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NANOSUSPENSION - A PROMISING TECHNIQUE FOR POORLY SOLUBLE DRUGS

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ABSTRACT: Most pharmaceutical drugs create problems during formulation as they are insoluble or poorly soluble in aqueous and non-aqueous mediums. It was proved that reducing the drug particle size increases the drug's Solubility, Dissolution and Bioavailability. Many conventional techniques may be used, but the desired amount of particle size may not be achieved, and Solubility, Dissolution and Bioavailability still be a problem. Nanotechnology is a promising technique for formulating poorly soluble drugs. Nanotechnology helps us to reduce the drug particle size to submicron level and due to this, drug particle surface area increases which lead to solubilization of the drug. An increase in solubility leads to increased dissolution and Bioavailability of drug which leads to an increase in the drug's effectiveness. Also, Nanotechnology has many advantages over conventional techniques. One of the most important advantages of Nanotechnology is that particle size can be reduced from 300 nm to 10µ. Nanotechnology helps us formulate insoluble drugs in aqueous and non-aqueous mediums into different dosage forms without using harsh organic solvents for solubilizing purposes, which reduces the risk of toxicity. This review describes how to formulate a drug into Nanosuspension and gives detailed information about the Advantages and Disadvantages of Nanosuspensions, Ingredients used in Nanosuspension, Methods of preparation, Characterization of Nanosuspension, and Application of Nanosuspension in Pharmaceutical Dosage Form.

INTRODUCTION: During the development of the new formulation, the parameters of the drug considered are aqueous solubility, stability, temperature, humidity, and compatibility with solvent and excipient. The most important parameter is aqueous solubility [1].

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From 1995 to 2022, many drugs were discovered and approved, from which 46% of the new drug belonged to class IV according to the BCS classification, and only 9% belonged to Class I of the BCS classification.

Drugs belonging to Class IV are poorly soluble in aqueous medium and non–aqueous medium and have low Permeability [2]. As most drugs have low Solubility, low Bioavailability and low Dissolution rate have been observed, and the drug's effectiveness is also affected [3]. Poorly soluble drugs have a major problem: poor Bioavailability, lack of proportional dose response, suboptimal dosing, *etc*.

When formulating such drugs, harsh excipients for solubility enhancement are used, but they are not orally accepted. To minimize this problem and improve drug property, various approaches have been made. In Last few decades, the main goal in drug development is to improve the Bioavailability of the drug. Many conventional techniques were used to enhance the effectiveness of the drug [3]. Conventional methods include Micronization, Solubilization using co-solvent, Salt formation technique, Precipitation technique, Oil solution, Solid dispersion, Emulsion, Milling technique, Complexation, Supercritical processing, *etc* [1 2]. The most common technique is Micronization (particle size reduction). Micronization is a technique where the surface area of the drug particles is increased by particle size reduction. In which particle size ranges between 2 µm to 5 µm, the Dissolution rate and Absorption rate in the GI tract are not increased to excepted rate. The common disadvantage of Size reduction techniques is the deterioration of the drug particles and their properties. Due to this, electrostatic charge is enhanced, and suspicious formulation development may occur. Conventional methods also have other disadvantages, such as broad particle size distribution, contamination of formulation, crystal structure variation, uncontrolled particle morphology, and many more. To tackle or to minimize the disadvantages of conventional technique use of advanced techniques like Nanotechnology has been carried out in the last few years [3].

Nano technique/technology is used to solve the problem arising due to the drug's poor solubility. Nano is a Greek word that means 'Small'. By using Nanotechnology, we can formulate drugs belonging to Class II and Class IV which have major solubility problems in both aqueous and non-aqueous mediums. Nanotechnology is safe, simple and most importantly, the advantages are more in comparison to conventional methods [4]. Nanosuspension is the formulation containing submicron colloidal nano-sized drug particles stabilized by the use of suitable surfactants. They are also defined as biphasic liquid dosage forms in which pure drugs are suspended or dispersed in an aqueous medium for oral, topical, or parental administration. Particle size distribution in Nanosuspension is less than 1 micron and the average particle size is 1µm.

Furthermore, in Nanosuspension, the pure drug is maintained in its crystalline form with a particle size less than 1µm. Due to a decrease in drug particle size, the surface area increases, enhancing the dissolution rate and bioavailability [5]. Nanotechnology also helps us to administer the poorly soluble drug intravenously as the particle size is less, due to which there are minimum chances of blockage of blood capillaries [2]. The most important advantage of Nanosuspension is that it prevents Oswald ripening as particles are absent with a large amount of difference in size. In Oswald ripening, molecules move from the high-concentration region (around small particles) to low concentration region (around large particles). When smaller particles in Nanosuspension move towards larger particles, supersaturation occurs, and due to the aggregation of smaller particles and larger particles, large crystals (micro particles) form. Stability is an essential parameter in any biphasic liquid dosage form. The stability of Nanosuspension is high in comparison to Micro-Suspension due to uniform particle size. Nanosuspension can also be incorporated into the solid matrix by lyophilization and spray drying techniques [5].

Criteria for Selection of Drug for Nano-suspension:

1) Drugs should be insoluble in aqueous and non-aqueous medium or soluble in lipid mediums.

2) Drugs should have a high log P value, *i.e.,* the Partition coefficient.

3) Drugs must have a high melting point.

4) Drugs should have low Bioavailability.

5) Drugs that require high dosing [4].

Some Examples of drugs that are hydrophobic in nature – Atorvastatin, Naproxen, Famotidine, Clofazimine, Buparvaquone, Simvastatin, Nimesulide, Revaprazan, Mitotane, Aceclofenac, Amphotericin, Omeprazole, Nifedipine, Spironolactone, and many more [1].

