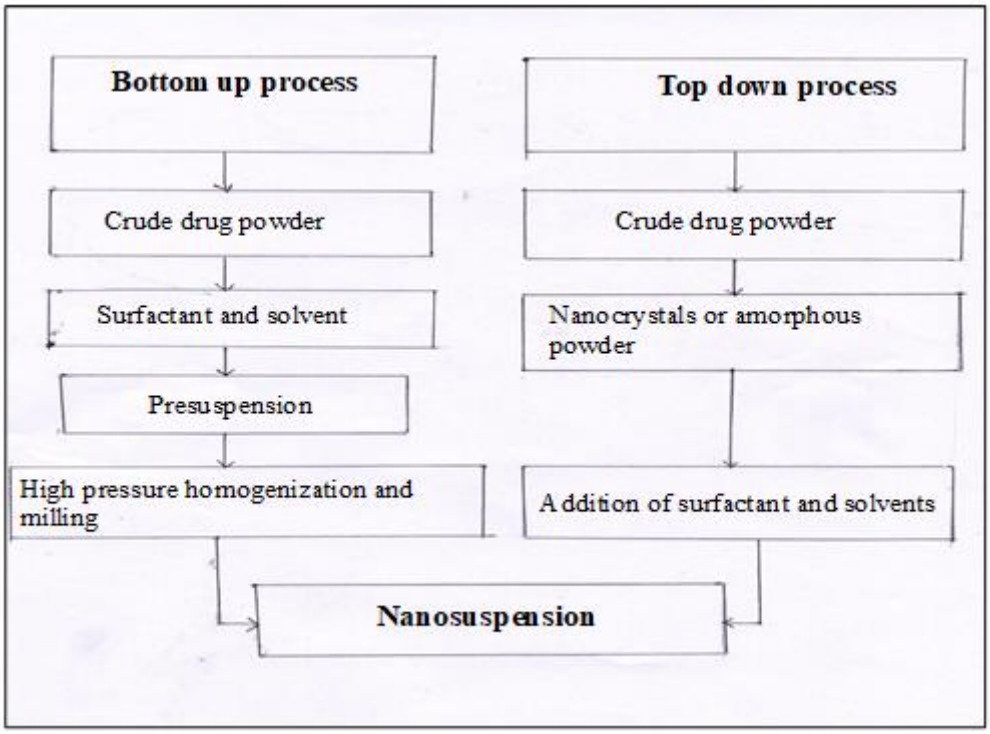

Figure No. 1: Approaches for preparation of Nano suspension

The traditional method of precipitation is called 'Bottom-Up Technology'. In the Bottom-Up Technology' is dissolved in a solvent, and then added to non-solvent precipitate crystals form[25]. Bottom-up technology is a collecting method to form nanoparticles like precipitation, microemulsion, melt emulsification method, and Top-Down technology require the disintegration of larger particles into nanoparticles, and examples of this method are high-pressure homogenization and milling method[26]. The principles of these methods are described in detail and their merits and demerits of the following table:

Table No. 2: Preparation techniques for Nano suspension with merits and demerits[27, 28]

Sr. No.	Techniques	Merits	Demerits
1	Precipitation	-Simple process -Low need for energy -Stable products	-Drug has been soluble at least in one solvent and miscible with non-solvent. -Growing of drug crystals needs to be limit by surfactant addition.
2	High-pressure homogenization	-Simple techniques -Low risk of product contamination. -Useful for the formation of very dilute as well as highly concentrate nanosuspension. -Aseptic production is possible.	-Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer. -High number of homogenization cycles. -Prerequisite for a drug to be in micronized state and suspension formation before homogenization.
3	Melt emulsification	-Avoidance of organic solvents compared to solvent diffusion.	-Formation of large particles solvent diffusion.
4	Microemulsion	-Ease to manufacture. -Stable products. -Long shelf life.	-Use of a high amount of surfactant and stabilizers. -Use of hazardous solvent.
5	Media milling	-High flexibility in handling large quantities of drugs. -Easy of scale-up. -Little batch to batch variation.	-Prolonged milling may induce the formation of amorphous leads to stability. -Require milling process for hours to days.

1) Precipitation method (Solvent-Antisolvent Method):

The precipitation method is a common method used to prepare submicron particles of poorly water-soluble drugs[29]. In this method, the first drug dissolved in a suitable solvent, and then the solution is mixed with a miscible antisolvent system in the presence of surfactants[30]. Rapid addition of drug solution into the solvent (Generally water) leads to sudden supersaturation drug in solution and forms ultrafine drug solids. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate primary requirements of the formation of stable suspension with the minimum particle size [31, 32].

