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NANOSUSPENSION TECHNOLOGIES: AN APPROACH TO IMPROVE SOLUBILITY OF DRUGS

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ABSTRACT

Solubility proves to be a major obstacle for the successful growth and commercialization of new drug products. Since 40% of the active substances being recognized through the new example in high - throughput screening are lipophilic. So, its feasibility as a possible new drug candidate reduces many. Because of this restraint, numerous pharmacologically active molecules have unsuccessful to attain the market. Therefore, Nanosuspensions have emerged as a promising approach for the competent delivery of hydrophobic drugs because of their multipurpose features and unique advantages. Technique like media milling and high stress homogenization has been used commercially for produce nanosuspensions. In latest times, the manufacturings of nanosuspensions spend emulsions and microemulsions as pattern have been dealed within the literature. A nanosuspension not only determines the troubles of poor solubility and bioavailability, but also modifies the pharmacokinetics of drug and thus progress drug safety and efficacy. These review articles explain the training methods, characterization and purpose of the nanosuspension.

KEYWORDS

Bioavailability, Poor solubility, Nanosuspension and Solubility.

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INTRODUCTION

More than 40% of the novel chemical articles being generated through drug discovery programmes are poorly water soluble or lipophilic compounds. Creating a poorly water soluble drug has always been a challenging problem deal with by the pharmaceutical scientist. The formulation of nano□sized particles can be apply to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to

boost their solubility and hence partition into gastrointestinal barrier. "Nanotechnology as explore and progress at the atomic, molecular, or macromolecular levels in the sub-100-nm range (w0.1-100nm) to create structures, devices and systems that have novel efficient properties".

The improvement of the bioavailability of poorly water soluble drugs is one of the major targets of drug development during the last decagons. Several methods have been developed relating to the optimization of the dissolution rate of these drugs. Such process includes particle size reduction, solubilization, salt formation and preparation of solid dispersion systems.

NANOSUSPENSION[1]

Nano suspensions are aqueous suspensions holding one or several sub micronsized drug substances and appropriate stabilizers. Stabilizers include excipients that enable nano grinding of the drug particles, prevent crystal growth or nano particle aggregation during storage, pH-buffering substances, preservatives and other components which will be needed for further processing (e.g., transforming into a solid form) or administration to patients (e.g., sweeteners, colorants).

BENEFITS

- Can be applied for the poorly water soluble drugs.
- Can be given by any route.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution and tissue targeting can be achieved by IV route of administration.
- Oral administration of nano suspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.
- Nanosuspensions can be incorporated in tablets, pellets, hydrogel and suppositories are suitable for various routes of administration.

DISADVANTAGES OF NANOSUSPENSION

- Physical stability, sedimentation and compaction can reason problems.
- Large enough care must be taken during handling and transport.
- Inappropriate dose.
- Consistent and precise dose cannot be achieved.

BOTTOM-UP TECHNOLOGY

The conservative methods of precipitation (Hydrosols) are called Bottom Up technology. Precipitation method is a common method used to practice submicron particles of poorly soluble drugs. In this process, drug is liquefy in solvent and then solution is mixed with solvent to which drug is insoluble in the occurrence of surfactant. Fast addition of solution to such solvent (generally water) leads to speedy super saturation of drug in the solution and development of ultrafine amorphous or crystalline drug. This process involves nuclei formation and crystal growth which are primarily needy on temperature[2]. High nucleation rate and low crystal growth rate are primary necessities for preparing a stable suspension with least particle size. The restraint of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent desires to be miscible with non solvent.

Bottom-up process is an assembly process forms nano particles from molecules.

An exemplar includes:

- Solvent- Anti solvent method
- Super critical fluid process
- Emulsification- Solvent evaporation technique
- Lipid emulsion/Micro-emulsion template.

Precipitation (solvent-anti solvent method) method

Precipitation has been useful to practice submicron particles, mainly for the poorly soluble drugs. The drug is first liquefying in a solvent and then this solution is mixed with a miscible anti-solvent in the occurrence of surfactants. Fast addition of a drug solution to the anti-solvent guided to sudden super saturation of drug and formation of ultrafine crystalline or amorphous drug solids. Precipitation process involves two phases - nuclei formation and crystal growth. When preparing a stable suspension with the least particle size, a high nucleation rate and but low growth rate is required. Both rates are

depending on hotness. In this system the drug needs to be soluble in at least one solvent which is miscible with non-solvent.