Advantages of Nanosuspension:

1. Nanotechnology is applicable to most of drugs.

2. Poorly soluble drugs are formulated as Nanosuspension without using harsh co-solvent.

3. Particle size range in Nanosuspension is between 300 nm to 10 µ.

4. Nanosuspension has low volume goes up to 10 to 100 mg per ml.

5. Due to small particle size, the penetration capacity of topical Nanosuspension is enhanced.

6. Micro-suspension resistance to hydrolysis and oxidation is low, but Nanosuspension resistance is high.

7. Rapid dissolution and high Bioavailability are observed in Nanosuspension.

8. Due to the fast dissolution rate, rapid onset of action is achieved.

9. In Nanosuspension, the absorption window is wide.

10. As nano-sized particles are present in Nanosuspension, the Sedimentation rate is low. Due to this, long-term stability is observed for up to 2 years at room temperature ±5 °C.

11. Nanosuspension can be incorporated in the solid matrix and can be used in Control and Target drug delivery system.

12. Use of harsh solvent or co-solvent for solubilization of drugs is avoided. Therefore, safety in the administration of Nanosuspension is increased.

13. Due to small particle size, Nanosuspension can be administrated through various routes like oral, respiratory, pulmonary, intramuscular, intravenous, ocular, topical, *etc.*

14. Due to Nanosuspension's small particle size range, the risk of blockage of capillaries is reduced when administrated intravenously.

15. Tissue targeting is achieved, and tissue irritation is reduced in IV using Nanosuspension.

16. Nanosuspension also overcomes delivery issues for many compounds as the drug does not need to be solubilize.

17. Passive targeting may be achieved by using Nanosuspension or Nanotechnology for poorly soluble drugs.

18. Nanosuspension has no large difference in particle size, which reduces the risk of Ostwald ripening.

19. Nanosuspension is also used in an ocular dosage form as the amount of dosing is reduced; it also maintains the release of a drug.

20. Nanoparticles are present in Nanosuspension. These nanoparticles adhere to the gastric intestinal mucosa and increase contact time. Due to this, absorption of a drug is also increased [6, 7, 8].

Disadvantages of Nanosuspension:

1) Nanosuspension or Nanotechnology is an advanced process. Therefore, skillful workers are required.

2) Physical stability and particle sedimentation rate may cause problems during the formulation of Nanosuspensions.

3) Nano toxicity can be observed in Nanosuspension.

4) Crystal growth (Ostwald ripening) may take place in Nanosuspension.

5) Uniform and accurate dosing of the drug may not be achieved in Nanosuspension.

6) Stabilizers are needed during the formulation of Nanosuspension [6, 7, 8].

MATERIALS:

Stabilizers: Both polymers and surface-active agents have been used as a stabilizer for Nanosuspension. The function of the stabilizer is to wet the nanoparticle thoroughly [9, 10]. The importance of a stabilizer in any formulation increases with the decrease in particle size and increase in free surface energy. In the absence of a stabilizer in Nanosuspension, Nano-sized particles gains high surface energy.

Due to this accumulation and aggregation of Drug Crystal increases. Due to this, Oswald ripening may occur. With the stabilizer, the surface energy of nano-sized particles decreases, and the risk of Ostwald ripening decreases [9, 10, 11]. The ratio of drug: stabilizer used in formulation varies from 1: 20 to 20:1 depending on the formulation type [10]. The stability of Nanosuspension depends on the type and amount of stabilizers used during formulation. Stabilizers add ionic charges to Nanosuspensions, resulting in the formulation's physical and chemical stability [9]. Mostly used stabilizers in Nanosuspension are Polysorbate, Tween 20, Tween 40, Povidone, Leucine, Albumin, has been used to produce a stable drug nanocrystal. Albumin is used as a Surface Stabilizer in Nanotechnology. Lecithin is preferred in most sterile products as a stabilizing agent. Other examples of stabilizers are Sodium lauryl sulfate, Polyvinyl Pyrrolidone K30, Pluronics F68 and F127, Tween 80, hydroxypropyl Methylcellulose, Pluronic F68, carboxy-methylcellulose sodium, polyvinyl alcohol, sodium alginate, *etc* [9, 10].

Poloxamers: Generally, Synthetic Polymers are regarded as safe to use in Oral, Parenteral and Topical pharmaceutical application by FDA. Poloxamers are non-ionic, Triblock Copolymer composed of central Hydrophobic chains of Polyoxypropylene franked by two hydrophilic chains of Polyoxymethylene. Poloxamers are polymer used in drug delivery for pharmaceutical formulation as Surfactants, Emulsifying agent, Solubilizing agent, Dispersing agent and as in vitro absorbance enhancers. Frequently used poloxamers in Nanosuspension are Poloxamer 188 and 407 [12].

Organic Solvent: Using organic solvent is the Basic Technique for preparing emulsion and microemulsion [11]. Most organic solvents are hazardous and toxic from physiological and environmental points of view. While considering Organic solvents for the preparation of Nanosuspension, Class III Organic solvents are chosen as they are less hazardous and less toxic. Class III organic solvents are Ethyl acetate, Butanol, Acetone, Ethyl formulate, methyl ethyl ketone, Ether triacetin, Methyl acetate, *etc*. Organic solvents should also be Pharmaceutically accepted and should not create problems during Nano-suspensions' formulation. One of the techniques for the preparation of Nanosuspension is the emulsion solvent evaporation technique. Which Organic solvent, water miscible, is selected for the internal phase of the suspension as they stabilized the drug [12]. An example of water-miscible solvent is Ethanol, Isopropanol which is also less toxic. Examples of Partially water Immiscible Organic solvents are Ethyl acetate; ethyl formulates, Propylene Carbonate, Benzyl alcohol, *etc* [9].