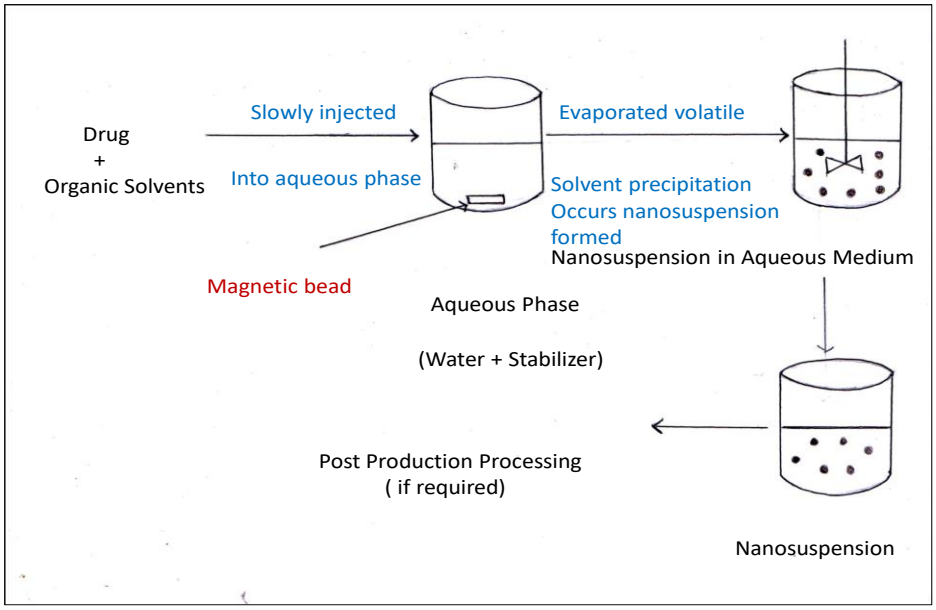

Figure No. 2: Nanoprecipitation Method for the preparation of Nano suspension

2) Homogenization

✓ **High-pressure homogenization(dissocubes):**

In this method, the suspension is forced by a pressure plunger pump through a narrow valve under high pressure[33]. When the suspension is permitted to pass through the orifice the static pressure will be lower below the boiling pressure of water which results in the boiling of water and formation of the gas bubbles[34]. After check out the orifice pressure will be normal and bubbles will implode so, surrounding particles will race into the surface which causes the size reduction[35, 36].

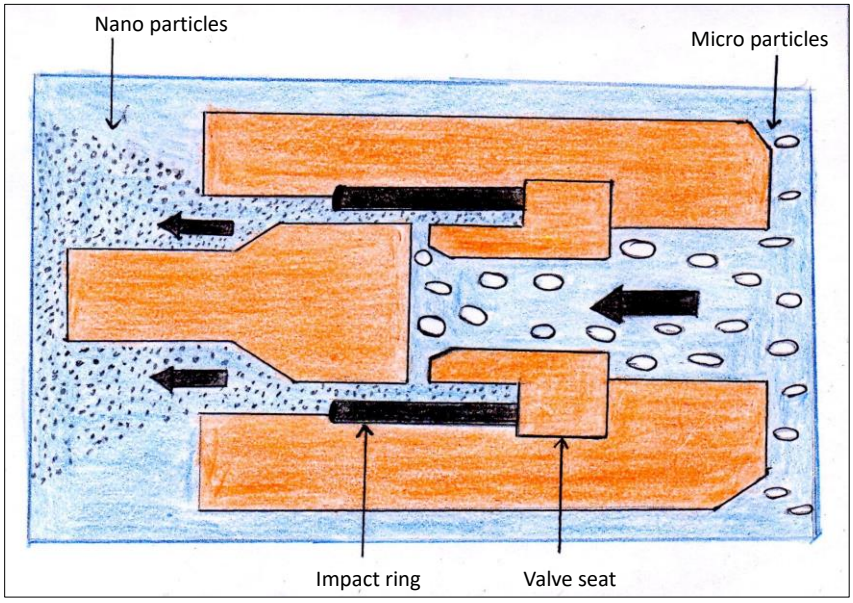

Figure No. 3: Schematic Representation of High-Pressure Homogenization Process.

✓ **Homogenization in non-aqueous media (nano-pure):**

It is a nanopore suspension homogenized in water-free media or water mixture. It is "deep-freeze" homogenization, the temperature will be O°C or sometimes below freezing point. Nanopure one of the best methods for thermolabile substances[37].

