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BREIF REVIEW ON FORMULATION AND EVALUATION OF NANOSUSPENSION OF NSAID FOR SOLUBILITY ENHANCEMENT BY QBD APPROACH

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ABSTRACT

The significance of the newly developed and auspicious future of "nanosuspensions," a novel dosage form, is mentioned in the current article. Reducing the size of particles, especially through nanonization, is a general and non-specific method to increase the bioavailability of poorly soluble medications. The significance of the planning, assessment, and ongoing research on different medications and their suitable applications is emphasized in the essay. Extremely low bioavailability is a key issue with poorly soluble medicines. To addresst hese issues, formulation as nanosuspension presents a compelling and optimistic substitute.The pure, poorly watersoluble medication in nanosuspension is suspended in a dispersion of no matrix material.Making a nanosuspension is easy and works with any medication that is insol uble in water.A nanosuspension not only addresses the issues of low solubility and bioavailab ility, but it also modifies the drug's pharmacokinetics, enhancing its safety and effectiveness.
The preparation techniques, characterization,and uses of the nanosuspension are covered in th is review paper.

KEYWORDS

Nanosuspension, Bioavailability ,Nanonisation,Solubility, Preparation & characterisation .

INTRODUCTION

The effective formulation of medications depends on a number of factors, including solubility, stability at room temperature, compatibility with solvents, excipients, and photostability. Lipophilic or poorly water-soluble compounds make up more than 40% of the novel chemical entities discovered so far through drug development programs. Drugs with limited solubility and low bioavailability can be solved using a variety of formulation techniques. Conventional methods such as micronization, fatty solution application, penetration enhancer or cosolvent application, surfactant dispersion method, salt creation, precipitation, etc. have limited effectiveness in improving the solubility of poorly soluble pharmaceuticals. Other strategies include inclusion complexes with cyclodextrins, dispersion of solids, emulsion and microemulsion techniques, and vesicular systems like liposomes, which have positive effects as be applied to improve the solubility of medications that have low solubility in lipid and water-based mediums. Increased solubility causes the active ingredient to flood at a faster

pace, reaching the maximum plasma level more quickly. This method works well for compounds that are difficult for formulators to work with because they have poor permeability, poor solubility, or both. Because of the smaller particle size, poorly soluble medications can be administered intravenously without obstructing blood vessels..

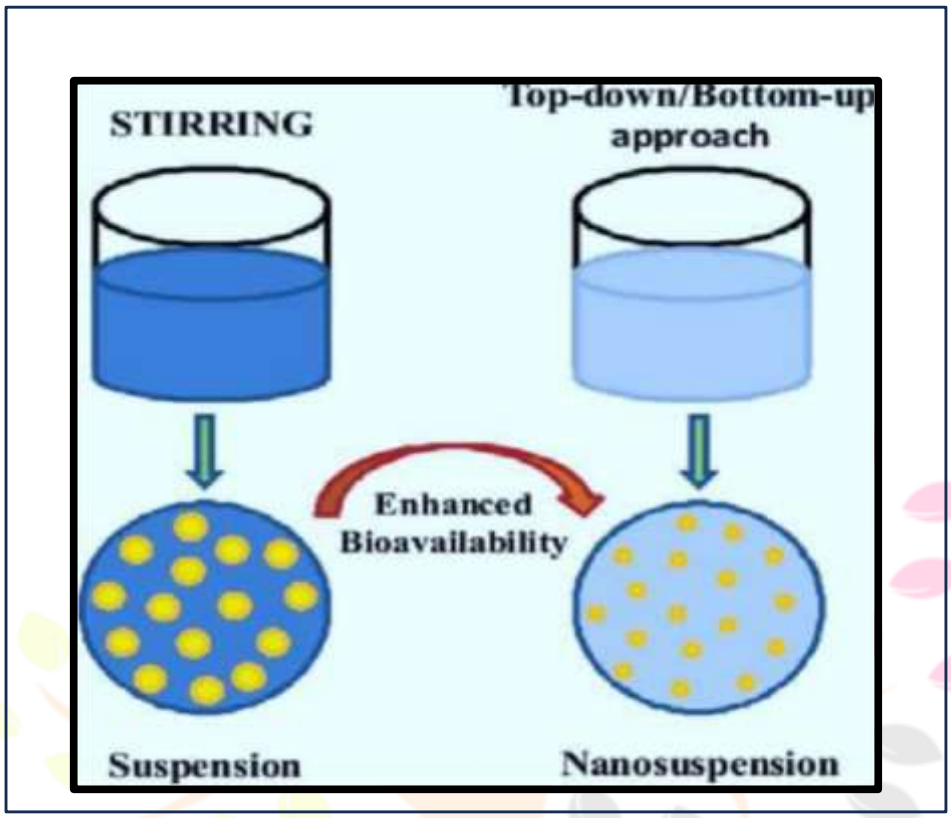

Fig1. Flow diagram for manufacturing process for nanosuspension

A class of drugs known as NSAIDs(nonsteroidal anti-inflammatory medicines) is prescribed to treat fever, pain, and other inflammatory conditions. The FDA has approved a family of medications known as (NSAIDs) (ibuprofen,mefanic acid,diclofanac ,melosicam,)for use as analgesics, antipyretics, and anti-inflammatory drugs. NSAIDs can be used to treat muscle pain, dysmenorrhea, arthritic diseases, pyrexia, gout, migraines, and, in some cases of acute trauma, they can be used to replace opioids.NSAIDs typically derived into growth based on their chemical structure and selectivity.