Surfactant and Co-surfactant: In Nano-suspension, the Role of the Surfactant is to improve the dispersion of the nanoparticles in the Medium and to reduce the interfacial tension between them [9]. Surfactants also act as wetting agents and deflocculating agents in Nanosuspensions. Using surfactant reduces the interfacial tension between the particles, producing a smooth dispersion is achieved [11]. Sometimes surfactant alone is insufficient during the formulation of Nanosuspension in such a condition; co-surfactants are added to the formulation. The role and selection of co-surfactant in Nanosuspension is critical. Co-surfactant influences the drug's phase behaviour and solubility in the formulation [9, 10, 12]. Drug loading in the internal phase also depends on the Co-surfactant. Examples of surfactants are Tween 20, Tween, 40, Tween 80. Bile salt, Dipotassium glycyrrhizinate, Glycofurol, Ethyl alcohol, and Isopropyl alcohol are an example of co-surfactants [12].

Other Additives and Excipients: Other additives and excipients are added depending on the route of administration of Nanosuspension. When Nanosuspension is prepared for ocular use, buffering agents are added to maintain the pH of the formulation. Examples of Buffering agents are Carbonates, Bicarbonates, and Hydrogen Phosphates. Osmogens are added to Nano-suspension when formulated for the Osmotic drug delivery system. NaCl is one of example of osmogens. A preservative may be added to the formulation to prevent the degradation of Nanosuspension. A preservative such as benzoate, nitrites, sulphides, sorbates may be added to the formulation. Nanosuspension is also formulated for topical uses; in such a formulation penetrating agent may be added. An example of a penetrating agent is sodium lauryl sulfate. Polyoxyethylene sorbitan monopalmitate, cetltrimethyl ammonium

bromide, *etc*. Cryoprotectant may be added to the Nanosuspension to avoid the formation of ice. A complexing agent also may be added to the Nanosuspension when required. Cyclodextrin derivatives are an example of a complexing agent. Polyols are added to the Nanosuspension as they are a reducing agent and a stabilizing agent with a high boiling point. They are also added to the formulation to control particle growth and prevent aggregation of particles. Propylene oxide, Ethylene oxide, Butylene oxide, and Tetrahydrofuran are example of Polyols. Organoleptic agents are also added to Nanosuspensions for patient compliance.

METHODS: To prepare stable formulation, there are two techniques Top-down technique and the bottoms up technique. In the top-down technique, the disintegration approach is shown in which large particle (microparticles) are converted into nano size particles. Bottoms up technique is an Assembling method in which nanoparticles are formed from molecules [11].

High-Pressure Homogenization - High-Pressure Homogenization technique is used for poorly soluble drugs in an aqueous medium. At the start of this method, the drug is mixed with the suitable stabilizer solution, and a pre-suspension is prepared. After preparation of pre-suspension at low pressure, the suspension is homogenized in High-Pressure Homogenizer for pre-milling. After pre-milling is done, the pressure is increased, and at high pressure, the suspension is again homogenized for 10 to 25 cycles until a desired size of nanoparticles is achieved [14]. Albendazole, Ibuprofen, Amphotericin, Atovaquone, and Azithromycin are considered for this method [5].

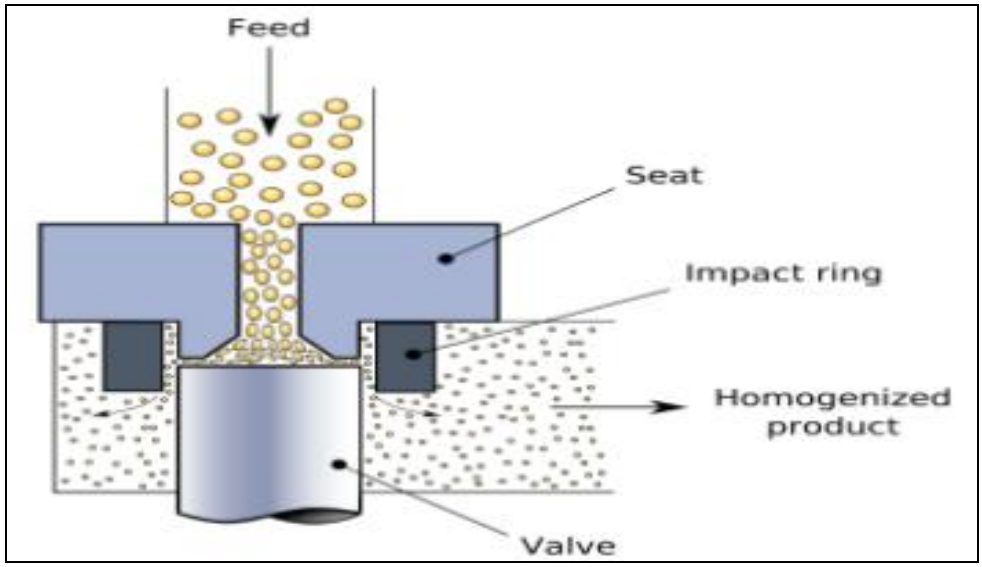

FIG. 1: HIGH-PRESSURE HOMOGENIZATION

There are some different methods in which the same principle is used to prepare Nanosuspension, which are as follows-

Disso-cubes (Homogenized in aqueous medium): In 1999, M.H. Muller was the first person to use the prison gap type of high-pressure homogenization technique. This technique is based on cavitation process and Bernoulli's law.

In this technique, the first drug and solution of stabilising agent (surfactant) together mix with results in the formation of dispersion i.e. micro-suspension. But the particle size is not reduced. To convert the micro suspension into Nanosuspension, this micro suspension is placed into a cylinder with 3 cm diameter and at a high pressure which is caused by pressure plunger pump. Then it is forced through a narrow nano-size opening called an aperture, which is only 25 µm in size. According to the Bernoulli's law, the flow of the volume of liquid in a closed system for cross-section is constant.

