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Overview of Nanosuspensions in Pharmaceutical Sciences

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ABSTRACT:

Poor water solubility of pharmaceuticals is a key issue in medication development. Nanoscale drug delivery devices have gained popularity as a solution to improve solubility difficulties. Reducing medication particles to the sub-micron range improves dissolving rate and bioavailability. Nanosuspensions have the potential to improve the dissolving of medications with low water solubility. Nanosuspensions are made up of pharmaceutical active component particles in a liquid phase stabilized with surfactants. Drugs can be produced as nanosuspensions for both oral and non-oral administration**.**

Keywords: Nanosuspension, Enhance bioavailability, Patient compliance, Preparation, Evaluation

INTRODUCTION:

As with any dosage form preformulation, solubility is one of the key and crucial parameters to be examined. The preparation of medications that dissolve in water is straightforward. However, pharmaceuticals exhibiting low water solubility will provide a number of challenges for formulation and research. Poor water solubility is present in 40% of newly tested pharmacological compounds. Classes II and IV of the BCS are reserved for drugs with minimal solubility.[1, 2]

A variety of conventional techniques are employed to address the solubility restriction, including the creation of an API salt, solid dispersions, crystal synthesis using a co-former, the inclusion of co-solvents, and complexation with cyclodextrins.[3, 4, 5, 6]

Definition: "Very finely colloid, biphasic, discrete solid drug particles in an aqueous vehicle, stabilized by way of surfactants, for either parenteral or pulmonary administration, oral and topical use, or, with decreased particle size, leading to a better dissolution rate and therefore increased bioavailability," is the definition of a pharmaceutical nanosuspension. The suspended particle's diameter is between 0.1 and 1000 nm, or less than 1 μm in size. Solid particles in nanosuspensions typically have an average particle size of 200–600 nm and a

particle size dispersion of less than one micron. When the size of the particles is smaller than 10 µm, the dissolution rate of such particles increases as the surface area and, in turn, the dissolution velocity rise. Due to the influence of vapour pressure, Nano size particles can accelerate the rate of dissolution.[7, 8]