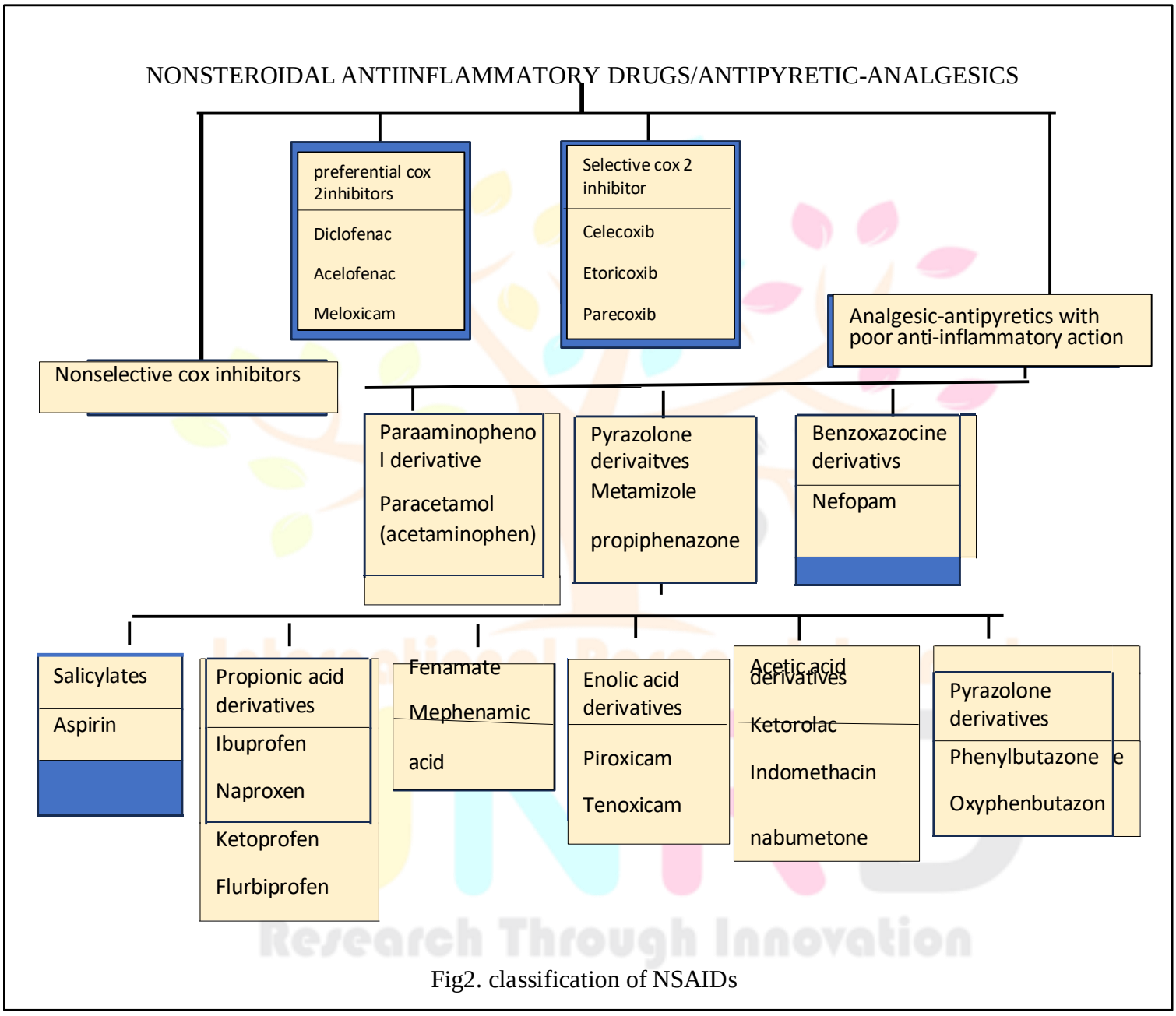

Fig2. classification of NSAIDs

MECHANISM OF ACTION

An inhibitory effect of NSAIDs is mostly seen on the enzyme cyclooxygenase (COX). Arachidonic acid cannot be converted into thromboxanes, prostaglandins, or prostacyclins without cyclooxygenase.The absence of these eicosanoids is thought to be responsible for the therapeutic benefits of NSAIDs. In particular, prostaglandins induce vasodilation, raise the hypothalamic temperature set-point, and contribute to anti-nociception, while thromboxanes are involved in platelet adhesion.