Due to the diameter reduction from 3 cm to 25 µm, dynamic pressure and static pressure increase are observed. Because of this, there is a decrease in the boiling point of water and boiling of water at room temperature and the formation of gas bubbles.

At the end of this process, when the micro-suspension containing gas bubbles leaves the gap, normal pressure is achieved. Due to this result in an explosion of the gas bubble, this force is sufficient enough to convert the microparticles into nanoparticles and the formation of Nanosuspension takes place [14, 15].

Nanopure: The principle of this method is similar to that of the above method. In this technique, water-free media or water mixture is used. They can be PEG 400 or PEG 1000 *etc* [14]. This technique is carried out at room temperature or at 0 °C or -20 °C. This technique is also called as Deep Freeze Homogenization technique. The advantage of this technique is that it can be used for thermolabile substances [15].

Nano Edges: This technique is similar to homogenizer and precipitation technique and it is the combination of both this technique. Basic principle is similar in this method [14]. Very small particle with better stability and better availability is achieved by this method [16].

First precipitation is carried out, but suspension formed by precipitation have risk of crystal growth and stability issue because of which this suspension is homogenized again to achieve smaller particles which is nanoparticles.

By performing homogenizer, disadvantages of precipitation technique is overcomed. Evaporation may be performed for the final product for better product of Nanosuspension [15].

Nano Jets: Nano jet technique is also called as opposite stream technique. In this technique, micro suspension is divided into two parts. At high pressure in homogenizer, these two parts are collided with each other. Due to high shear force produced by collision, Size reduction of micro particles into nano particles takes place [14, 16].

Advantages:

1) The high-pressure homogenization technique is applicable to most of the drugs.

2) The technique is useful for the formation of very dilute or very high-concentration formulations.

3) High-pressure homogenization technique is a simple process.

4) Production of the aseptic formulation is possible [5].

Disadvantages:

1) A number of cycles must be performed to get the desired nano-size particles.

2) Risk of contamination by metal ions coming off the walls of the homogenizer.

3) High-pressure homogenization of aqueous medium technique is not suitable for Drugs that are thermolabile in nature [5].

Media Milling: It is a top-down technique [16]. Liversidge developed this technique in 1992 [14]. Nanosuspensions are prepared by high share media milling technique or pearls [15]. The milling machine consists of a milling chamber, recirculating chamber, milling shaft, milling media, *etc*. Milling media concepts of glass or balls slash pearls made up of Zirconium Oxide or Aluminium Oxide.

The Micro suspension is then filled in the milling Chamber and rotated with a very high share rate under control temperature for 2 to 7 days. Due to the impact of milling media on the particle and friction between the particle, Size reduction of microparticle takes place, and Nanosuspension is prepared [14, 15, 16].

Drugs that are considered for this method are Cilostazol, Danazole, and Naproxen [5].

Advantages:

1) Media milling technique provides ease of scale-up.
2) Very little batch-to-batch variation is observed.
3) This technique is very flexible in handling a large quantity of drugs [5].

Disadvantages:

1) Nanosuspension prepared by this technique can generate residue in hours or in days.

2) This technique also leads to the formation of amorphous substance, which leads to instability of the Nanosuspension [5].

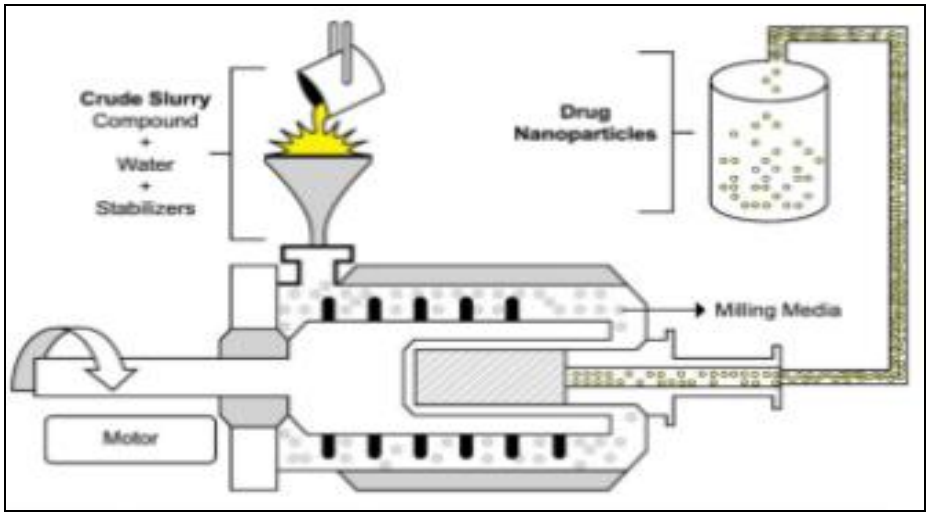

FIG. 2: MEDIA MILLING

Emulsification Solvent Evaporation Technique: In this technique, a Suitable solvent is selected in which the drug is dissolved. The solvent may be organic or inorganic. In the last few decades, dichloromethane and chloroform have been replaced by ethyl acetate, which has less profile toxicity. A solution for the drug is prepared. Then a non-solvent for the drug is selected. The drug's solution and non-solvent are mixed in the presence of a suitable surfactant, and emulsion is prepared. After emulsion formation, solvent evaporation is carried out either by continuous magnetic stirring or under reduced pressure. Due to solvent evaporation, precipitation of the drug takes place, the drug is dispersed in non-solvent, and the formation of Nanosuspension takes place. A high-speed stirrer controls crystal growth and particle aggregation, which creates high sheer force [14, 15].