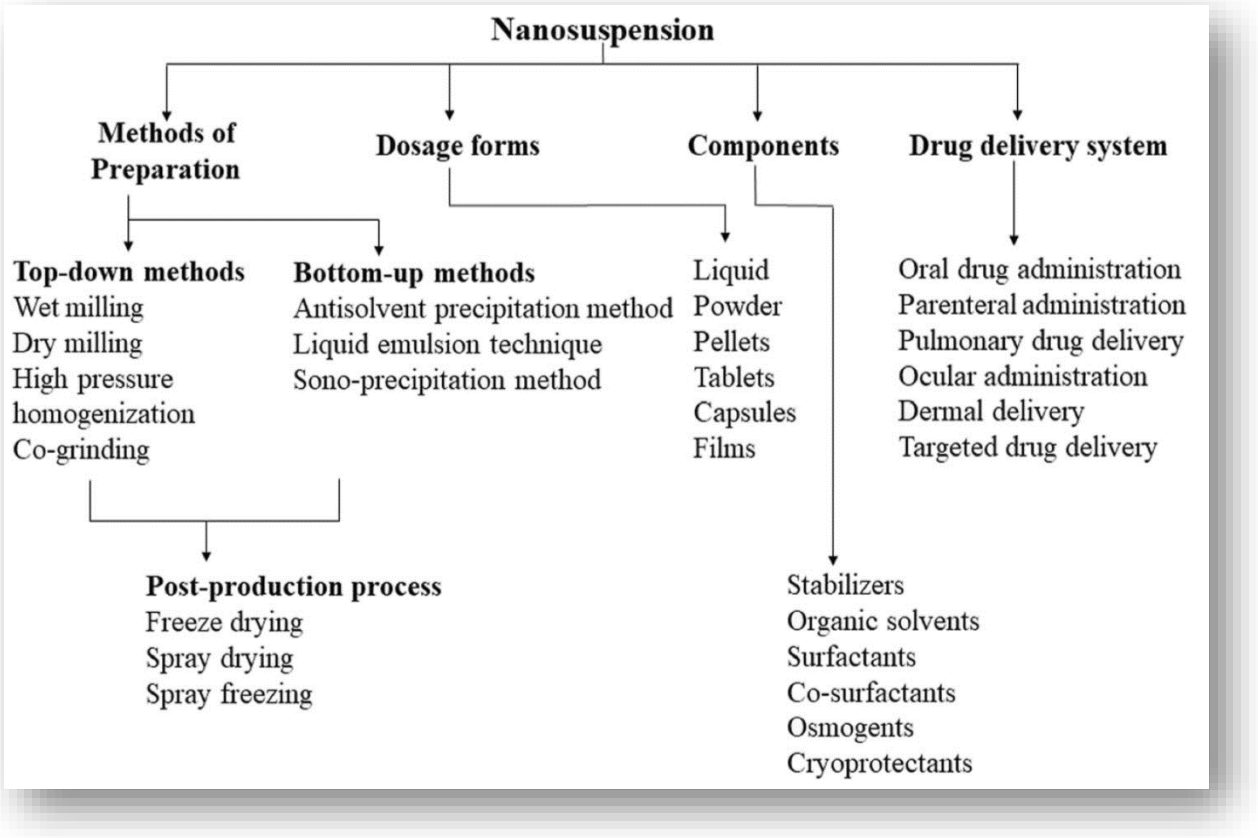

Fig 1: Schematic representation of method of preparation, dosage forms, components and applications of nanosuspensions in drug delivery systems [9]

Need of nanosuspension: [10]

When a compound has a high log P value and is insoluble in both water and organic media, it is preferable to prepare nanosuspensions rather than using lipidic systems. This formulation approach works best for drugs with high log P values, high melting points, and high dosages.

Advantages & disadvantages:

Advantages: [7]

1. Its simplicity and broad applicability to the majority of medications.
2. It may be helpful for medications that are poorly water soluble.
3. Any route can be used to deliver it.
4. In the event of subcutaneous or intramuscular administration, less tissue sensitivity.
5. The intravenous mode of delivery allows for rapid breakdown and tissue targeting.
6. Nanosuspensions administered orally offer enhanced absorption, a lowered fed/fasted ratio, and a quick onset.

7. A decrease in particle size can lead to an increase in the medications' absorption from the absorption window.
8. In case of ocular administration and inhalation delivery, higher bioavailability and more consistent dosing
9. To increase their absorption, medications with high log P-value can be made into nanosuspensions.
10. Biological performance is improved because of the drug's high saturation solubility and dissolving rate.
11. Simple production with little batch-to-batch differences.
12. Hydrogel, suppositories, pills, and pellets can all contain nanosuspensions, making them appropriate for a variety of delivery methods.
13. Increasing the amount of amorphous material in the particles is crucial for possible crystalline structural changes and increased solubility.
14. The potential for site-specific delivery by the surface modification of nanosuspension
15. Possibility of large production, a requirement for launching a delivery system in the marketplace

Disadvantages: [11]

1. Compaction, sedimentation, and physical stability can all lead to issues.
2. Because of its size, handling and transportation require extra caution.
3. Achieving a precise and uniform dosage requires suspension.
4. Incorrect dosage.

