Development and Characterization of Fluconazole- Loaded Nanosuspension Systems for Improved Solubility, Dissolution Rate, and Oral Bioavailability

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***Abstract*— A type of drug delivery systems based on nanoparticles called nanosuspension has shown promise in addressing the drawbacks of conventional drug delivery techniques, especially for hydrophobic medications. Very low bioavailability is one of the main issues with poorly soluble medications. For medications like itraconazole, fluconazole, simvastatin, and carbamazepine that are poorly soluble in both aqueous and nonaqueous conditions and fall under BCS class II according to the biopharmaceutical categorization system, the issue is even more complicated. An appealing and potential substitute for these issues is formulation as nanosuspension. The pure, weakly water-soluble medication, free of any matrix ingredient, is suspended in dispersion as nanosuspension. Nanosuspension is easy to prepare and works with any medication that is insoluble in water. A nanosuspension increases medication safety and efficacy by changing the pharmacokinetics of the medicine in addition to resolving issues with low solubility and bioavailability. Nanosuspension technique can increase the medications' stability and bioavailability. Nanosuspension is easy to prepare and works with any medication that is aqueously insoluble. Wet mills, high pressure homogenizers, melt emulsification, emulsion-solvent evaporation, and super critical fluid processes are used to create nanosuspensions. Oral, parenteral, pulmonary, and ophthalmic methods can all be used to administer nanosuspensions. Incorporating nanosuspensions into mucoadhesive hydrogels and ocular inserts can also be utilized for targeted medication delivery. This review article explains the nanosuspension's characterisation, applications, and preparation techniques.**

***Index Terms*— Nanosuspensions, Solubility enhancement, High pressure homogenization, Media milling, Drug delivery.**

I. INTRODUCTION:

Colloidal dispersions of medication particles that are nanosized and created using an appropriate technique and stabilized with an appropriate stabilizer are known as nanosuspensions [1]. They may alternatively be described as a biphasic system made up of pure drug particles that are suspended in an aqueous medium with a diameter of less than 1µm [2]. Drug particles reduced to the nanometre range have a higher rate of dissolving due to saturated solubility and increased surface area [3]. Solid particles in nanosuspensions typically have an average particle size of 200–600 nm, with a particle size dispersion of less than one micron [4,5]. Nanoparticles are not the same as nanosuspensions.

Solid lipid nanoparticles are lipidic drug transporters, while nanoparticles are often polymeric colloidal drug carriers. By maintaining the medicine in the necessary crystalline form with smaller particles, nanosuspension technology improves bioavailability by increasing the rate of dissolution. Increases in surface area and, hence, dissolution velocity is associated with higher rates of dissolution of micronized particles (particle size < 10 µm). Because of the vapor pressure effect, nanoparticles can improve saturation solubility and solution velocity. Because of their ease of use and the benefits they offer over alternative approaches, nanosuspensions have demonstrated their ability to address issues related to the administration of poorly water-soluble and poorly water-and lipid-soluble medications. The several facets of nanosuspensions and their promise as a viable medication delivery method are the main topics of this review. A weakly water-soluble medication without any matrix material suspended in dispersion makes up nanosuspensions [6]. These can be used to improve the solubility of medications that are not very soluble in lipid or water media. Increased solubility causes the active ingredient to flood more quickly, reaching the maximum plasma level sooner. 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 the blood vessels. It is also possible to lyophilize the suspensions and turn them into a solid matrix. In addition to these benefits, liquid formulations are superior than other types [7].

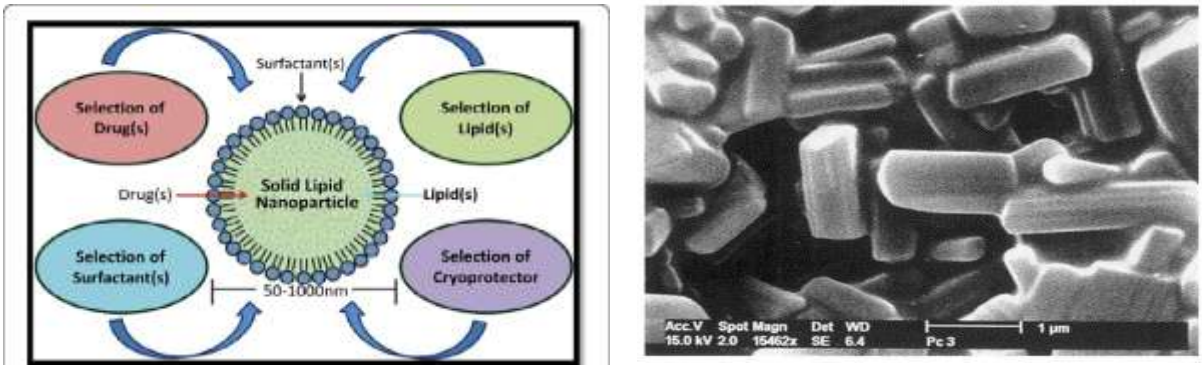


Fig 1. Diagrammatic Representation of Nanosuspension Particle

Table 1. Structural Composition of Nanosuspension [8]