Advantages

Trouble-free process, Ease of scale up and reasonable production.

Disadvantages

Increasing of crystals needs to be border by surfactant addition. Drug have to be soluble at smallest amount in one solvent.

Supercritical fluid process

This method utilizes solubilization and nano sizing tools through the super critical fluid process for particle size reduction. Super critical fluids (SCF) are non condensable dense fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). This process allows the micro ionization of drug particles to submicron level. Recent advances in SCF process are to create nano particulate suspension of particle size of 5 to 2000nm in diameter. The short solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure necessary for these progressions restrict the function of these tools in the pharmaceutical industry.

Solvent evaporation

The solutions of polymer are formulated in volatile solvents and emulsions. The emulsion is transformed into a nano particle suspension on evaporation of the solvent for the polymer, which is allowable to diffuse during the continuous phase of the emulsion. Conventionally, two main strategies are being used for the formation of emulsions, the preparation of single emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in water, (w/o)/w. These techniques entail high-speed homogenization or ultra-sonication; follow by evaporation of the solvent, through continuous magnetic stirring at room temperature or below reduced pressure. The solidify nano particles are accumulated which was washed with distilled water to eliminate the additives like surfactants and subsequently it was lyophilized.

Lipid emulsion/micro emulsion template

This method related for drugs that are soluble in any volatile organic solvents or partially water miscible solvents. Here the drug was liquefied in suitable organic solvent and it is emulsified in aqueous phase by means of suitable surfactants. Then the organic solvent was gradually evaporated below reduced pressure to form drug particles precipitating in the aqueous phase forming the aqueous suspension of the drug in the necessary particle size. The suspension produced can be suitably diluted to obtain nanosuspensions. Furthermore, micro emulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable and isotropic ally apparent dispersions of two immiscible liquids such as oil and water stabilized through an interfacial film of surfactant and co surfactant. The drug can be also loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by warm mixing. Appropriate dilution of the microemulsion gives way the drug nanosuspension.

Advantages

High drug solubilization, long shelf life and easy to manufacture.

Disadvantages

Use of hazardous solvent

Use of high amount of surfactant and stabilizers

Melt emulsification method

In this method drug is dispersed in the aqueous solution of stabilizer and heated higher than the melting point of the drug and homogenized to provide an emulsion. During this method, the sample holder was enwrapped through a heating tape fitted with temperature controller and the temperature of emulsion was maintained more than the melting point of the drug emulsion was then cooled down either slowly to room temperature or on an ice bath[3].

Advantages

Melt emulsification technique relative to the solvent evaporation method is total avoidance of organic solvents during the production process.

Disadvantages

Formation of larger particles and few compliant objects than solvent evaporation.

Emulsification-solvent evaporation technique

This method engages preparing a solution of drug goes behind by its emulsification in another liquid that is a nonsolvent for the drug. Evaporation of the solvent directed to precipitation of the drug. Crystal growth and particle aggregation be able to be controlled by creating high shear forces employing a high-speed stirrer.

TOP-DOWN PROCESS

The top down process involves the disintegration from large particles, microparticles to nano sized particles.

- High pressure homogenization
- Nanoedge
- Nanopure
- Media milling
- Dry-co-grinding

High pressure homogenization[4]

- It is most broadly used method for formulating nanosuspensions of numerous poorly aqueous soluble drugs. It entails three steps.
- Firstly drug powders are dispersed in stabilizer solution to create pre-suspensions.
- Secondly the pre-suspension is homogenised in high pressure homogeniser at small pressure for premilling.
- In the end homogenized at air mass for 10 to 25 cycles until the nano suspension of desired size are formed.

Nanopure

Nanopure is suspensions homogenized in water-free medium or water blend like PEG 400, PEG 1000 etc. The homogenization be able to be complete at room temperature, 0°C and under freezing point (-200C), therefore it is known as "deep freeze" homogenization.

Nanoedge[5]

It is a combined technique of precipitation and homogenization. This method is as well called opposite stream skill, uses a chamber where a stream of suspension is separated into two or more element. Both streams are colloid among each other at high pressure. The high shear force produced during the process results in particle size reduction. Dearns have prepared nanosuspensions of atovaquone by means of the micro fluidization procedure. The main drawback of this method is the high number of passes through out the micro fluidizer and that the product attained contains a relatively bigger fraction of microparticles.