✓ **Nanoedge:**

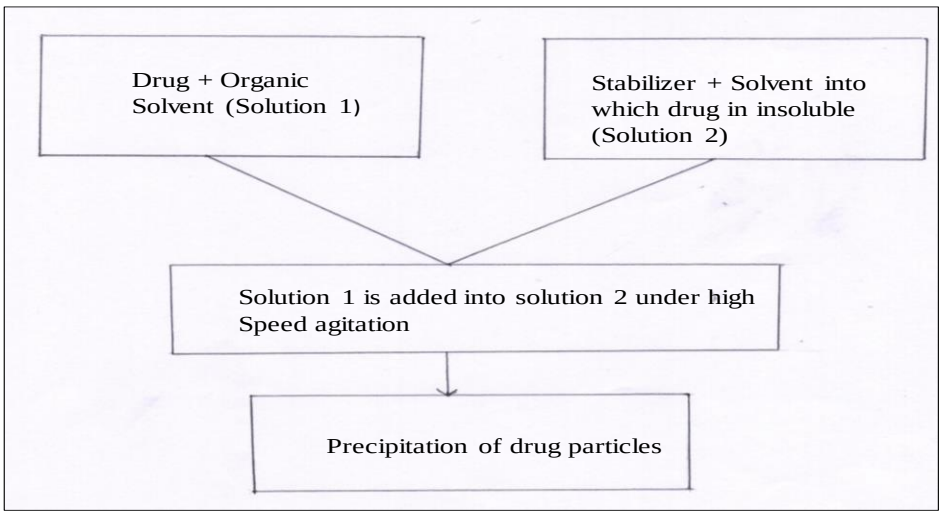

Figure No. 4: Method for preparation for nano edge

These techniques are also called as microprecipitation-high pressure homogenization method and it is a combination technique of homogenization method or precipitation method[38]. This combination of both methods leads to better stability and bioavailability. The homogenization method is used in the preparation of suspension obtained to reduce the particle size and prevent crystal growth. This method prepared solutions i.e. solutions 1 and 2. First solution in the organic solvent and second in aqueous solution. Then the solution 1 is added into solution 2 under high-speed agitation, after precipitation of the drug particles[39, 40].

3) Media milling:

In this technique, Nanosuspension is formulated by high shear media mills or pearl mills for nanoparticle production. It consists of a milling chamber, recycles chamber, and a milling shaft[41]. Milling media consists of pearls or balls which are made up of ceramic sintered aluminum oxide or zirconium oxide. The milling chamber will be charged with milling media, drug, water, and stabilizer. The chamber is rotated at a very high shear rate to generated suspension. The finally nanosized particles will be obtained[42].

- **Applications of Nanosuspension:**

❖ **Oral drug delivery:**

Oral drug delivery is the common route for many of the drugs, because of many advantages like painlessness and self-medication is possible. In the pharmaceuticals industry several advantages such as easy manufacturing, reasonable production cost, and short production time. In these cases orally administering antibiotics such as atovaquone and bupravaquone[44]. It's making in nano-size, solubility and bioavailability will be increased. The oral administration of naproxen drug leads to nanoparticles in an area under the curve (AUC). Other study about buparvaquone nanosuspensions reduced and reduced infection from 2.0 to 1.02 and micronized particles only to 1.47[45].

❖ **Parenteral drug delivery:**

Nanosuspension can be administered in different parenteral administration routes like Intravenous injection, Intra-articular, and Intraperitoneal. In this first choice in emergency conditions like cardiac arrest, anaphylactic shock[45]. This route administration of the drug has to be solubilized and particle size below 5µm. Clofazimine nanosuspension showed improved

stability as well as efficacy above the liposomal clofazimine in mycobacterium avium-infected female mice[46].

❖ **Ocular drug delivery:**

Ocular drug delivery is mainly applied in hydrophobic drugs. It increases the residence time. One of the best examples of nanosuspension is ibuprofen. The anti-inflammatory activity of ibuprofen increased contract with the aqueous preparation[47].

❖ **Pulmonary drug delivery:**

There are using nano-preparations for the drugs, which have poor solubility in pulmonary secretions. Using the mechanical and ultrasonic nebulizer by lung delivery it is nebulized. Budesonide corticosteroid has been the successfully prepared formulation of nanosuspension for pulmonary drug delivery[48].

- **Characterization and Evaluation Parameter:**

Evaluation of nanosuspension- [49, 50]

❖ In-vitro evaluation

✓ Particle size and size distribution

✓ Particle charge (Zeta potential)

✓ Crystalline state and morphology

✓ Saturation solubility and dissolution rate

✓ Stability

❖ *In-vivo* evaluation

❖ Evaluation of surface-modified

✓ Surface hydrophobicity

✓ Adhesion properties

✓ Interaction with body proteins

CONCLUSION:

Nanosuspension formulation has been solved the problems of solubility as well as dissolution of drug it improves drug absorption. It has mostly advantages formulation of nanosuspension such as the simple method of preparation, less requirement of excipients, saturation solubility will be increase and dissolution velocity of the drug. Several drug candidates are identified but mostly used in the poorly soluble drug. For the large scale-production of nanosuspensions media milling and high-pressure homogenization techniques have been successfully used. Nanosuspension is a commercially possible approach to solve the poor solubility as well as poor bioavailability problems of the drugs.

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