Component	Description	Function/Role
Nanoparticles	Solid, submicron particles typically ranging from 1 nm to 1000 nm. They can be made from lipid, polymer, or inorganic materials.	Provide the core structure of the nanosuspension, offering increased surface area for drug dissolution and absorption.
Drug (Active Ingredient)	The pharmacologically active substance encapsulated or adsorbed onto the nanoparticles. This can be a poorly water-soluble drug.	The therapeutic agent being delivered, often chosen for its low solubility in aqueous media.
Surfactants (Stabilizers)	Non-ionic, anionic, or cationic surfactants like polysorbate 80, PVA, cetyl alcohol, or sodium dodecyl sulphate (SDS).	Stabilize the nanosuspension by preventing aggregation, controlling particle size, and improving solubility.
Co-Surfactants	Low molecular weight co-surfactants like poloxamers or ethanol.	Enhance the action of primary surfactants, reduce interfacial tension, and improve stability and bioavailability.
Solvents (Water or Organic Solvents)	Water is commonly used as the dispersion medium, though organic solvents (e.g., ethanol, acetone) may be used in preparation.	Solvent serves as the continuous phase in which nanoparticles are dispersed and stabilized.
Polymeric Stabilizers	Polyvinyl alcohol (PVA), polyethylene glycol (PEG), polysorbate 80, or hydroxypropyl methylcellulose (HPMC).	Form a protective layer around the particles, reducing the tendency to aggregate and stabilizing the nanosuspension.

Table 2. Historical Development of Nanosuspension [9]

Time Period	Milestone	Key Developments
1990	Discovery of Nanosuspensions	Nanosuspensions were first introduced as a means to improve the bioavailability of poorly water-soluble drugs. They are colloidal dispersions of nanoparticles in a liquid.
1994	Early Development	Initial studies focused on improving the solubility and stability of poorly soluble drugs by reducing particle size using techniques like precipitation and homogenization
1999	R.H. Muller's Contribution	R.H. Muller developed a high-pressure homogenization technique for preparing nanosuspensions, which became a foundation for many later methods.
2000	First-Commercial Application	The first nanosuspensions entered commercial use in drug delivery, notably in the formulation of poorly soluble drugs such as paclitaxel.

2004	Approval of Nanosuspension-based Drug Products	The first drug product based on nanosuspension (e.g., Rapamune®) was approved, marking a significant milestone in the pharmaceutical industry.
2010	Advanced Techniques	New techniques, such as the use of supercritical fluids, high-speed homogenization, and microemulsion templates, began to be explored for nanosuspension production
2014	Increased Research and Applications	The focus expanded to incorporate therapeutic applications such as targeted drug delivery and gene therapy, showing potential in various medical fields.
2014	Therapeutic Use and Commercialization	Nanosuspensions continue to gain importance for drug delivery systems, with formulations for cancer, neurological disorders, and other complex therapies in development.
Present	Future Prospects	Ongoing research focuses on improving stability, scalability, and regulatory approvals, with new applications emerging in personalized medicine and biologics

Table 3. Unique Properties of Nanosuspension [10]

Property	Description
Reduced Particle Size	Nanosuspensions contain nanoparticles typically in the range of 1–1000 nm, providing a significantly larger surface area than their micro meter-sized counterparts.
Enhanced Solubility	The smaller particle size increases the surface area, which can significantly improve the solubility of poorly soluble drugs, making them more bioavailable.
Increased Drug Stability	Nanoparticles in a suspension can offer better stability, protecting sensitive drugs from degradation due to environmental factors like pH and temperature.
Improved Bioavailability	The higher surface area and smaller particle size allow for faster dissolution rates, enhancing the absorption and bioavailability of poorly soluble drugs.
Controlled Drug Release	The particles in nanosuspensions can be engineered to release drugs at controlled rates, providing sustained or targeted release over time.
No Need for Organic Solvents	Nanosuspensions are usually water-based, avoiding the need for harmful organic solvents, which can be toxic or difficult to remove.
Versatility in Formulation	Nanosuspensions can be formulated into various dosage forms like oral, parenteral, ocular, or topical, offering flexibility in drug delivery.
Enhanced Drug Penetration	Due to their small size, nanoparticles can penetrate biological barriers more efficiently, improving drug delivery to specific tissues, such as the brain or tumors.

Stabilization of Hydrophobic Drugs	Nanosuspensions are particularly useful for stabilizing hydrophobic (lipophilic) drugs, which would otherwise have poor solubility in aqueous solutions.
Reduced Side Effects	Due to controlled release and targeted delivery, nanosuspensions can minimize side effects by directing the drug to specific sites of action and reducing systemic exposure.
Increased Patient Compliance	The improved bioavailability and reduced dosing frequency associated with nanosuspensions can improve patient adherence to treatment regimens.
Possibility of Sterile Formulations	Nanosuspensions can be produced sterile for injectable drug formulations, ensuring safety and efficacy for parenteral applications.
High Drug Loading Capacity	Nanosuspensions can accommodate high drug concentrations without compromising the formulation's stability or release profile.