CRITERIA FOR SELECTION OF DRUG: [12, 13]

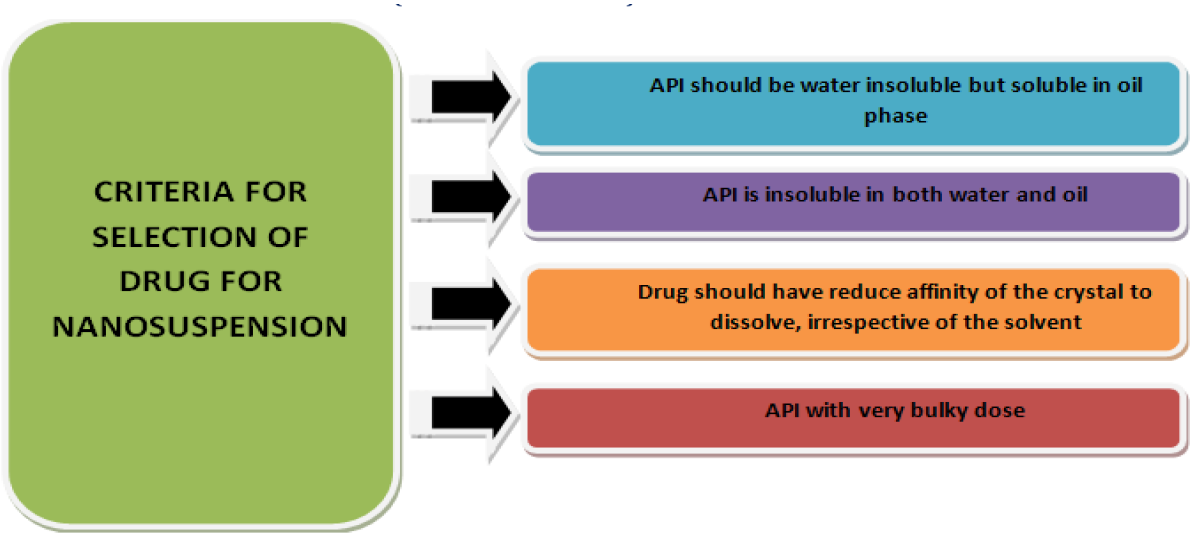

Fig 2: Criteria for Nanosuspension Selection [13]

FORMULATION CONSIDERATION:

1. Stabilizer
2. Organic Solvent
3. Surfactants
4. Co surfactants
5. Other additives

Nanosuspension formulation requires basically stabilizer or surfactant, proper solvent system and other ingredients for its preparation:

1. Stabilizer

A stabilizer is an essential component of the nanosuspensions technique. The high floor strength of nanoparticles might cause agglomeration or aggregation of the drug crystals in the absence of an appropriate stabilizer. The primary function of a stabilizer is to provide steric or ionic barriers that prevent Ostwald's ripening and agglomeration of nanosuspensions while also thoroughly moistening the drug particles. This creates a stable physiological formulation.[7, 14]

2. Organic solvents

When creating nanosuspensions using emulsion or microemulsion technologies as a template, organic solvents are frequently utilized. These solvents pose a serious threat to human health and the environment, while some water-miscible solvents, such as methanol and ethanol, pose less of a risk.[15]

3. Surfactants

By lowering the interfacial tension, surfactants are combined to improve the dispersion. Additionally, they serve as deflocculating or wetting agents.[14]

4. Co surfactants:

The preference of co surfactant is critical when using micro emulsions to formulate nanosuspension. Since co surfactants can substantially affect section behaviour the impact of co surfactant on uptake of the inside section for chosen micro emulsion composition and on drug loading ought to be investigated.[14]

5. Other additives

Adding agents such buffers, salts, polyols, cosmogenic, and cryoprotectants to nanosuspensions can depend on the drug's moiety's characteristics as well as the mode of administration.[16]

PROPERTIES OF NANOSUSPENSION:

1. Physical long term stability
2. Internal structure of nanosuspension
3. Adhesiveness
4. crystalline state and morphology

1. Physical long term stability

Ostwald ripening causes distributed systems to physically become unstable, which in turn causes crystal development to produce microparticles. The difference in the saturation solubility and dissolving velocity of tiny and large particles is what causes Ostwald is ripening. Diffusion of molecules occurs between areas with a lower concentration of drug surrounding larger particle and the higher concentrated area around small particle. This causes a supersaturated solution to develop surrounding the big particles, which in turn causes the drug to crystallize and the big particles to grow. The drug dissolves from the small particles which leaves a region surrounding the small particles that is no longer saturated.[17]