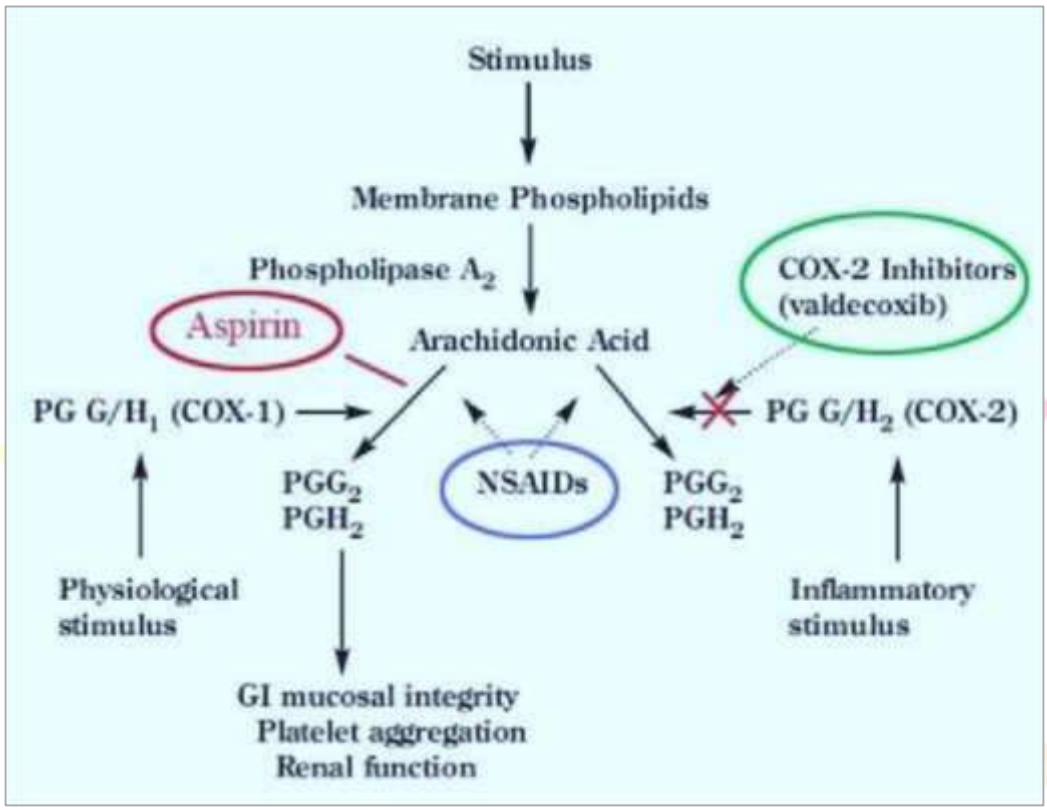

Fig3. MECHANISM OF ACTION OF NSAIDs

There are COX-1 and COX-2, two isoenzymes of cyclooxygenase.
In addition to its role in maintaining renal function, platelet aggregation, and the mucosa linin g the gastrointestinal tract, COX1 is constitutively produced in the body.Inducible expression of COX-2 occurs during an inflammatory reaction, rather than constitutively in the body.
Because they block both COX-1 and COX-2, the majority of NSAIDs are nonselective.
But because they only target COX-2, COX-2 selective NSAIDs—like celecoxib have a different profile of adverse effects.
COX2 selective NSAIDs are important because they should reduce inflammation without har ming the gastric mucosa because COX1 is the primary mediator for maintaining gastric mucosal integrity while COX-2 is primarily involved in inflammation .
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THE FORMULATION OF NSAIDS AS NANOSUSPENSION

1. Diclofenac

2. Mefanic acid
3. Aceclofenac
4. Ibuprofen
5. Aspirin

An inhibitory effect of NSAIDs is mostly seen on the enzyme cyclooxygenase (COX). Arachidonic acid cannot be converted into thromboxanes, prostaglandins, or prostacyclins without cyclooxygenase.The absence of these eicosanoids is thought to be responsible for the therapeutic benefits of NSAIDs. In particular, prostaglandins induce vasodilation, raise the hypothalamic temperature set-point, and contribute to anti-nociception, while thromboxanes are involved in platelet adhesion

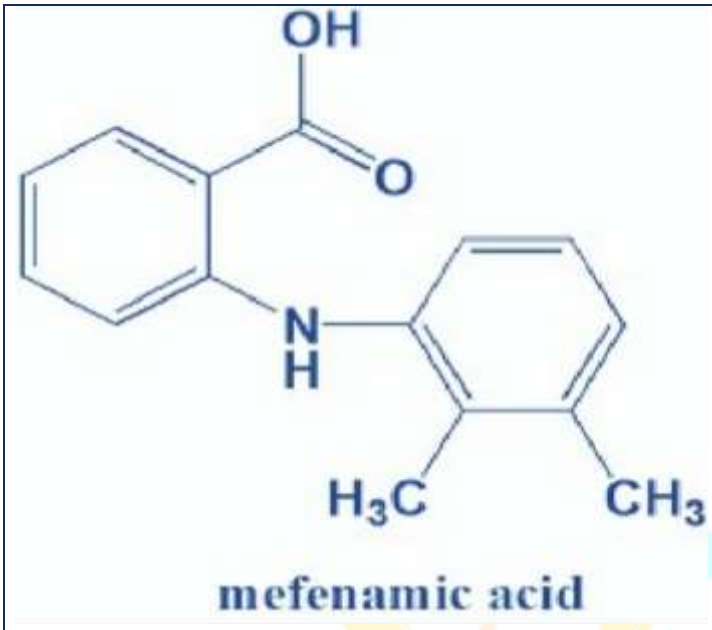
1) EUDRAGIT S100-BASED NANOSUSPENSION FILLED WITH DIGLOXAFERONE

It was made using the nanoprecipitation method, and its in vivo ocular anti-inflammatory activity, in vitro release, particle size, and morphology were all evaluated. The Eudragit S100 nanosuspension loaded with diclofenac exhibited a very consistent particle size of 172 nm, a polydispersibility index of 0.14, and a zeta potential of −23.7 ± 6.07 mV. It was discovered that the nanosuspended particles had a spherical shape. It was discovered that the nanosuspension produced an extended in vitro release that adhered to the Higuchi square-root release kinetics. The outcomes showed that a mix of dissolution and diffusion was used by the nanosuspension to release the medication. The assessment of nanosuspension in vivo When compared to the diclofenac aqueous solution, PGE2-induced polymorphonuclear leukocyte migration and lid- closure scores were considerably ($p < 0.05$) inhibited in the rabbit model of PGE2-induced ocular inflammation.

2) DEVELOPMENT, CHARACTERIZATION, IN VITRO DISSOLUTION, AND DIFFUSION STUDIES OF DICLOROFENAC-PROLINE NANO-CO-CRYSTALS WITH FAVORABLE PHARMACOLOGICAL EFFECTS

diclofenac is one of the most well-liked non-steroidal anti-inflammatory drug (NSAID) medications on the market. In addition to treating arthritis and soft injuries, it is also used as an anti-inflammatory and local pain reliever. Due to its high permeability and low solubility, diclofenac, a medication classified as class II under the Biopharmaceutics Classification System (BCS), is mostly offered as salts, such as diclofenac sodium or diclofenac potassium, rather than in its acid form. While many current medications exhibit strong pharmacological efficacy, When compared to the diclofenac aqueous solution, PGE2-induced polymorphonuclear leukocyte migration and lid-closure scores were considerably ($p < 0.05$) inhibited in the rabbit model of PGE2-induced ocular inflammation. There have been several changes reported to increase diclofenac's solubility.