Table 4. Recent Advancements [11]

Advancement Area	Description	Year	Key Findings
Targeted Drug Delivery for Cancer	Nanosuspensions designed for targeted delivery to cancer cells using surface-modified nanoparticles.	2023	Surface functionalization (e.g., with folic acid, antibodies) enhances tumor targeting, improving therapeutic efficacy and reducing side effects.
Nanosuspensions for Brain Drug Delivery	Nanosuspensions using nanoparticle-based carriers for overcoming the blood-brain barrier (BBB).	2022	Brain-targeted nanosuspensions enhance the bioavailability of drugs like antipsychotics and anticancer agents by improving BBB penetration.
Gene Delivery Systems	Nanosuspension-based delivery systems for genes, such as DNA, RNA, and CRISPR components.	2023	Nanocrystal-based systems improve the stability and efficiency of gene therapy, showing potential for safer gene editing and RNA-based treatments.
Ophthalmic Nanosuspensions	Nanosuspension formulations for improved ocular drug delivery and treatment of diseases like glaucoma.	2023	Enhanced ocular penetration of drugs like corticosteroids and antivirals. Nanosuspensions allow for sustained release, improving therapeutic outcomes.
Oral Drug Delivery of Hydrophobic Drugs	Use of nanosuspensions to improve the solubility and bioavailability of poorly water-soluble drugs.	2022	Solid-state nanosuspensions show improved stability and dissolution rates, providing a promising approach for oral administration of hydrophobic drugs.
Long-Acting Drug Formulations	Sustained release nanosuspensions for prolonged therapeutic effects and reduced dosing frequency.	2024	Long-acting formulations provide controlled release of drugs like insulin and antipsychotics, reducing the frequency of administration and improving patient adherence.
Nanoparticle-Mediated Immunotherapy	Nanosuspensions used in immune checkpoint inhibition and vaccines for targeted cancer.	2023	Immuno-nanosuspensions enhance the targeted delivery of immune-stimulating agents, improving efficacy in cancer therapy with reduced off-target effects.

II. Advantages [12]

a. Improved Solubility
b. Enhanced Bioavailability
c. Controlled Release
d. Reduced Side Effects
e. Targeted Drug Delivery
f. Versatility in Formulation
g. Improved Therapy

III. Disadvantages [12]

a. Stability Issues
b. Complex Manufacturing
c. Limited Long-term Stability
d. Limited to Certain Types of Drugs
e. High Cost of Production
f. Viscosity Issues
g. Risk of Toxicity

Table 5. Types of Nanosuspension: Structure, Characteristics, and Applications [13]

Type of Nanosuspension	Structure	Characteristics	Applications
Polymeric Nanosuspension	Nanosized drug particles stabilized by polymers (e.g., polyvinyl alcohol, polyethylene glycol).	-Improved drug solubility -Controlled drug release -Enhanced bioavailability -Biodegradable and biocompatible	-Oral and parenteral drug delivery -Targeted therapy -Cancer treatment -Vaccine delivery
Liposome-based Nanosuspension	Nanosized vesicles made of lipid bilayers enclosing the drug.	-Biocompatibility -High drug loading -Ability to deliver both hydrophilic and hydrophobic drugs -Controlled release properties	-Targeted drug delivery -Cancer therapy -Gene therapy -Vaccine carriers
Solid Lipid Nanoparticles (SLNs)	Solid lipid particles (e.g., stearic acid, glycerides) stabilized by surfactants.	-Biocompatible and biodegradable -Enhanced drug stability -Controlled and sustained release -High drug encapsulation efficiency	-Drug delivery (oral, topical, and parenteral) -Cosmetic formulations -Gene therapy -Anti-cancer treatments
Nanocrystals (Drug Nanosuspensions)	Pure drug particles (without excipients) reduced to the nanoscale, stabilized by surfactants.	-Enhanced drug solubility and dissolution rate -Improved bioavailability -No chemical modification of the drug -Physical stability	-Oral formulations for poorly water-soluble drugs -Parenteral formulations -Targeted delivery -Biopharmaceutical enhancement
Micellar Nanosuspension	Self-assembled nanosized aggregates of surfactants (micelles) with drug incorporated in the core.	-Solubilization of poorly water-soluble drugs -Stability in aqueous systems -Drug release depends on micelle properties	-Oral drug delivery -Anticancer therapies -Dermal and topical drug delivery

Synthesis of Nanosuspension Using Different Techniques [14]