MEDIA MILLING

Nanosuspensions are formed by using high-shear media mills or pearl mills. The mill consists of a milling cavity, milling pipe and a recirculation chamber. An aqueous suspension of the drug is then feed into the mill containing small grinding balls/pearls. Since these balls rotate at a very high shear rate below restricted temperature, they fly during the grinding jar interior and impact against the sample on the reverse grinding jar wall. A Nanosuspension of Zn-Insulin with a mean particle size of 150nm was formulated using the wet milling technique[6]. The main drawback of this skill contain the erosion of balls/pearls that can leave remains as contaminants in the final product, degradation of the thermo labile drugs due to heat generated during the process and occurrence of relatively elevated proportions of particles ≥5µm.

DRY CO-GRINDING[7]

Since several years, nanosuspensions are formulated during wet grinding processes by via pearl ball mill. Currently, nanosuspensions can be formulated by dry milling technique. Stable nano suspensions are formulated by using dry grinding of poorly soluble drug with soluble polymers and copolymers later than dispersing in liquid medium. Itoh *et al.* Include the colloidal particles development of many poorly water-soluble drugs like nifedipine, griseofulvin and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizer.

Table No.1: Benefits of Nanosuspension

S.No	Route of administration	Disadvantages of conventional formulations	Benefits of Nanosuspension
1	Oral	Slow on set of action/poor absorption	Rapid onset of action/Improved solubility and Bioavailability
2	Ocular	Lacrimal wash off/low bioavailability	Higher bioavailability / dose consistency
3	Intravenous	Poor dissolution/non-specific action	fast dissolution
4	Intramuscular	Low patient compliance thanks to pain	Reduced tissue irritation, High bioavailability, Rapid onset of action
5	Inhalations	Low bioavailability due to low solubility	Rapid dissolution / high bioavailability/dose regulation