FIG. 3: EMULSIFICATION SOLVENT EVAPORATION TECHNIQUE

Advantages:

1) Emulsification solvent evaporation technique is very simple to perform.
2) Requires a very short period to prepare Nanosuspensions.
3) Contamination-free Nanosuspension can be prepared by this technique [5].

Disadvantages:

1) Hazardous organic solvents are used in this process.
2) Crystal growth and particle aggregation need to be controlled throughout the process [5].

Lipid Emulsion / Microemulsion Template: The Lipid Emulsion /Microemulsion Template technique is used for soluble drugs in either a volatile organic solvent or a partially water-miscible solvent. First, a suitable organic solvent is selected in which the drug is soluble. A solution for the drug is prepared. Another aqueous solution of a suitable surfactant is prepared. After the preparation of both solutions, they are slowly mixed, and microemulsion formation occurs. This microemulsion is thermodynamically stable. A microemulsion is isotopically clear dispersion of two immiscible liquid which is stabilized by surfactant and Co-surfactant. Drugs can be easier loaded in the internal phase or preformed microemulsion can be saturated with drugs by initiated mixing. This microemulsion is further used as a template to produce Nanosuspension. The organic solvent in which microemulsion is formed, is then evaporated under reduced pressure to form drug particle precipitation in aqueous phase, resulting in the formation of aqueous suspension in the required particle size [14]. Then the suspension is diluted to get Nanosuspension. Breviscapine,

Griseofulvin, Ibuprofen, Mitotane such drugs are considered for this method [5].

Advantages:

1) Nanosuspensions are easy to prepared by lipid emulsion/ microemulsion template.
2) Easy for scale up.
3) Solubility of drug is enhanced by micro-Template method.
4) Longer shelf life is achieved [5].

Disadvantages:

1) Hazardous organic solvents are used in this process.
2) Large amount of surfactant and stabilizer are needed [5].

Precipitation Technique: Precipitation technique is also called as Solvent Anti-solvent method. From the last few decades, precipitation technique is being performed for preparation of submicron particles. Precipitation technique used for the drugs which are insoluble or poorly soluble in aqueous medium. In the precipitation technique, solution of the selected drug is prepared by mixing a suitable solvent and the drug. Another mixture of anti-solvent and surfactant is prepared. Now the drug solution is rapidly mixed with anti-solvent and surfactant solution. These rapid addition of solution leads to formation of Ultrafine Crystals or amorphous drug solid particles [14, 16]. Carbamazepine, Cyclosporine, Griseofulvin, Rentinoic acid are used in this technique [5].

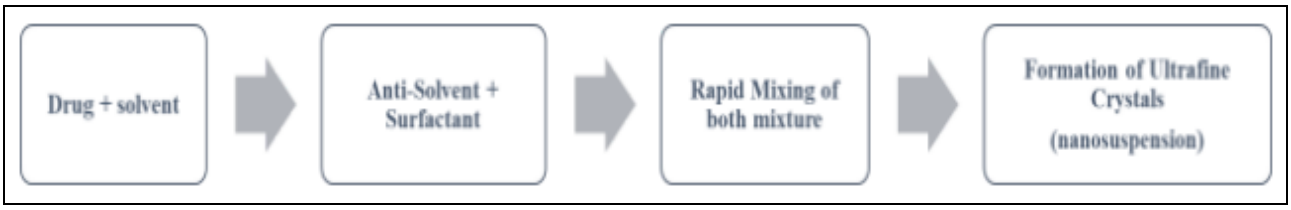

FIG. 4: PRECIPITATION TECHNIQUE (SOLVENT ANTI-SOLVENT METHOD)

Advantages:

1) It is a very simple process.
2) Low-cost equipment are used in precipitation technique.
3) Ease of scale up [5].

Disadvantages:

1) Growth of crystal need to be limited by the addition of surfactants.
2) Drug must be soluble is at least in one solvent and the solvent needs to be miscible with non-solvent [5].

Supercritical Fluid Process: Supercritical fluid process is an advanced technique in which smaller particle sizes can be achieved more than other techniques. This method is a combination of solubilizing techniques and nano-sizing techniques. Supercritical fluid processes use non-condensable dense fluid whose temperature and pressure are greater than that of Critical Temperature (Tc) and Critical Pressure (Tp). The critical temperature for pure substance is the temperature above which the gas cannot become liquid, regardless of applied pressure. Critical pressure is the pressure above which the liquid and gas cannot coexist at any temperature. This method is used to convert micro-drug particles into submicron particles. The supercritical fluid process achieves particle size of 5 nm to 2000 nm in diameter. As this technique or process requires high pressure for preparation of Nanosuspension.

This technique has been restricted in many industries [14, 16].

Advantages:

1) Smaller particle size can be achieved through the supercritical fluid process in comparison to other techniques [5].

Disadvantages:

1) High pressure is required for converting Micron particles into nano particles.
2) Supercritical fluid is required for this process [5].

Melt Emulsification Method: Melt Emulsification method combines the emulsification technique and melting of disperse phase. In this technique, an aqueous solution of stabilizer is prepared. The drug

is dispersed in the aqueous solution of the stabilizer solution. This mixture is filled in the sample holder. Then the sample holder is wrapped with heating tape and a temperature controller to maintain the mixture above the melting point of the drug, and a homogenization technique is also carried out. Due to the heating and homogenization process, emulsion formation takes place. After emulsification, the emulsion is cooled down either slowly at room temperature or in an ice bath. Due to emulsion cooling, droplets or disperse phase in emulsion is converted to spherical solid nanoparticles [14].