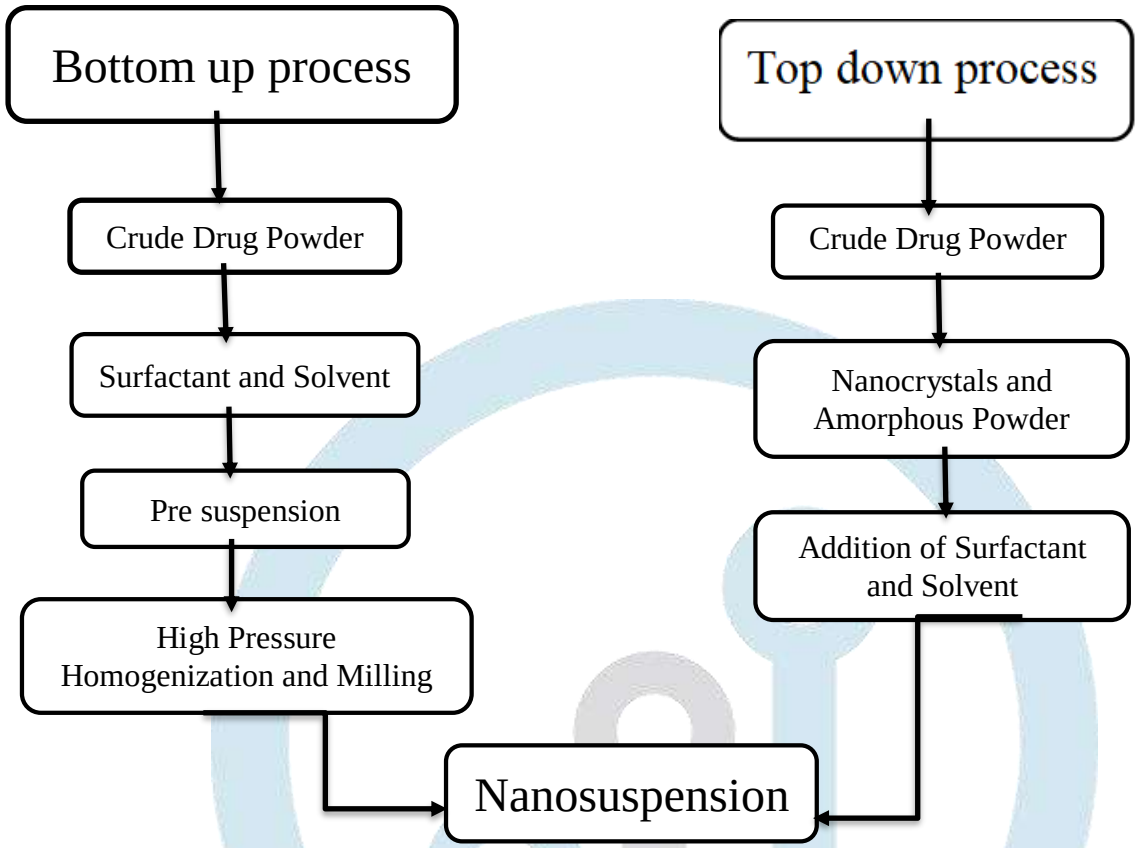
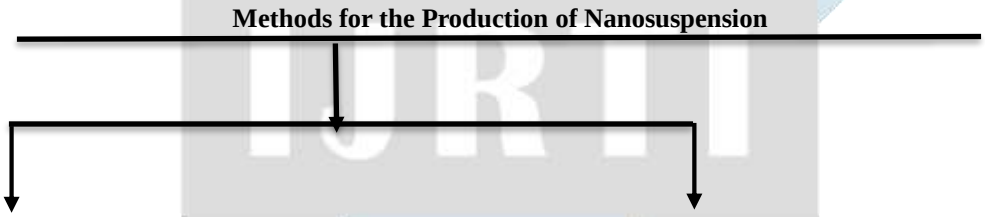


Fig 2. Approaches for preparation of nanosuspension.



1. TOP DOWN METHOD

- Media milling (Nano Crystals)
- High pressure homogenization
- Nanoedge
- Nanopure

2. BOTTOM UP METHOD

- Emulsification solvent-evaporation technique
- Lipid emulsion/micro-emulsion template
- Solvent evaporation process
- Melt emulsification method
- Supercritical fluid process

IV. Methods for Production:

Media Milling (Nanocrystals) [15]

This technique uses pearl mills or high-shear media mills to create the nanosuspensions. A milling chamber, a milling shaft, and a recirculation chamber make up the media mill. As shown in Figure 3, the milling media or pearls are rotated at a very high shear rate after the milling chamber is filled with the milling media, water, medication, and stabilizer. The temperature of the milling operation is regulated.

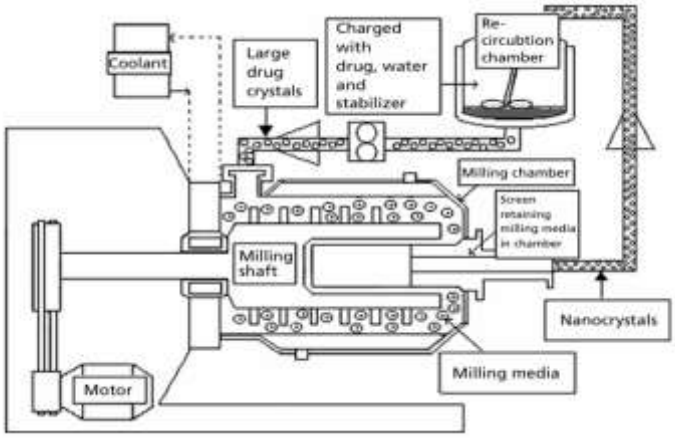


Fig 3. Schematic Representation of the media milling process

Drug Containing Solid Dispersion

↓

Dissolved in Organic Solvent e.g. Dichloromethane/ Ethanol

↓

Ensure the Solubility of Drug in Organic Solvent

↓

Tween 80 and Soluplus Dispersed in Water and Kept for Homogenization

↓

Later Drug Dispersion in Organic Solvent Added Dropwise to Surfactant

↓

High Energy and Shear Forces are Applied in Milling Chamber

↓

Drug Particles Breakdown into Nanoparticles

High Pressure Homogenization [16]:

It is the most popular technique for creating nanosuspensions of numerous medications that are not very soluble in water. There are three steps involved. Presuspension is created by first dispersing drug powders in stabilizer solution, then homogenizing the presuspension at low pressure for premilling in a high-pressure homogenizer, and then homogenizing at high pressure for 10 to 25 cycles to create the desired size of nanosuspensions. This idea has led to the development of several techniques for creating nanosuspensions, including Dissocubes, Nanopure, Nanoedge, and Nanojet.