1. MEFANIC ACID



IUPAC name **2-(2,3-dimethylphenyl)aminobenzoic acid**

1.1 INTRODUCTION

Mefenamic acid, also known as N-[(2, 3-dimethyl phenyl) amino] benzoic acid, is a strong NSAID with low oral bioavailability because of its poor aqueous solubility and inadequate dissolution. One of the most important factors in formulation and development is the solubility of MA. Currently, 40% of newly developed medications have low water solubility and low porosity.The biopharmaceutical categorization system (BCS) class II medication MA is a microcrystalline powder with limited aqueous solubility and high permeability. This poses a significant problem for the medicine's distribution in pediatric settings. This could imply that the rate at which a medicine dissolves has a significant impact on the bioavailability and therapeutic efficacy of MA. In one of the trials, MA showed noticeably greater antipyretic effectiveness than ibuprofen in the 2–4 hour range and paracetamol during the whole observation period.In comparative clinical research including 124 pediatric patients, it was discovered that MA (4 mg/kg) was equally as acceptable as paracetamol and more effective in treating fever. However, it is challenging to produce poorly water-soluble compounds as therapeutic products, particularly liquid medicines, and traditional formulation approaches are often abandoned at an early stage of the discovery process. Therefore, in order to further improve it, the solubility of MA must be enhanced. Other than the premix, there is currently no effective nanosuspension for MA.

2. MATERIAL & METHODS

1. Material

Hydroxypropyl methylcellulose (HPMC-K4M), sodium dodecyl sulfate (SLS), polysorbate 80 (Tween® 80), hydrochloric acid (HCl), methanol (MeOH), dimethyl sulfoxide (DMSO), sodium hydroxide (NaOH), potassium dihydrogen phosphate (KH2PO4), sodium chloride (NaCl), ethanol (C2H5OH), potassium chloride (KCl), dis-odium hydrogen phosphate dodecahydrate (Na2HPO4.12H2O), N,N-dimethylformamide (DMF), and acetonitrile (CH3CN) were all graciously given the sample of MA (purity > 99.5%). All of the trials used high-purity/deionized water.

2. Solubility Study

The mechanical shaker method was used to determine the solubility of MA [22]. By combining the excess MA in water with an improved MA nanosuspension formulation, a concentrated suspension of MA was

produced. To achieve equilibrium, every sample was kept in a mechanical shaker at 25 ◦C for 72 hours. Following equilibrium or saturation, the samples were removed, filtered using Whatman filter paper (0.45 µm), and then, after an appropriate dilution at 240 nm, the MA content in each sample was measured using UV spectrophotometry

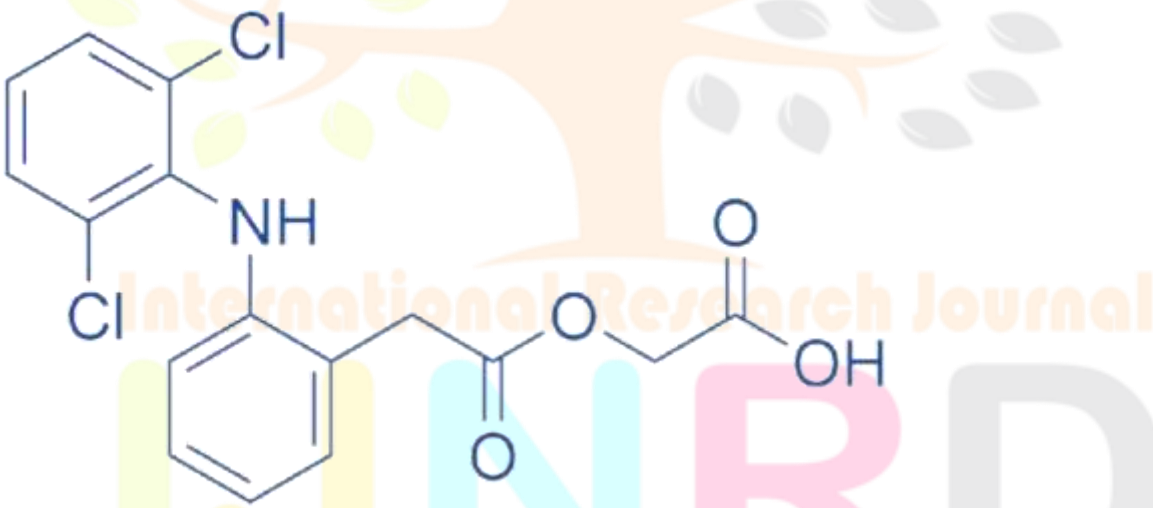
1.2.3 Partition coefficient

The shake-flask method was used to calculate the MA's partition coefficient, which can be represented as the ratio of the drug's concentration in the organic phase to its concentration in the aqueous phase.

1.2.4 Formulation development

Water was used as an antisolvent in the antisolvent precipitation procedure to create the nosuspension.
To put it briefly, the medication was soluble in acetone, an appropriate organic solvent, and the MA was dissolved in it.
The resultant solution was stored at a low temperature on a bath sonicator and gradually injected using a syringe into the antisolvent (water) containing a growth inhibitor or stabilizer (HP MC-K4M or Tween 80) For one hour, the organic solvent was allowed to evaporate while the nan osuspension was slowly magnetically stirred at ambient temperature.
The process's scalability was attained by producing batches of 100 mL under ideal formulation and processing parameters that were identified from 25 mL of small- scale nanosuspension batches.
After being gathered into glass jars, the nanosuspensions were labeled and put to use for subsequent test .