2. Internal structure of nanosuspension

Inside the drug particles structural changes are brought about by the high energy input during the disintegration process. Particle in the medication undergo a change from crystalline to amorphous when exposed to high pressure homogenization. Particles the medication undergo a transition from crystalline to amorphous from when subjected to high pressure homogenization. The drugs chemical makeup, consistency, number of homogenization cycles and power density napped by the homogenizer all affect the exchange in the state.[17]

3. Adhesiveness

Ultra-fine powders have more adhesiveness than coarse powders. The ability of tiny medicine nanoparticles to stick together can be used to better administer poorly soluble medications orally.[14]

4. **crystalline state and morphology**

A potential alteration to the crystalline structure of nanosuspensions, such as a rise in the percentage of amorphous particles or the creation of distinctly amorphous particles, is a feature worth taking into account. It was once discovered that applying high pressures during the nanosuspension generation process encouraged the amorphous form.[18]

PREPARATION TECHNIQUES

In the bottom-up technique, molecules are dissolved in a solvent and precipitated by different methods such as solvent addition, spray freezing, evaporative precipitation and liquid solvent change process. TOP-DOWN process are mechanical processes that include milling and homogenization .Top down processes are widely used. The mechanical processes have some drawbacks such as time consumption, more energy used, chances of impurities, chances of impurities, inadequate control of particle size

1. Top down method
2. Bottom up method
3. Combined Method

1. Top down method

a. High pressure homogenization

The following three phases are part of this method: to create a pre-suspension, tranquilize powders are first dispersed throughout a stabilizing solution. Next the pre suspension is homogenizer at a low stress in many cases for pre-milling. Finally the homogenization is done at an excessive pressure for 10 to 25 cycles or until the nanosuspensions are formed with the desired measurement.[19]

b. Media milling

Pearl mills can be used to prepare nanosuspensions. Are circulation chamber, a milling shaft and a milling chamber are used in this operation. First an aqueous medium and a medication suspension are added to the mill, along with small grinding jar, which efficiently reduces the size of the particles.[20]

Usually composed of sturdy materials like zirconium oxide, the milling media exhibit outstanding resilience against abrasion and damage. Particle sizes smaller than 0.1 μm are achievable with sophisticated equipment such planetary ball mills, like the PM200 and PM100 versions. In one study, for example, scientists used a wet milling process to create a Zn-Insulin nanosuspension with a particle size of approximately 150 nm. It is crucial to acknowledge that media milling has several limits. These include the possibility of contamination resulting from the erosion of milling material, the possibility of thermolabile drug degradation due to heat generation, and the presence of particles with a size of approximately 5 μm.[21]