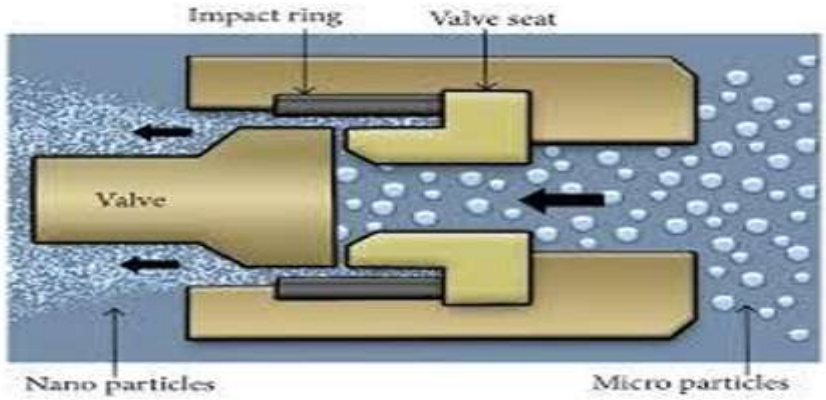


Fig 4. Diagrammatic representation of Homogenization

Drug Powders + Stabilizer Solution

↓

Form Presuspension

↓

Homogenization at Low Pressure (Premilling)

↓

High Pressure Homogenization (10-25 Cycles)

↓

Nanosuspension of Desired Size

↓

Different Methods: - DissoCubes - Nanopure - Nanoedge – Nanojet

Homogenization in Aqueous Media (Dissocubes) [17]:

In 1999, R.H. Muller created this technology with a high-pressure homogenizer of the piston-gap type. This technique involves forcing a drug and surfactant suspension through a high-pressure homogenizer's nanosized aperture valve while it is under pressure.

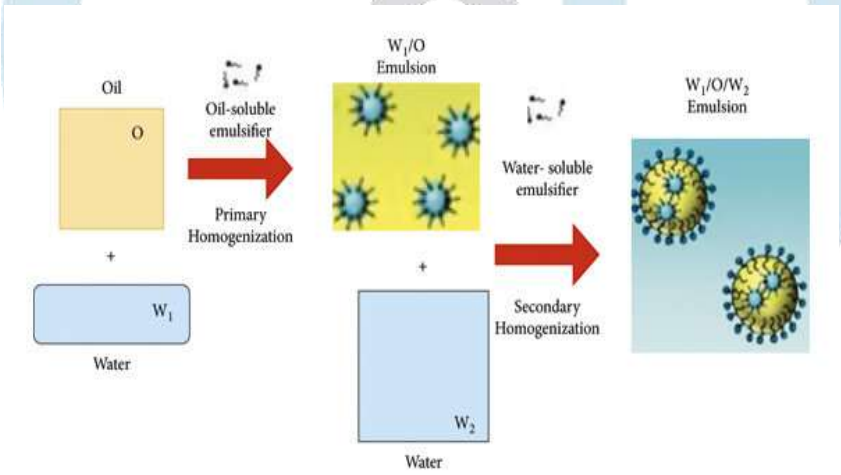


Fig 5. Diagrammatic Representation of Dissocubes

Forced Under Pressure through Nanosized Aperture Valve (25µm)

↓

Reduction in Diameter (3cm → 25µm)

↓

Increase in Dynamic Pressure & Decrease in Static Pressure

↓

Water Boils at Room Temperature

↓

Formation of Gas Bubbles

↓

Cavitation (Bubbles Implode)

↓

Nanoparticle Formation (from Micro-particles)

Homogenization in Nonaqueous Media (Nanopure) [18]:

Suspensions homogenized in water-free media or water mixes, such as PEG 400, PEG 1000, etc., are known as Nanopure. The process is referred to as "deep freeze" homogenization because it may be carried out at room temperature, 0°C, and below the freezing point (-200°C).

Suspension Homogenized in Water-Free Media or Water Mixtures (e.g., PEG 400, PEG 1000)

⇩

Homogenization at Various Temperatures (Room Temperature, 0°C, or Below Freezing Point)

⇩

"Deep Freeze" Homogenization

Microprecipitation (Nanoedge) [19]:

Precipitation and homogenization are used to create nanoedge technology. The fundamental idea is the same as that of homogenization and precipitation. The Nanoedge technology can be used to solve the main drawbacks of the precipitation process, including crystal development and long-term stability. It is possible to produce particles with improved stability and reduced size quickly.

Combination of Precipitation and Homogenization

⇩

Overcomes Disadvantages of Precipitation (e.g., Crystal Growth, Long-term Stability)

⇩

Smaller Particle Size and Better Stability Achieved

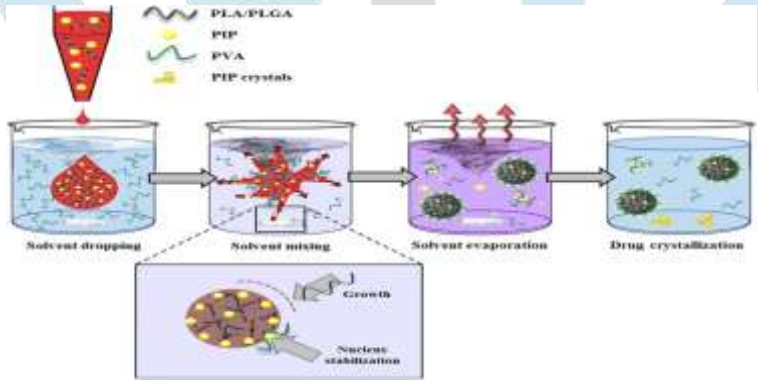


Fig 6. Diagrammatic representation of Nanoedge

Nanojet [20]:

The opposing stream method, which uses a chamber to split a stream of suspension into two or more sections that colloid with one another at high pressure, reduces particle size because of the tremendous shear forces created during the operation.