2.ACECLOFENAC



IUPAC name **2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid**

The current study's objective was to create and assess positively charged aceclofenac nanoparticles for ocular administration. Eudragit RS 100 was utilized in the nanoprecipitation process to create the nanoparticles. It was discovered that the optimized nanoparticles had a nearly spherical shape, a narrow particle size range (238.9 ± 8 nm), and a positive zeta potential (40.3 ± 3.8). Aceclofenac's entrapment efficiency was likewise higher (94.53 ± 1.0%) when the in vitro drug release profiles were longer. Studies using differential scanning calorimetry and powder X-ray diffraction revealed a drop in the drug's crystallinity within the nanoparticulate polymeric matrix. When compared to an aceclofenac aqueous solution, the formulation was shown to have greater permeability. The formulation of nanoparticles was discovered to be quite steady, well-tolerated, and showing no symptoms of harm to the cornea.

The best results were obtained from the in vivo investigations on rabbits' arachidonic acid- induced ocular

inflammation, where the nanoparticles dramatically reduced the migration of polymorphonuclear leukocytes

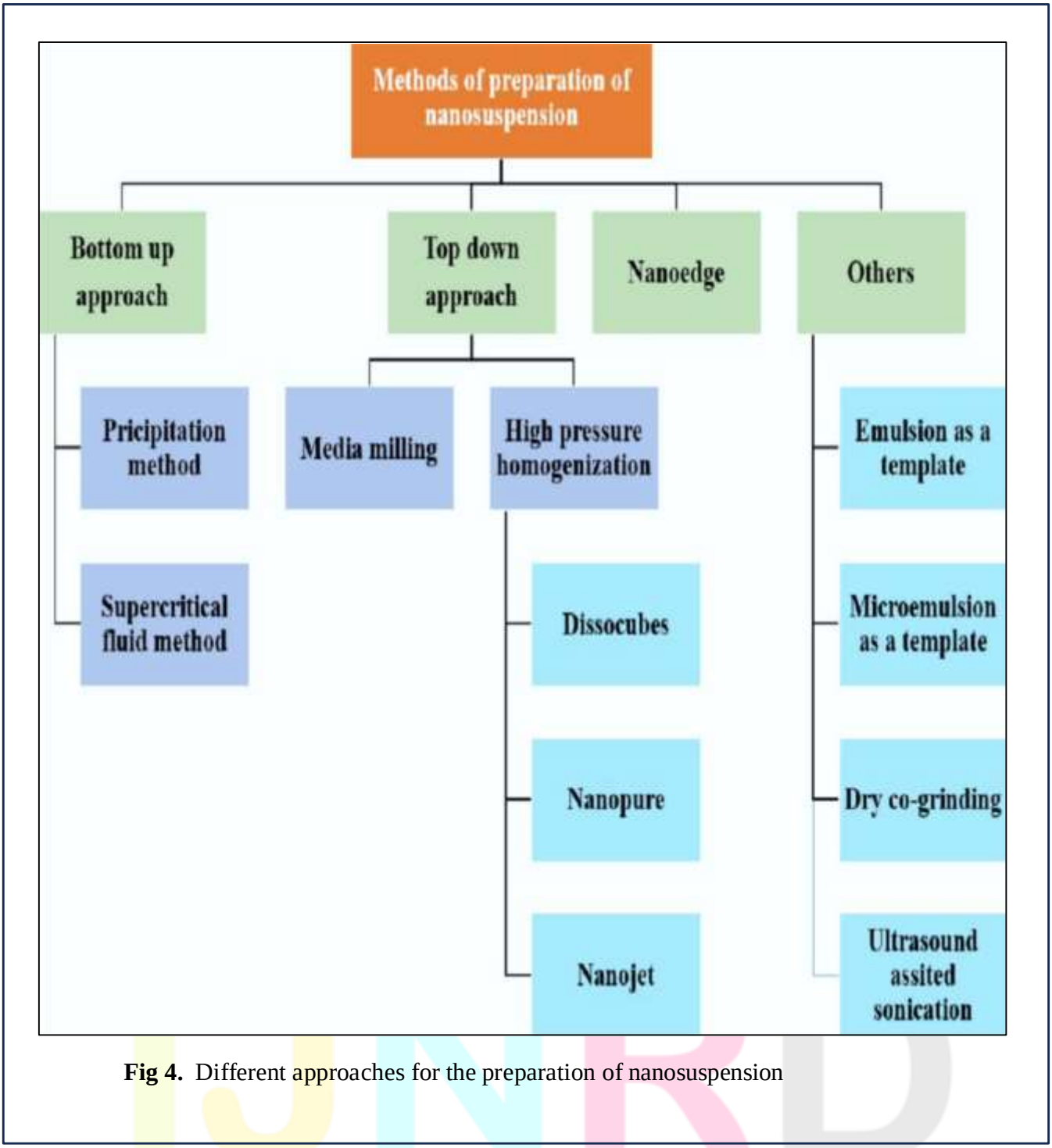


Fig 4. Different approaches for the preparation of nanosuspension

($p<0.05$) and lid closure scores.PREPARATION OF NANOSUSPENSION

As seen in Figure , "**Bottom up technology**" and "**Top down technology**" are the two main techniques used to prepare nanosuspensions.Top down technology involves breaking down bigger particles into nanoparticles;

Examples of this process include high-pressure homogenization and milling techniques. Bottom up technology involves assembly ways to make nanoparticles, such as precipitation, microemulsion, and melt emulsification processes. These approaches' guiding concepts are thoroughly explained, and Table lists their advantages and disadvantages.