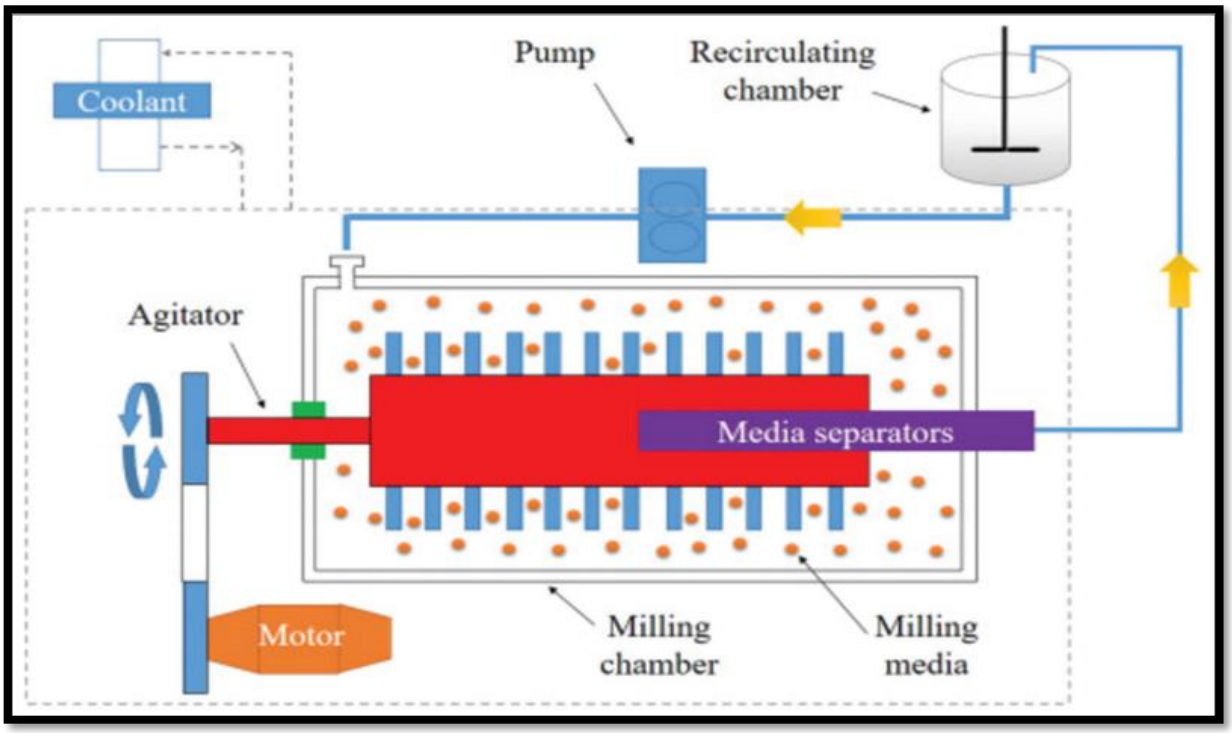

Fig 3: Diagrammatic illustration of the Media milling [31]

c. Homogenization in non-aqueous media (Nano pure)

Drug suspensions in non-aqueous media were homogenized below 0°C, or even below the freezing point, and are hence referred to as "deepfreeze" homogenization. Nanopure is suspension homogenized in water-free media or water mixes. Since the results were similar to dissocubes, thermolabile substances can be used successfully in milder environments.[22]

d. Nano jet

It uses a chamber where a stream of suspension is divided into two or more parts. These sections colloid with one other under high pressure because to the high shear forces produced during the process, which reduces particle size. This technique is also known as opposite stream technology.[23]

2. Bottom up method:

a. Emulsification solvent evaporation technique: [14]

Using this method, a drug solution is made and then it is emulsified in all other liquids that are not the drug's solvent. The drug precipitates after the solvent evaporates. With the use of a high-speed stirrer, it is possible to control the formation of crystals and the aggregation of particles by increasing the shear pressure.

b. Nanoprecipitation method: [24]

Mostly for medications that are poorly soluble, it is employed. In a suitable solvent, the first medication is dissolved. After that, this solution is combined with a miscible antisolvent system that contains surfactants. Ultrafine drug solids are formed when the drug solution is quickly added to the antisolvent, causing the drug to suddenly become supersaturated in the mixed solution. The nucleus creation and crystal development phases are the two stages of the precipitation process. A strong nucleation rate combined with a low growth rate is required to prepare a stable solution with the smallest possible particle size. The temperature affects both rates. For this method to work, the medication must dissolve in at least one solvent and mix well with a non-solvent.

c. Precipitation method

Precipitation is a popular method for producing submicron, poorly soluble drug particles.[25] Prior to adding the solution to the solvent—which the medication cannot dissolve in—the drug must first be dissolved in a solvent. The drug soon becomes supersaturated in the solution upon rapid addition of the solution to such a solvent (often water), forming an ultrafine amorphous or crystalline drug.[26] The formation of nuclei and the development of crystals are two processes involved in this process that are heavily temperature-dependent.[27] High nucleation rate, low crystal growth rate, and small particle size are necessary to produce a stable suspension.[28]