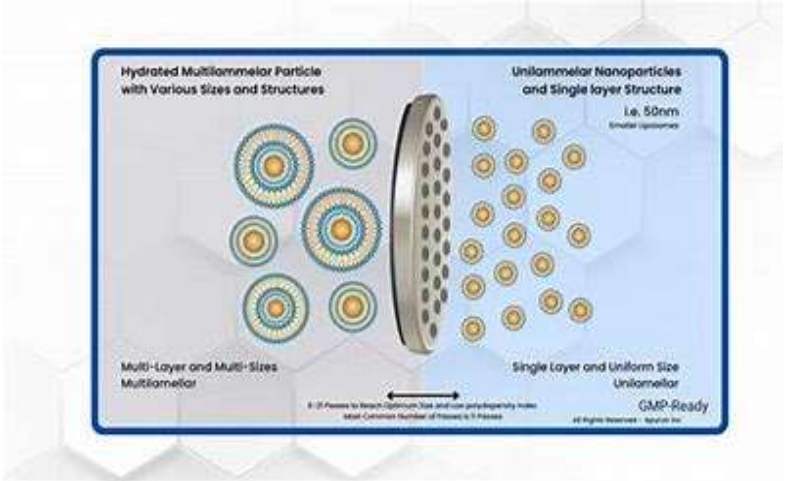


Fig 7. Diagrammatic representation of Nanojet

Suspension Stream Divided into Two or More Parts

⇩

Streams Colloid with Each Other at High Pressure

⇩

High Shear Forces Produced During the Process

⇩

Particle Size is Reduced

Emulsion Solvent Diffusion Method [21]:

This method entails making a drug solution and then emulsifying it in a different liquid that isn't a solvent for the medication. The substance precipitates when the solvent evaporates. A high-speed stirrer can be used to generate high shear forces, which will control crystal development and particle aggregation.

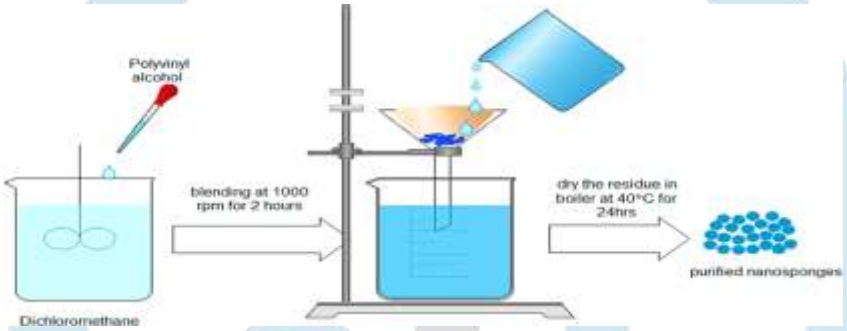


Fig 8. Diagrammatic representation of Emulsion solvent diffusion method

Prepare Solution of Drug

⇩

Emulsify Drug in Nonsolvent Liquid

⇩

Evaporation of Solvent

⇩

Precipitation of Drug

⇩

Control Crystal Growth & Aggregation (Using High Shear Forces from High-Speed Stirrer)

Precipitation [22]:

Precipitation has been used in the past ten years to create submicron particles, particularly for medications that are poorly soluble. Prior to being combined with a miscible antisolvent in the presence of surfactants, the medication is first dissolved in a solvent. When a drug solution is quickly added to the antisolvent, the drug becomes suddenly super-saturated and forms ultrafine crystalline or amorphous drug solids.

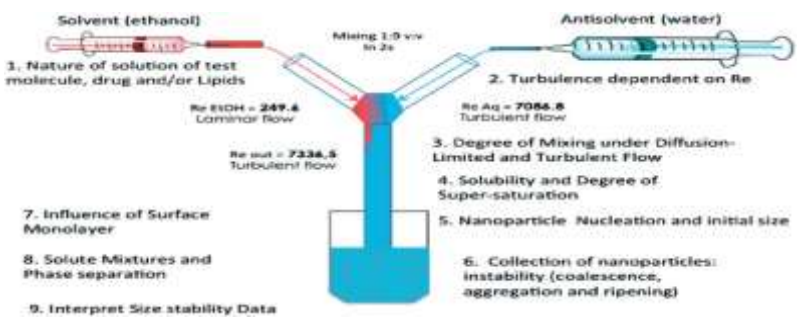


Fig 9. Diagrammatic representation of Precipitation

Dissolve Drug in Solvent

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Mix Drug Solution with Miscible Antisolvent

↓

Add Solution Rapidly to Antisolvent

↓

Sudden Supersaturation of Drug

↓

Formation of Ultrafine Crystalline or Amorphous Drug Solids

Supercritical Fluid Method [23]:

By using the ultra-critical fluid method, solubilization and nanosizing technologies were able to reduce the particle size even more. Noncondensable dense fluids with temperatures and pressures higher than their critical temperature (Tc) and critical pressure (Tp) are known as super critical fluids (SCF). Drug particles can be micronized to a submicron size thanks to this method. The creation of nanoparticulate suspensions with particle sizes ranging from 5 to 2000 nm in diameter is a recent development in the SCF process. The use of this technique in the pharmaceutical sector is limited by the high pressure needed for these procedures and the low solubility of weakly water-soluble medications and surfactants in supercritical CO2.