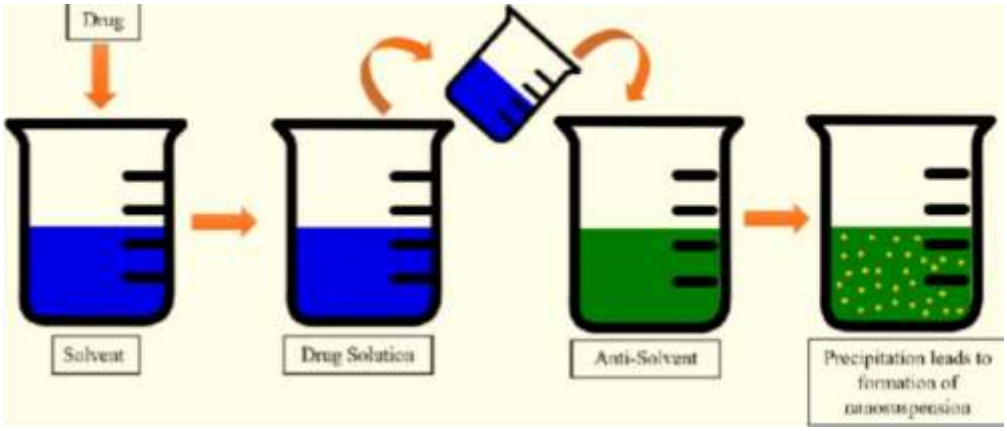


Figure 5. Formulation of nanosuspension by the solvent-antisolvent method

1. DISSOCUBES: HOMOGENIZATION IN AQUEOUS MEDIA

The technology behind Dissocubes was created by Muller (1999). With a volume capacity of 40 ml (for laboratory scale), the instrument can be operated at pressures ranging from 100 to 1 500 bars (2 800 – 21 300 psi) and up to 2000 bars. Using a high-speed stirrer, prepare a presuspension of the micronized medication in a surfactant solution before proceeding with the creation of the nanosuspension. The liquid flow volume per cross section in a closed system is constant, according to Bernoulli's Law. Below the room temperature water boiling point, the reduction in diameter from 3 cm to 25 µm results in an increase in dynamic pressure and a decrease in static pressure. Because of this, at normal temperature, water begins to boil and produces gas bubbles that explode when the suspension passes through the opening (known as cavitation), and normal air pressure is achieved. The temperature, the number of homogenization cycles, the homogenizer's power density, and the homogenization pressure are the primary determinants of the size of drug nanocrystals that can be produced. Preprocessing, such as medication micronization and the use of expensive equipment, raises the dosage form's overall cost. Using this technique, nanosuspensions of a number medications were made, including Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine, and Dexamethasone.

2. IN NONAQUEOUS MEDIA: HOMOGENIZATION (NANOPURE)

A water-free medium is used to homogenize the suspension of nanopure. The drug suspensions in nonaqueous media are homogenized using a process known as "deep-freeze," which involves freezing the mixture at or below 0°C. Water, oils, and fatty acids have very high boiling points and low vapor pressures, hence the In nanopure technology, a static pressure drop alone is insufficient to trigger cavitation.

1. METHOD OF PRECIPITATION

A common technique for creating submicron particles of poorly soluble medications is precipitation. This approach involves dissolving the drug in a solvent, mixing the solution with a solvent that contains a surfactant, making the drug insoluble. Quick addition of the drug in the solution to such a solvent (usually water), causing the drug to quickly become supersaturated and form ultrafine crystalline or amorphous drug particles. This process involves the creation of nuclei and the development of crystals, both of which are temperature-dependent. The preparation of a stable suspension with the smallest possible particle size primarily requires a high nucleation rate and a low crystal growth rate.

2. HIGH PRESSURE ADSORPTION

The three phases involved in this technique are as follows: To create presuspension, drug powders are first dispersed in a stabilizing solution. Presuspension is then homogenized using a high pressure homogenizer at low pressure occasionally for premilling. Finally, high pressure homogenization is performed for 10 to 25 cycles to create nanosuspensions of the desired size.

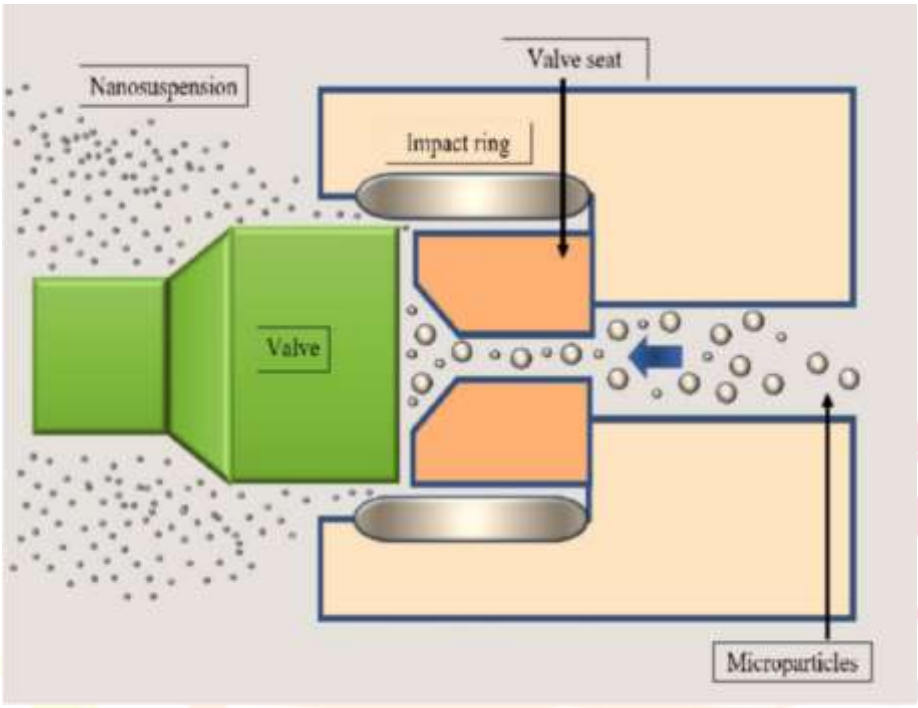


Figure 6. Schematic representation of the High-pressure homogenization process

3. METHODS OF MILLING

3.1 MILLING MEDIA

A patent for nanocrystal technology was held by Liversidge et al. This method produces nanoparticles by media milling pharmaceuticals. The medications' impaction with the milling media provides the necessary energy for the microparticulate system to break down into nanoparticles. In order to create suspension, the medication, stabilizer, water, or appropriate buffer are added to the milling media inside the chamber, which is then rotated at a very high shear rate. One of the main issues with this process is the residues that are left in the final product.