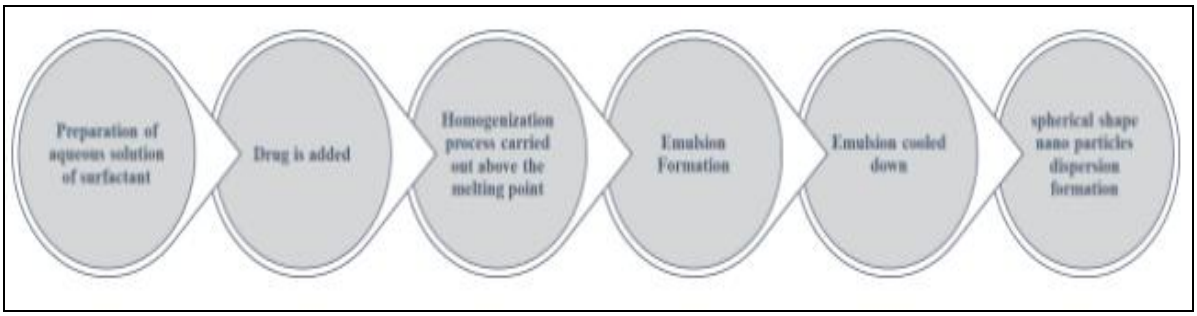

FIG. 5: MELT EMULSIFICATION METHOD

Advantages:

1) Melt emulsifying method is relative to the solvent evaporation method. In both techniques, the organic solvent is avoided, and toxicity is reduced [5].

Disadvantages:

1) Formation of the large particles may take place.
2) Possibility of contamination by metal ions coming off the walls of the homogenizer.
3) High-cost equipment are used in this process [5].

CHARACTERIZATION OF NANO-SUSPENSION:

Particle Size Distribution and Mean Particle Size: Particle size distribution and mean particle size (Polydispersity Index) are very important characteristics as they govern the saturation solubility, dissolution velocity, and biological performance of the Nanosuspension. The particle size of Nanosuspension should be low as possible for long-term stability [17]. They also affect the *in-vivo* and *in-vitro* performance of the Nanosuspension. It was proved by Muller and Peters in 1998, that a change in particle size of the drug can show variation in Saturation solubility and dissolution velocity [23]. Also, according to the Noyes-Whitney equation, which is based on Fick's first law of diffusion, the dissolution rate increases with the solid's surface area. Another equation given by Oswald Freundlich states that an increase in solubility is observed when the Particle size is reduced [22].

Photon correlation spectroscopy (PCS) is a very versatile technique, but it has a very low measuring range of about 3 nm to 3 µm. In this technique, the Brownian motion of the particle is measured as the function of time if larger particle size is present in the Nanosuspension particle, they may settle down in the measuring zone and due to this PCS is not accurate when the particle size is more than 3 µm. PCS can even be measured and used to measure the width of the particle (Polydispersity Index), which should be low as possible. A polydispersity index (PI) between 0.1 to 0.25 indicates a fairly narrow particle distribution, whereas PI greater than 0.5 indicates a very broad distribution of particles. Nanosuspension can also be analyzed by laser diffractometer (LD). LD detects and quantify drug particle size during the production of Nanosuspension. It measures particle size from 0.05 to 80 µm up to 2000 µm [17, 19]. An absolute number of particles for volume unit can be measured by using the Coulter Counter method. The Coulter counter technique is more effective and accurate than the laser diffractometer in measuring drug particle size. It is also used to detect the contamination of Nanosuspension [19, 20]. Atomic force spectroscopy is used to visualize the drug particle shape, whereas field emission low voltage scanning electron microscope takes images of individual particles [17, 19]. Differential Scanning Calorimetry (DSC) is used for sedimentation rate studies [19]. Other techniques like Fluorescence Correlation Spectroscopy, Nanoparticle Tracking Analysis (NTA), Flow Field Flow Fractionalization

(FFFF), Scanning Electron Microscope (SEM), and Transmission Electron Microscopy (TEM) is also used to detect particle size of Nanosuspension [22].

Crystalline State and Particle Morphology: Differential Scanning Calorimetry (DSC), Differential Thermal Analysis (DTA), and X-ray Powder Diffraction are used to study crystalline state and particle morphology in Nanosuspension [17]. Assessment of crystalline structure and morphology of particles together helps in understanding the polymorphic or morphological change that has occurred during the production of nano-sizing techniques [18, 20].

Most morphological and polymorphic changes occur due to the high-pressure homogenization technique. If the drug has a high-energy amorphous form, the Nanosuspension becomes thermodynamically unstable, which may change into crystalline form during storage. Therefore, a low-energy amorphous drug is preferred [19, 20, 21]. From the above technique, X-ray powder diffraction is the most approved method for evaluating crystalline state and particle morphology. X-ray Powder Diffraction and Differential scanning colorimetry (DSC) measure the changes in physical state and amount of amorphous fraction in Nanosuspensions [22]. The differential thermal analysis (DTA) Technique is used to measure the temperature and heat flow associated with the transition of drug crystalline structure [19].

To get the actual idea of the morphology of drug particles, Sometimes Scanning Electron Microscope (SEM) is also preferred for evaluating Nanosuspension which was performed by Muller and Holmes in 1998 [20]. In case No changes are observed between the crystalline structure of raw material and Nanosuspensions, the crystal structure is said to be intact during Nano sizing technology.