PREPARATION METHODS OF NANOSUSPENSION

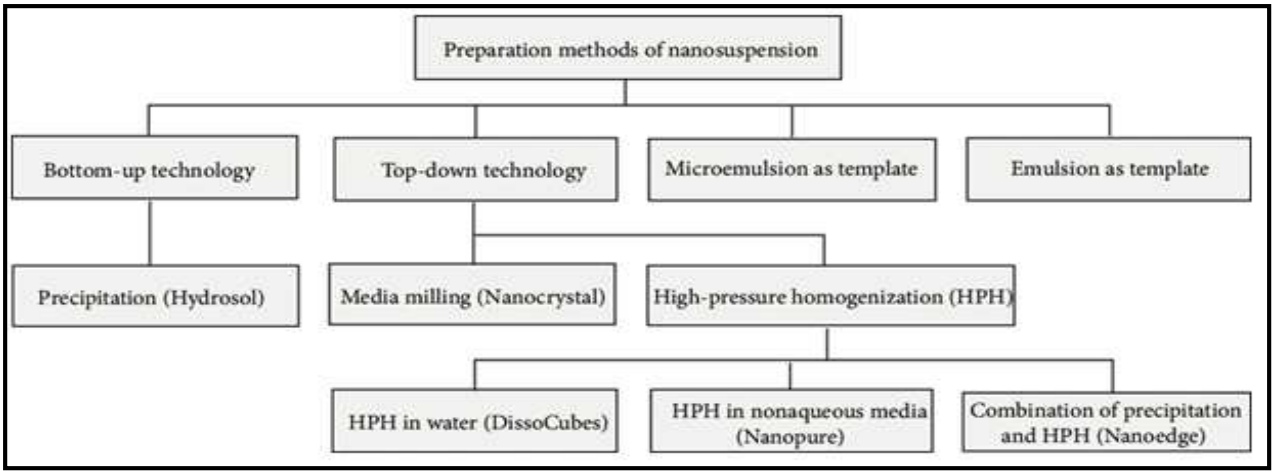

Figure No.1: Representation diagram of Preparation Methods of Nano suspension

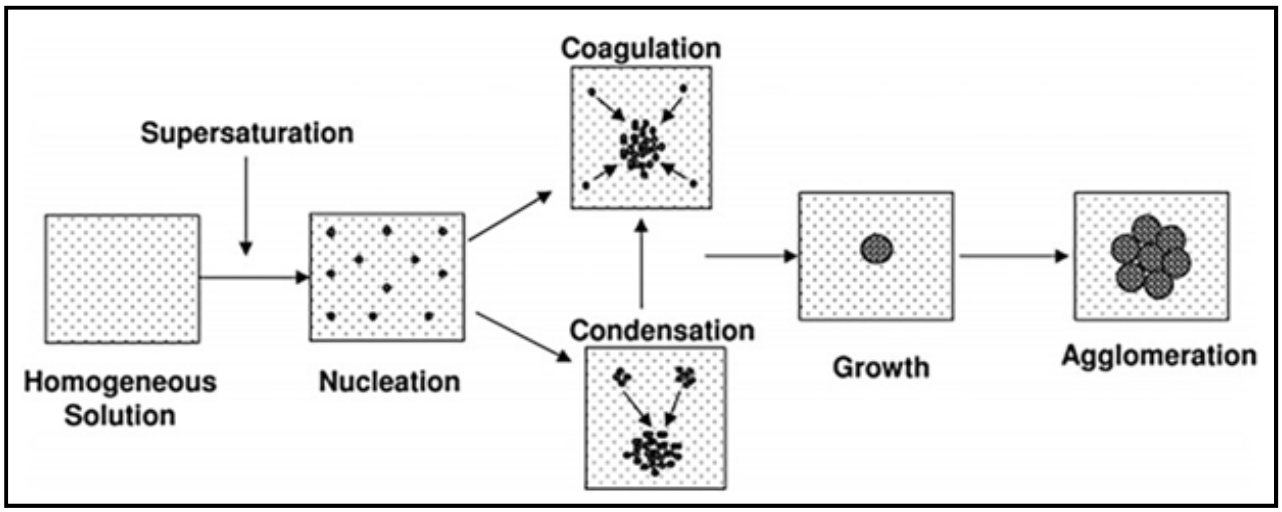

Figure No.2: Bottom-Up Technology of Nano suspension

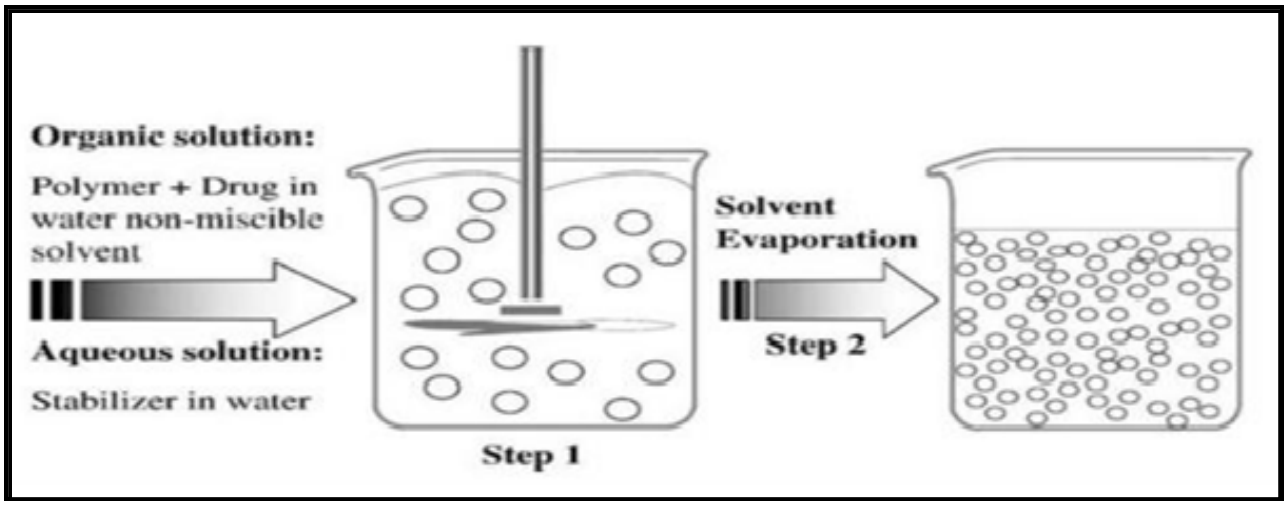

Figure No.3: Solvent evaporation method

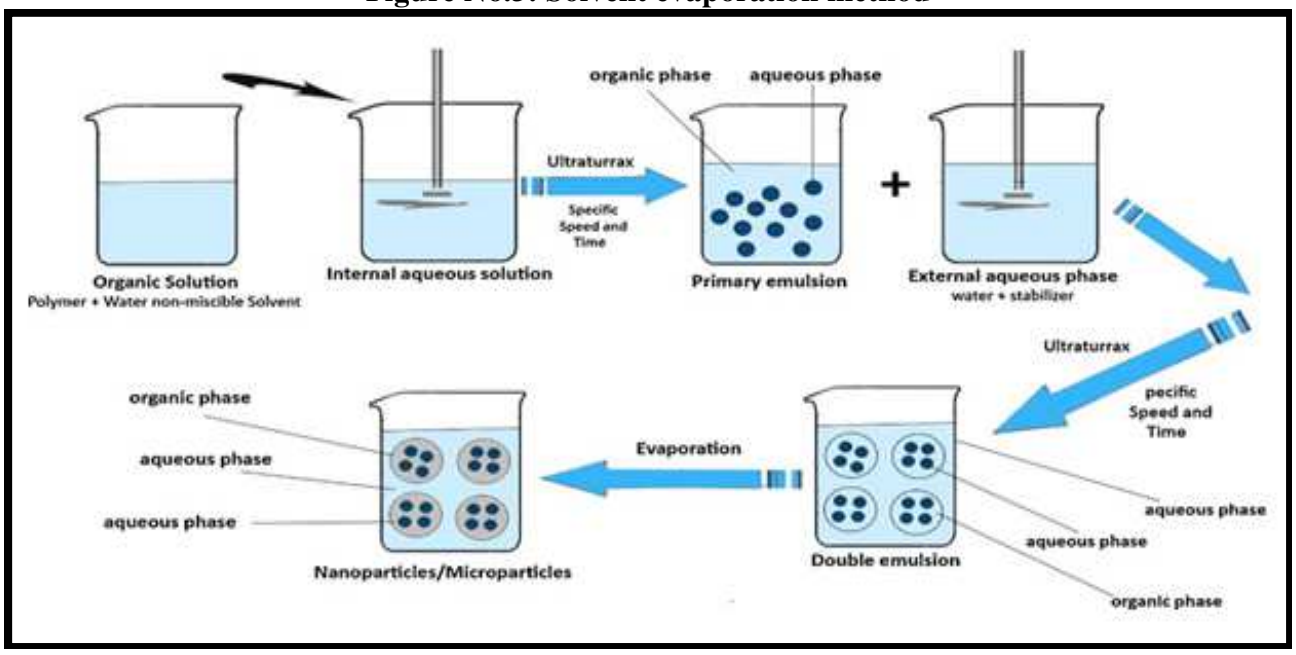

Figure No.4: Emulsification-solvent evaporation technique

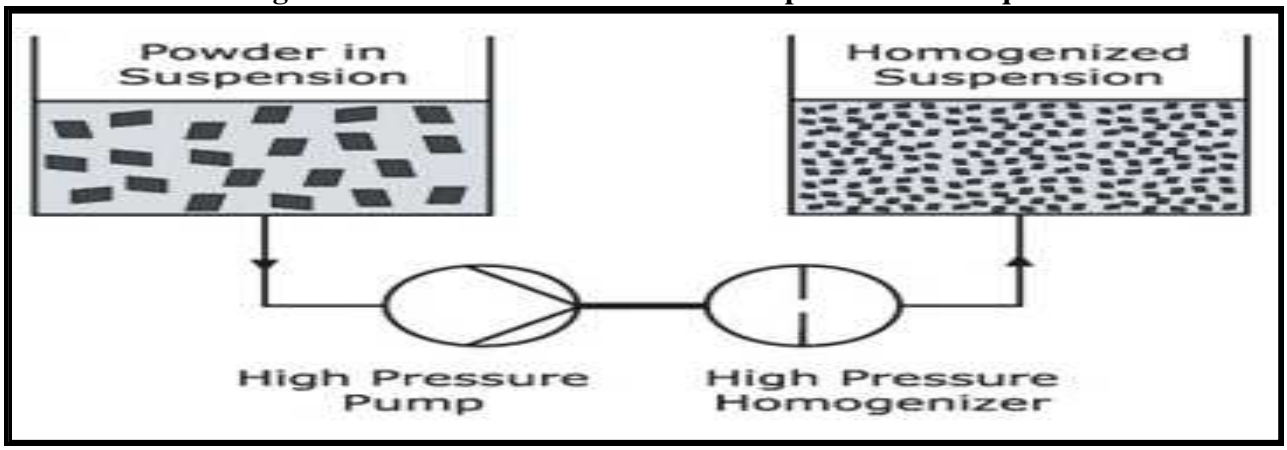

Figure No.5: High pressure homogenization technique

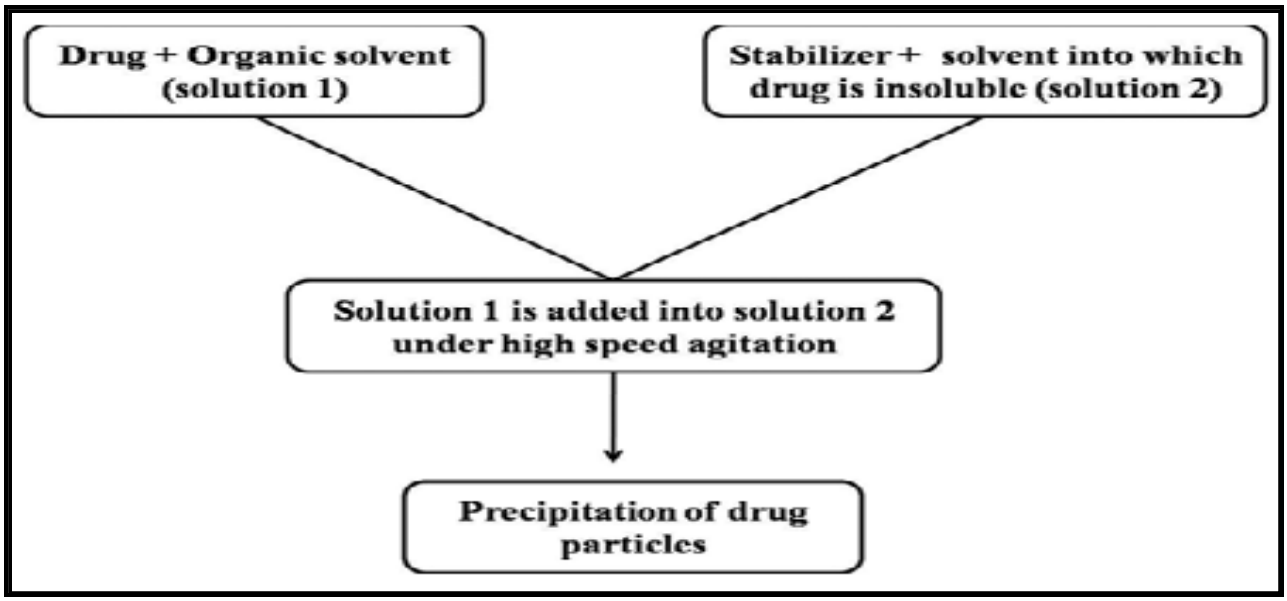

Figure No.6: Nano edge technique

CONCLUSION

Nanosuspensions are characteristic and commercially possible move toward to resolve the troubles of hydrophobic drug such as low solubility and low bioavailability. For large-scale manufacture of nanosuspensions, media milling and high-pressure homogenization skill have been successfully used. prominent characteristics, like development of dissolution rate, improved saturation solubility, enhanced bioadhesivity, flexibility in surface modification, and easiness of post-production processing, have extended the functions of nanosuspensions for different routes of administration. The purposes of nanosuspensions in oral and parental routes have been very well recognized, although applications in pulmonary and ocular delivery have to be examined. Though, their release through buccal, nasal and topical delivery is yet to be complete. The collection of stabilizers is extremely complicated and demanding as it takes too much point and efforts. In detail, in the field of pharmacy, the well-stabilized nanosuspensions that do not own any stabilizers are in the scream. As such, nanosuspensions are more companionable with the human body and also decrease the difficulty of imparting stabilizers. For this reason, some scientists are functioning on the self-stabilization perception. However, this field is quite challenging with numerous difficulties, consequently this field necessitate extreme research work for developing nanosuspensions without the stabilizers. By manufacturing importance on nanosuspension skill, human society shall be benefitted due to its ease, enhanced solubility and dissolution.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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