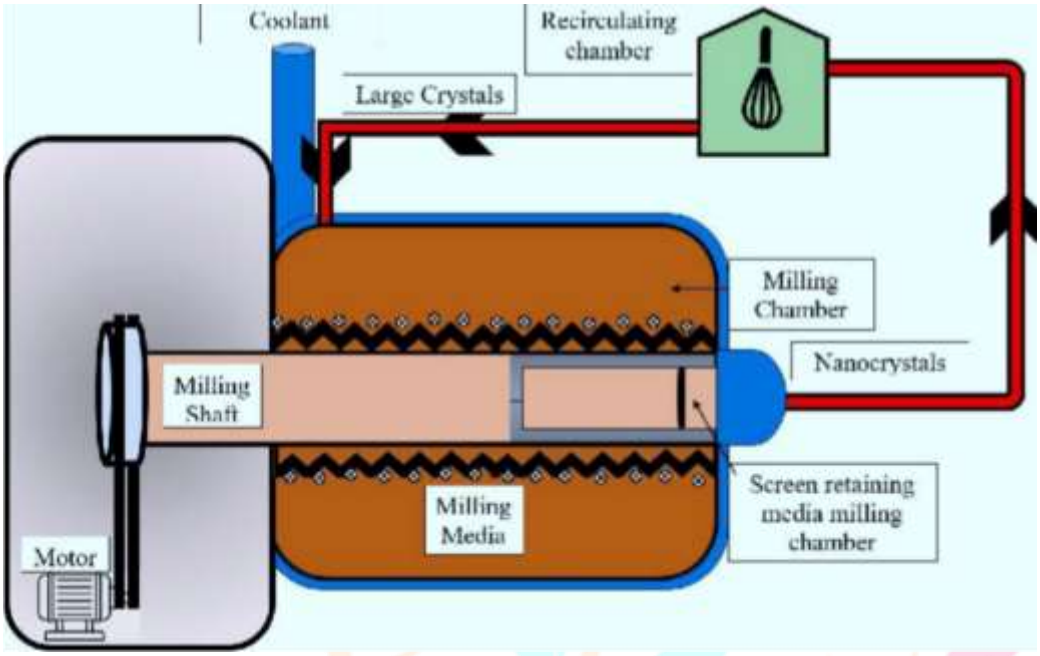


Figure 7. Media milling process: Schematic representation

3.2 ARID COGRINDING

For many years, pearl ball mills have been used in wet grinding procedures to prepare nanosuspensions. Currently, nanodispersions can be ready using techniques for dry milling. After dispersing in a liquid medium, poorly soluble drugs are dry ground with soluble polymers and copolymers to create stable nanosuspensions. Many weakly water-soluble medications, including glibenclamide, griseofulvin, and nifedipine, have been shown to form colloidal particles when stabilized with sodium dodecyl sulfate and polyvinylpyrrolidone by Itoh et al.

4. METHOD OF MELT EMULSIFICATION

The primary technique for creating solid lipid nanoparticles is melt emulsification. Kipp and colleagues initially use the melt emulsification approach to generate ibuprofen nanosuspensions. Here's the four-step process. First, the drug is added to a stabilizer-containing aqueous solution. To create an emulsion, the solution is heated to a temperature greater than the drug's melting point and then homogenized using a high-speed homogenizer. Throughout the entire procedure, the temperature is kept above the drug's melting point. The emulsion is then chilled to the particles to precipitate. The concentration of the drug, the kind and concentration of stabilizers employed, the cooling temperature, and the homogenization process are the primary factors that affect the size of the particles in the nanosuspension.

5. NANOJET TECHNOLOGY

This method, also known as opposite stream technology, divides a suspension stream into two or more sections within a chamber. High pressure exists between the two streams as they collide. Particle size is reduced as a result of the process's high shear force. Dearns had used the microfluidization method to create atovaquone nanosuspensions. The primary drawback of this method is the high number of passes through the microfluidizer and the comparatively higher fraction of microparticles in the final product.

6. SUPERCRITICAL FLUID TECHNIQUES

Many techniques, such as the supercritical expansion of the supercritical solution (RESS) process, Nanoparticles are produced using the compressed antisolvent (PCA) technique and the antisolvent process. The

RESS process involves expanding a drug solution through a nozzle into a supercritical fluid, which causes the supercritical fluid's solvent power to evaporate and precipitate the drug as small particles. Young et al. synthesized 400–700 nm diameter cyclosporine nanoparticles by employing the RESS technique. The drug solution is atomized into the CO2 compressed chamber in the PCA procedure. The solution becomes supersaturated as the solvent is removed, leading to precipitation in the end. The drug solution is injected into the supercritical fluid during the supercritical antisolvent procedure, which extracts the solvent and causes the drug solution to become supersaturated.

CHARACTERIZATION OF NANOSUSPENSION

Numerous methods, including organoleptic properties, particle size, assay, crystalline state, dissolution, zeta potential, and in-vivo dissolving studies, are used to characterize nanosuspension.

1. PARTICLE SIZE DISTRIBUTION AND MEAN PARTICLE SIZE

The Polydispersibility Index is a size-based metric for sample heterogeneity (PI). With the use of PI, mean particle size and size distribution are determined. PI will affect several parameters of the nanosuspension, such as physical stability, saturation solubility, in-vivo performance, and dissolving rate. A high PI number implies that particles are dispersed throughout a broad size range, whereas a low PI value indicates a limited size distribution. A tight size distribution is indicated by PI values of 0.1 to 0.25, but values greater more than 0.5 denotes a wide size range. Low PI values are better for creating stable nanosuspensions.