Zeta Potential (Particle Surface Charge): By studying Zeta Potential, we can get an idea of the surface Charge property of a Drug in Nanosuspension. Particle Surface charge of drugs is determined by the electrophoretic mobility of Particles present in Nanosuspension. Furthermore, Zeta potential is a very important Surface characteristic that affects the long-term physical stability of Nanosuspension [17]. Suppose there are electrical charges present on the particle surface. In that case, electrostatic repulsion between drug nanoparticles takes place, and aggregation of nanoparticles is prevented, reducing the risk of Precipitation formation risk. The zeta potential of Nanosuspension depends upon the amount and type of stabilizer used during preparation and the drug itself. The stability of Nanosuspension is also due to the presence of steric charge known as stearic stabilization [18, 19]. Stearic stabilization is caused by the absorbed and hydrated polymer layer on the dispersed particle. When Nanosuspension is only electrically stabilized, the minimum Zeta potential should be ±30 mV. In case when Nanosuspension is stabilized with a combination of static and electrical charge, the minimum Zeta potential should be ±20 mV. Another technique that measures potential is called as Electroacoustic technique [19, 20]. This technique can also measure Zeta Potential by applying an ultrasound wave to the Nanosuspension.

Saturation Solubility and Dissolution Velocity: As most drugs have very low saturation solubility and dissolution velocity, Nanotechnology was introduced to enhance the saturation solubility and dissolution velocity of drug [20]. Enhancing saturation, solubility, and dissolution velocity is the most important advantage of Nanosuspension over other techniques. Saturation solubility is a compound-specific constant dependent on the dissolution medium's temperature and properties; therefore, it should be studied in different physiological buffers and at different temperatures [18]. Ostwald Freundlich gives the relation between the relationship between the saturation solubility and particle size in which its states that solubility is enhanced when particle size is reduced, and relationship between dissolution velocity and particle size is given by Noyes Whitney equation which states that the rate of dissolution (Dissolution velocity) increases with increase in particle surface area (reduction in particle size). According to both the above theory, it is clear that for better saturation solubility and dissolution velocity, particle size reduction must be reduced [17]. By studying saturation solubility and dissolution velocity, it is easy to determine in vitro behaviour of the formulation.

Surface Hydrophilicity: Surface Hydrophilicity is an additional characteristic of Nanosuspension when it has to be intravenously injected. Surface hydrophilicity is a very important parameter that affects the *in-vivo* organ distribution after intravenously injected. In this technique, drug Particle and cell interaction are studied before phagocytosis. It is a very relevant parameter for the adsorption of Plasma protein which is a key factor for organ distribution. Moreover, Surface hydrophilicity needs to be determined in the original environment of the drug nanoparticles, which means in an aqueous dispersion medium. Other techniques like Hydrophobic Interaction Photography (HIC) is also used to study the interaction between drug and cells [18].

Stability of Nanosuspension: Nanosuspension particle size is much less, due to which the Surface energy of drug particles is very high. It results in the destabilization of Nanosuspension. Using a stabilizer prevents the drug particles from coming close to each other and reduces the possibility of Ostwald ripening.

And long-term stability of Nanosuspension is achieved. Polysorbates, Poloxamers, Lecithin, Cellulose Polymerase, and Polyoleate are some stabilizing agents used to prepare Nanosuspension. The mixture of surfactant and polymers is also very beneficial in preparing Nanosuspension, which can act as an ionic barrier. This mixture inhibits the close interaction of particles in the suspensions, and long-term stability is achieved.

The amount and type of stabilizer or surfactant used in the preparation of Nanosuspension also define the long-term stability of the suspension. As it creates an electrostatic charge on the surface of the particles, due to which repulsion between the particles takes place. Another phenomenon, the precipitation of drug particles, should be studied when studying of stability of Nanosuspension. Sedimentation of suspension is also studied using Stokes's law of sedimentation. It states that decreasing particle size, decreasing density difference of solid phase and increasing the viscosity of medium can decrease the sedimentation rate. Due to this, precipitation velocity is also reduced and the long-term stability of Nanosuspension is achieved [21].

Pharmaceutical Applications of Nano-suspension:

Oral Drug Delivery System: The drug delivery system is the most preferred type as it has numerous advantages. A drug's efficacy, when administered through oral drug delivery, depends upon solubility and rate of dissolution. Most of the drug discovered nowadays belongs to class II of BCS classification. Drugs belonging to Class II of BCS classification have very low solubility in aqueous medium and a very low rate of dissolution, creating a major problem when a drug is to be formulated in oral formulation. To resolve the issues related to the solubility and dissolution rate of the drug, the drug is formulated as Nanosuspension. In Nanosuspension, size reduction occurs due to the increased surface area of the drug, and Saturation solubility and rate of dissolution are enhanced. For example, when Azithromycin is formulated in Nanosuspension, more than 65% of the drug is dissolved in 5 hours [22].

Most drugs also have Very poor Bioavailability, which is enhanced by nanotechnology. An example drug named Danazol, a gonadotropic inhibitor shows very poor Bioavailability. When this drug is formulated in micro-suspension, Bioavailability is only 5.2%, but when it is formulated in Nanosuspension, there is drastic improvement in Bioavailability from 5.2% to 82.3% [23].

Cyclodextrin shows the same bio-availability, but there is an enhancement in onset of action, reduction of fed/fasted ratio and dose proportionality is also increased by nano sizing the drug. In the case of Naproxen, Gastric irritation is observed. But fast absorption is seen when its size is reduced from 20 µm to 270 nm. Due to the fast absorption of drugs, the Gastric retention time of the drug is reduced, and a decrease in gastric irritation is achieved [25].

An increase in Bioavailability is also observed in the case of Oleanolic acids. It is because of Fast dissolution from 15% in 20 minutes to 90% in 20 minutes, due to nano sizing technology [24]. Nanosuspension can also be incorporated in various dosage forms like tablets, capsules, *etc*. Ketoprofen has been successfully incorporated in pellets for sustained drug release for 24 hours [22].