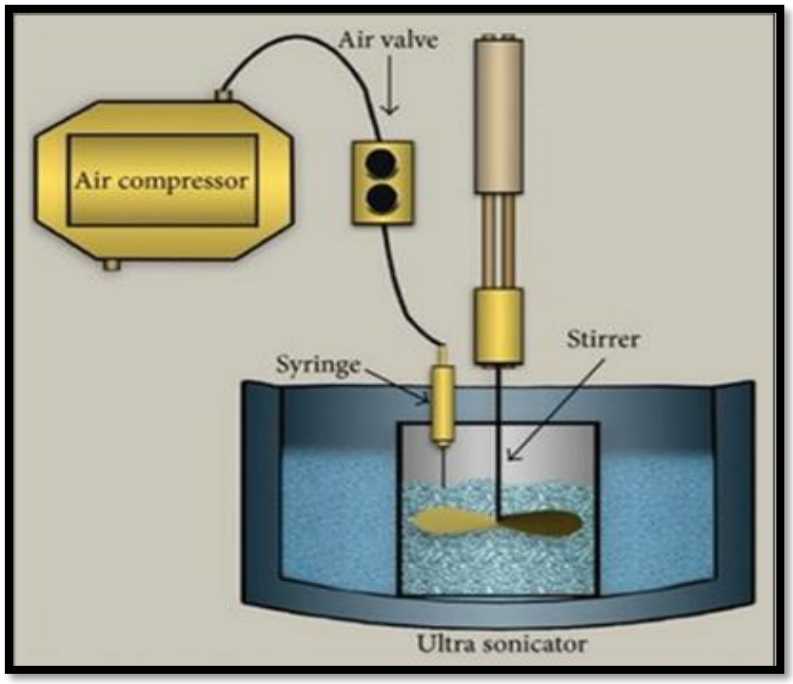

Fig 3: Diagrammatic illustration of the precipitation technique [29]

d. Combined precipitation and homogenization (Nano edge)

The drug is dissolved in an organic solvent, which is combined with a miscible anti-solvent to precipitate the drug. Because of its poor solubility in the water-solvent mixture, the medicine precipitates. Precipitation has also been used in conjunction with high-shear processing [15]. This is achieved by high-pressure homogenization and rapid precipitation. The Nano edge proprietary process from Baxter depends on the precipitation of friable materials in high shear and/or thermal energy environments to fragment materials. The blended solution unexpectedly becomes supersaturated and generates fine crystalline or amorphous particles when a medicine solution is added quickly to an antisolvent.

Precipitation of an amorphous material at high supersaturation can also occur when the amorphous state's solubility is surpassed. The essential concepts of homogenization and precipitation are the same as those of nanoedge. When these methods are combined, stability improves more quickly and particle sizes are reduced. The main shortcomings of the precipitation approach, such as crystal formation and long-term stability, can be addressed via nanoedge technology.[30]

3. Combined Method

a. Micro emulsion as template

In addition to being a medication delivery mechanism, emulsions can also be used as templates to make nanosuspensions. Emulsions can serve as templates for medications that have the ability to dissolve in both a volatile organic solvent and a solvent that is relatively water-miscible. An organic solvent or combination of solvents loaded with drugs is diluted in an aqueous phase using the appropriate surfactants to form an emulsion. When the organic phase subsequently evaporates at reduced pressure, the drug particles precipitate quickly to form a nanosuspension stabilized by surfactants. [32]

b. Hydrosol method

This is similar to the emulsification-solvent evaporation method. The main distinction between these two methods is the miscibility of the drug solvent and drug anti-solvent. Greater shear pressures inhibit crystal growth and Ostwald ripening, ensuring that the precipitates remain smaller.[33]

APPLICATIONS OF NANOSUSPENSIONS:

1. Oral drug delivery
2. Parenteral drug delivery
3. Pulmonary drug delivery
4. Ocular drug delivery
5. Enhancement of bioavailability

1. Oral drug delivery

Because of the significantly higher surface to volume ratio and smaller particle sizes. To improve the rate of absorption and bioavailability of poorly soluble medications, oral nanosuspensions are utilized.[34]

2. Parenteral drug delivery

Additionally, the parenteral drug delivery method makes use of nanotechnology. This method's benefit is that it requires a significantly smaller quantity of harmful cosolvent for medications with low solubility. When compared to the traditional oral formulation, this will improve the drug's therapeutic impact and target the drug's effect on macrophages. The medication clofazimine is administered as IV when, for the majority of Mycobacterium avium strains, the concentration in the liver, spleen, and lungs reaches an excessive level, or higher than minimum inhibitory concentration. Tarazepide is designed as a nanosuspension to circumvent the need for cyclodextrins and surfactants to increase the drug's bioavailability.[35]

Pulmonary drug delivery

For medications that are poorly soluble in pulmonary secretions, we use Nano preparations in pulmonary drug delivery. It is nebulized using a mechanical or ultrasonic nebulizer for lung delivery. It is feasible for the medication to be distributed uniformly, and each droplet includes at least one drug particle. The drug's solubility and diffusion are enhanced by Nano size. It prolongs the drug's residence duration at the site of absorption and improves its adhesion to the mucosal membrane. The majority of pulmonary nanosuspensions have a rapid onset of activity at the beginning, followed by a regulated release of the active moiety.[36]

3. Ocular drug delivery

For supported release, nanosuspensions are used in the visual delivery of the drugs. Liang and colleagues used Eudragit to set up cloricromene Nanosuspension for visual supply. Improved drug accessibility in rabbit eye fluid humour was confirmed by check. Therefore, after ophthalmic software, nanosuspension components offer a viable way to improve the drug's shelf life and bioavailability.[37]

4. Enhancement of bioavailability the pharmacies

Oral bioavailability of a medication is negatively impacted by its gastrointestinal tract permeability and solubility. By addressing the issues of poor solubility and poor permeability across membranes, nanosuspension provides a solution to the problem of inadequate bioavailability.[38, 39]

EVALUATION PARAMETER OF NANOSUSPENSION: [40, 41, 42, 43]

The following evaluation parameter was performed on nanosuspensions made using every formulation.

1. PH
2. Particle size & shape
3. Morphology
4. Particle size (Zeta potential)
5. Osmolarity
6. Crystalline state and particle morphology

1. pH

A pH meter was used to measure the pH of the prepared nanosuspension, which was placed in a 10 ml beaker.

2. Particle size and shape

3.

The saturation solubility, dissolving rate, stability, and in vivo behaviour of nanosuspensions are all influenced by two crucial parameters: particle size and particle size distribution. There will be a change in solubility and dissolution with any change in particle size. The physiochemical behaviour of the medication is dependent on particle size. One method for determining particle size is laser diffraction (LDF) or photon correlation spectroscopy (Pcs). In the polydispersity index (pi), the particle size distribution will be expressed. A moderately broad distribution is indicated by a pi value of more than 0.5, whereas a fairly narrow distribution is indicated by a value of 0.1-0.25.

4. Morphology

SEM, or scanning electron microscopy, is used to determine the morphological inspection of the nanosuspension.

5. Particle charge (zeta potential)

The stability of the nanosuspension will be determined by zeta potential. When using a combined electrostatic or steric stabilizer, a zeta potential of 20 mV would be adequate, but a minimum of 30 mV is needed.

6. Osmolarity

Osmometer was used to measure osmolarity.

7. Crystalline state and particle morphology:

The drug's crystalline structure and particle shape will alter during the nanosizing process. Scanning electron microscopy is utilized in addition to X-ray diffraction analysis to determine the particle's solid state.

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