2. ZETA POTENTIAL

The value of zeta potential determines whether a nanosuspension is stable. The zeta potential is the amount of charge generated during the change from the distributed solid to the liquid continuous phases. The unit of zetapotential is millivolt. Particles need an electric charge on their surface in order to repel one another. Agglomeration won't occur, and the nanosuspension will be stable. A stable nanosuspension can be produced with a zeta potential as low as 30 mv .

3. ANALYSIS OF CRYSTAL MORPHOLOGY

Regarding the stability of nanosuspension, it is essential to determine the kind of particle— crystalline or amorphous. A drug's morphology might change from crystalline to amorphous or polymorphic as a result of particle reduction to the nanoscale. Modifications in the degree of crystallinity or polymorphic form of API have an impact on its properties. Because of its high energy, the medication is likely to change from an amorphous to a crystalline form.

4. CONSISTENCY

The suspended particle's surface area increases significantly due to its reduced size. Surface free energy increases with increasing surface area. The stability problem with nanosuspension is exacerbated by this increased surface free energy. In an attempt to lower the surface free energy, nanosuspension particles aggregate, which triggers the beginning of crystal formation. Therefore, several stabilizers are utilized to decrease agglomeration and promote stability. The expedited stability examination Studies on the stability of nanosuspension can be conducted using the ICH recommendations. One such application is thermal cycling.

5. ANALYSIS OF SATURATION SOLUBILITY AND DISSOLUTION

The investigation of saturation solubility and dissolving rate is essential to understanding the behavior of nanosuspension in vitro. A variety of techniques detailed in the literature can be used to ascertain the saturation solubility in various physiological buffers and temperatures. The dissolving rate of a drug can be used to predict its release, and this is important when using sustained-release nanoparticle dosage forms .

IMPLEMENTATION OF NANOSUSPENSIONS

1. ORAL ADMINISTRATION:

This is the recommended method of administration. However, some medications have restricted absorption and solubility, which limits their bioavailability and decreases their effectiveness. When this happens, nanosuspensions can help by increasing surface area and adhesiveness, which improves the absorption and dissolution rate. By improving mucoadhesion, nanosuspensions can also lengthen the time that food travels through the gastrointestinal tract, which increases bioavailability. Increases in the nanosuspension's adhesiveness, saturation solubility, and surface area are thought to be responsible for the improved oral bioavailability. Moreover, nanosuspensions make it simple to hide the flavor of particulate matter.

2. PARENTERAL ADMINISTRATION:

Using nanosuspensions, non-injectable medications with poor solubility must be transformed into formulations suitable for intravenous delivery. Making nanosuspensions for parenteral use is crucial, and recent advancements in Studies in this field have demonstrated that the use of Nanosuspen for injectable formulations is effective. Today's highly regulated nanosuspension technologies allow for the production of homogeneous particles with superior control over the maximum particle size. Several research publications highlight the value of nanosuspensions for parenteral administration.

3. OCULAR DELIVERY:

Nanosuspensions are a possible way to provide medications with limited lachrymal fluid solubility. They are the ideal method for administering medications to the eyes because they make hydrophobic medicines more soluble at saturation. Effective nanosuspension delivery systems have been developed by researchers for certain medications, such as glucocorticoids (Kassem et al.

4. DELIVERY THROUGH THE LUNGS:

Nanosuspensions may be advantageous for the delivery of medications with low solubility in the lungs. The restrictions on Present-day pulmonary administration methods, like aerosols and dry powder inhalers, have a short residence time and restricted diffusion to the target location. Nanosuspensions provide a way around these limitations. The effective formulation of fluticasone and budesonide as nanosuspensions for pulmonary delivery are two examples.

5. TOPICAL ADMINISTRATION:

Medications in nanocrystalline form can improve saturation solubility, which raises the drug's penetration. Nanocrystals are a good choice for cutaneous application due to their enhanced permeability, adhesiveness, and increased membrane penetration.

6. TARGETED DELIVERY:

The drug's absorption rate is influenced by the size of its nanoparticles. Targeted delivery is achieved by modifying the in vivo behavior of nanoparticles by the modification of their surface properties. Targeted medication delivery systems can be developed by methods such as developing intelligent crystals or covert nanocrystals of less than 100 nm in particle size.

FUTURE SCOPE

In summary, potential avenues for future research encompass

1. boosting in vivo bioavailability and linking in vitro and in vivo bioavailability data
2. employing biocompatible matrix polymers to achieve controlled and sustained drug releas e over an extended duration*
3. developing stimuli-responsive systems like pH, light, temperature, and magnetic field, which is especially cru cial for highly toxic drugs
4. additional investigations that are essential to comprehend the behavior of nanosuspension s in vivo, such as interactions with cells and various biological barriers like the blood- brain barrier
5. surface engineering of nanosuspensions for active or passive targeting to enhance their ab ility to

reach the target

6. A unique and cutting-edge method for resolving issues with the delivery of hydrophobic medications, such as those with restricted solubility in both aqueous and organic environments, is nanosuspension technology.
7. Methods like media milling have shown promise in producing nanosuspensions in large quantities.
8. The use of parenteral products in addition to traditional dosage forms like pills, capsules, and pellets is made possible by nanosuspension technology.
9. The field of nanosuspension drug delivery will keep expanding and be interesting for both oral and non-oral administration methods because of its simple formulation processes and broad variety of applications.

CONCLUSION

This review study highlights the latest developments in therapeutic nanosuspensions made possible by a number of methods, including Bottom up approach,Top down approach emulsification, media milling, and high pressure homogenization.But early on, a number of in vivo investigations make it abundantly evident that these drug delivery methods have applications in parenteral, oral, ophthalmic, topical and pulmonary administration.These systems do, however, offer flexibility and the chance to further customize particles, surface characteristics to maximize in vivo responses, and the creation of novel therapeutic approaches for the treatment of various illnesses. Working on the size optimization of medication

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