Parental Drug Delivery System: Quick onset of action, rapid targeting, and reduction in drug dosage are some advantages of the parental drug delivery system. The parental route is the most preferred route for the drug undergoing first-pass metabolism and undergoes degradation in GIT that is not absorbed in GIT [24]. The micellar solution, Salt formation, solubilizing using Co-solvent complexation, and, more recently, liposomes and niosomes are some techniques presently being approached. But these methods have limitations like solubilization capacity, parental acceptance, high manufacturing Costs, *etc*. To overcome all of these problems, Nanosuspension was used to prepare parental drug delivery systems. The most important application of Nanosuspension is the parental drug delivery system. Intramuscular, subcutaneous intravenous, Intraarticular, Intraperitoneal, *etc*., can be prepared using nanotechnique in Nanosuspension. Drug efficacy in parenteral drug delivery systems shows enhancement when formulated in Nanosuspension.

The risk of blockage of arteries and veins is reduced as particle size in Nanosuspension is too small. Clofazimine is formulated in the form of Nanosuspension to improve its stability, as well as increase its efficacy [22]. Most of the drug's tolerance rate is observed to increase when formulated in Nanosuspension. For example, the maximum Tolerance rate of Paclitaxel in Nanosuspension is 3 times greater than that marketed Taxol [23]. Poorly soluble drugs are also being formulated in the form of injectable Nanosuspension. For example, Tarazepide is a poorly soluble drug but has been formulated as injectable Nanosuspension to overcome the limited success achieved using conventional solubilizing techniques [24].

Antineoplastic agents, Anaesthetic agents, Anti-fungal agents, antibacterial agents, and many more successfully formulated in the form of Nanosuspension [25]. Omeprazole which Degrades when orally administered, has been formulated in intravenous injectable form [24].

Pulmonary Drug Delivery System: To target deep inside the lung, respiratory aerosol should contain mean drug particle size of 1 to 5 µm in diameter. In aerosols that are prepared using the conventional ways, Solid drug particles are compatible, but the main problem arises in the homogeneity of particles which is achieved by preparing the Nanosuspensions. Due to the nano-size particles present in the Nanosuspensions, each droplet of aerosol contains uniform amount of drug particles and homogeneity is achieved. Such aerosol is prepared using nebulization of Nanosuspension by mechanical or ultrasound nebulizer. Drugs that are poorly soluble in pulmonary secretion can be administered through pulmonary route by formulating it in the form of Nanosuspension. Enhancement in adhesiveness of the drug particle in the lungs is also achieved, due to which an increase in prolonged time is observed. For example, Budesonide is a poorly water-soluble corticosteroid that has been successfully nebulized using an ultrasonic nebulizer for administration through the pulmonary route. In phase I of the clinical trial, the Nebulized Nanocrystal of Budesonide suspension achieved double Cmax and almost half of the Tmax. AUC of Nanocrystal of Budesonide was comparable. Due to the nano-size particles, fast absorption and High Peak plasma level are achieved. Other drugs formulated using nano-sizing techniques in the aerosol are Ketotifen, Ibuprofen, Indomethacin, nifedipine, Itraconazole, Interlenkin-2, Leuprolide, Doxorubicin, etc [25].

Ocular Drug Delivery System: Nanosuspension also can be delivered through ocular route. Advantages of Nanosuspension in ocular drug delivery system is that it increases residual time in Cul-de-sac, which is the most important parameter for all the ocular disease for effective treatment [24]. Sustained drug release is also achieved in ocular drug delivery system by incorporating Nanosuspension in suitable hydrogel base, Mucoadhesive base even in ocular inserts [23]. Lang and co-workers formulated Cloricromene in Nanosuspension for ocular drug delivery system using Eudragut, which shows higher availability of drugs in aqueous humour of rabbit according to the experiment performed [22]. Polymeric Nano-suspension was evaluated for sustained drug release and it was found to be 24 hours [23]. Ibuprofen's polymeric Nanosuspension is also developed for intended through the Ophthalmic route. Glucocorticoid drugs also show enhancement in the rate of drug absorption when formulated in the form of Nanosuspensions [24].

Targeted Drug Delivery System: Nanosuspension is the formulation suitable for the target drug delivery system due to its surface property [22, 23]. Versatility, ease of scale-up, and commercially available are some advantages of Nanosuspension for target drug delivery systems. *In vivo* behaviour can also be altered by changing the stabilizer. Kayser has successfully formulated Aphidicolin into Nanosuspension for a targeted drug delivery system. Nanosuspension is also used for drug targeting against Leishmania-infected macrophages [23]. Other drugs formulated in Nanosuspension for Target drug delivery system are Anti-fungal agents, Anti-mycobacterium agents, Anti-leishmanial agents, *etc.* [22]. For Example- Targeting of Cryptosporidium parvum, which cause cryptosporidiosis was achieved by surface modification of mucoadhesive Nanosuspension of Buparvaquone [24].

Topical Drug Delivery System: Micro suspensions are formulated in creams, water-soluble ointment, and topical use, but they lack in Saturation solubility of the drug, which is overcome by formulating the Nanocrystals of the drug. Nanocrystals lead to increased saturation solubility of drugs in topical dosage form, which enhances drug diffusion into the skin [24].

CONCLUSION: Nanosuspension technique offers us to reduce the drug particle to nano size. By nano sizing of the drug particle, the solubility of the drug has drastically increased. Due to the increase in solubility, the drug's effectiveness increases as the dissolution rate and Bioavailability of the drug is enhanced. Nanosuspension overcomes the disadvantages or issues created by conventional methods of size reduction technique. Nanosuspensions helps us administer poorly soluble drugs without using any harsh organic solvent for solubility. Nanosuspension can be administered through almost all routes. When administered through the oral route, Rapid onset of action is seen; dose consistency is seen when administered through the ocular route. The risk of blockage of veins and arteries is reduced when administered through the Parental route as the drug particle size is very low. As drug particle size is reduced to nano-sized, the Sedimentation rate of Nanosuspension is decreased, and long-term physical stability is observed.

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