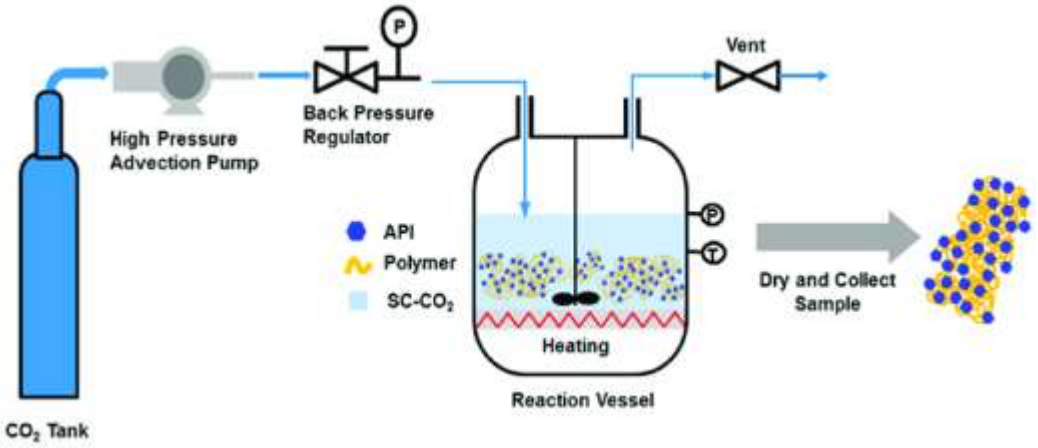

Fig 10. Diagrammatic representation of Supercritical fluid method

Supercritical Fluid (SCF) - Dense Fluid

(Temperature > Critical Temperature, Pressure > Critical Pressure)

↓

SCF Process Used for Micronization of Drug Particles

Achieves Particle Size Reduction to Submicron Level

↓

Creates Nanoparticulate Suspension (5 to 2000 nm)

Melt Emulsification Method [24]:

This process involves dispersing the medication in the stabilizer's aqueous solution, heating it over the drug's melting point, and homogenizing the mixture to create an emulsion. The temperature of the emulsion was kept above the drug's melting point throughout this procedure by wrapping the sample holder in a heating tape that was equipped with a temperature controller. After that, the emulsion was chilled on an ice bath or gradually to room temperature.

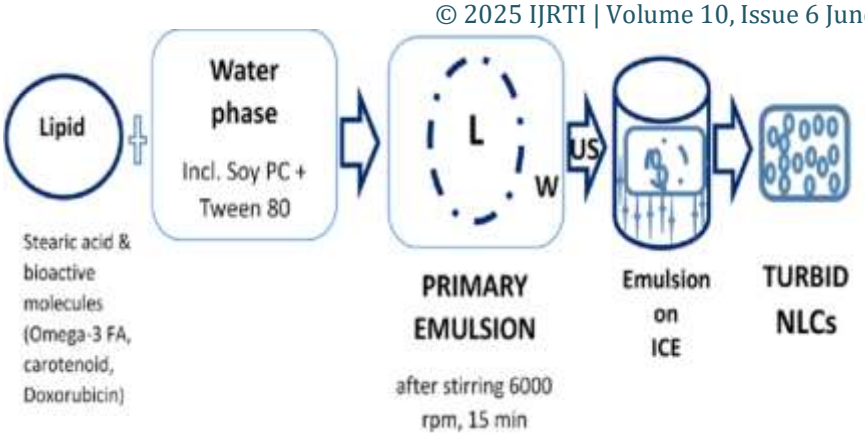

Fig 11. Diagrammatic representation of Melt emulsification method

Disperse Drug in Aqueous Solution of Stabilizer

⇩

Heat Above the Melting Point of the Drug

⇩

Homogenize to Form Emulsion

⇩

Enwrap Sample Holder with Heating Tape & Temperature Controller

⇩

Maintain Temperature Above Melting Point

⇩

Cool Emulsion (Slowly to Room Temp or Ice-Bath)

Lipid Emulsion/Microemulsion Template [25]:

This approach works best with medications that dissolve in partly water miscible solvents or volatile organic solvents.

Dissolve Drug in Suitable Organic Solvent &

Emulsify Drug in Aqueous Phase (Using Surfactants)

⇩

Slowly Evaporate Organic Solvent under Reduced Pressure

Drug Particles Precipitate in Aqueous Phase

⇩

Form Aqueous Suspension of Drug with Desired Particle Size

Dilute Suspension to Obtain Nanosuspensions

⇩

Use Microemulsions as Templates (if applicable)

Drug Loaded into Internal Phase or Microemulsion Saturated

⇩

Dilute Microemulsion to Form Nanosuspension

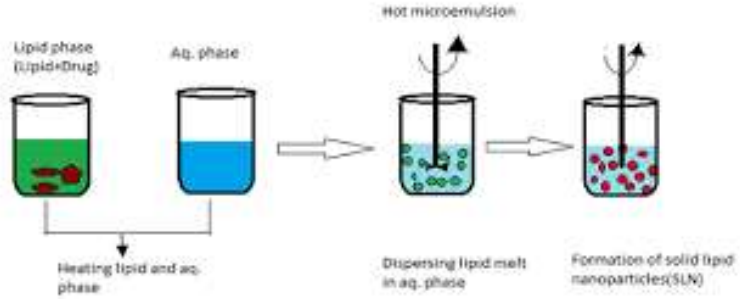

Fig 12. Diagrammatic representation of Lipid emulsion/microemulsion template

Solvent Evaporation [26]:

Polymer solutions are made in volatile solvents and emulsions using the solvent evaporation method. When the solvent for the polymer evaporates and the polymer is let to diffuse into the continuous phase of the emulsion, the emulsion transforms into a suspension of nanoparticles. A single emulsion, such as oil-in-water (o/w), or a double emulsion, such as water-in-oil (w/o)/w, are prepared using the two primary methodologies for emulsion production in conventional procedures. These techniques call for ultrasonication or high-speed homogenization, followed by continuous magnetic stirring or solvent evaporation. After being collected by ultracentrifugation, the solidified nanoparticles were lyophilized after being cleaned of additives like surfactants using distilled water.

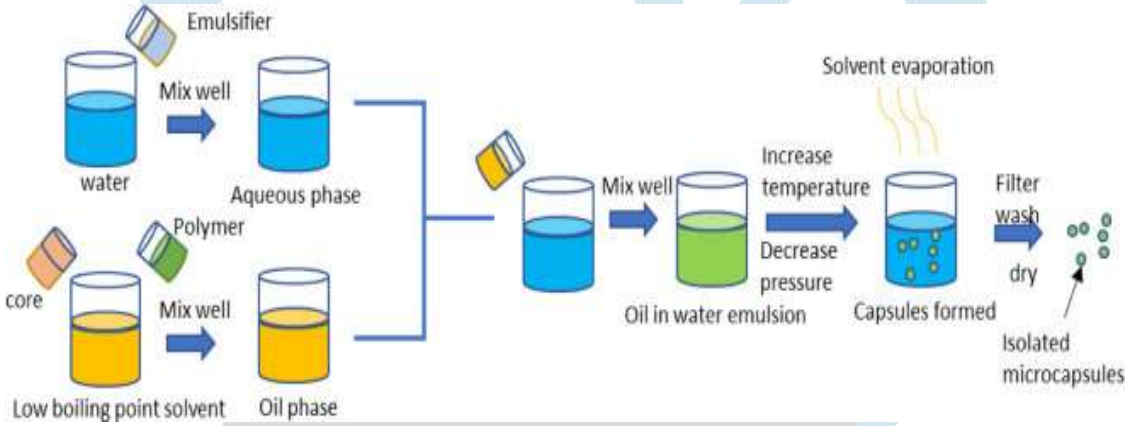

Fig 12. Diagrammatic representation of Solvent Evaporation

Prepare Solution of Polymer in Volatile Solvent (e.g., Ethyl Acetate)

↓

Form Emulsion (Single or Double Emulsion)

↓

Homogenize or Ultrasonicate to Form Emulsion

↓

Evaporate Solvent (Room Temperature or Reduced Pressure)

↓

Solvent Evaporates, Forming Nanoparticle Suspension

↓

Collect Solidified Nanoparticles by Ultracentrifugation
Wash Nanoparticles with Distilled Water

↓

Lyophilize Nanoparticles (Nanosuspension)

V. Techniques Used for Characterization of Nanosuspension:

Particle Size Analysis [27]:

A Coulter Electronics LS 230 was used for laser diffraction in order to analyse the particle size. The mean particle size and width of the particle size distribution, which dictate the physicochemical characteristics including physical stability, dissolution velocity,

saturation solubility, and even biological performance, are the most suitable characterisation parameters for the nanosuspension. Saturated solubility and dissolving velocity vary with particle size. Saturated solubility and dissolution will be higher for smaller particle sizes.

Zeta Potential (Particle Charge) [28]:

The physical stability of nanosuspension is determined by its zeta potential. Long-term stability can be predicted using the zeta potential, an indirect indicator of the diffusion layer's thickness. A minimum zeta potential of ±30 mV is necessary for an electrostatically stabilized nanosuspension in order to achieve satisfactory stability, while a minimum zeta potential of ±20 mV is preferred for a combined electrostatic and steric stabilization.

Crystal Morphology [29]:

The zeta potential of nanosuspension determines its physical stability. The zeta potential, an indirect measure of the thickness of the diffusion layer, can be used to forecast long-term stability. To attain sufficient stability, an electrostatically stabilized nanosuspension requires a minimum zeta potential of ± 30 mV, whereas a combined electrostatic and steric stabilization requires a minimum zeta potential of ±20 mV.

Saturation Solubility and Dissolution Velocity [30]:

The dissolving rate and saturation solubility are both increased by nanosuspension. The dissolving pressure rises as the size decreases. A change in surface tension that results in greater saturation solubility could be the primary cause of an increase in solubility that happens with relatively little particle size reduction.

Fourier-Transform Infra-Red Spectroscopy (FT-IR) [31]:

Fourier-transform infrared (FTIR) spectroscopy identifies and analyses materials by measuring their infrared absorption spectra. It detects specific vibrational modes of molecules, providing information about functional groups, molecular structures, and bonding types. FTIR is widely used in chemistry, biology, and material science for identification, quantification, and monitoring reactions.

Solubility Measurement [32]:

Solubility measurement determines how much solute dissolves in a solvent at specific temperature and pressure. Methods include the Saturation Method, Titration, Gravimetric Analysis, Spectroscopic Methods (UV-Vis, NMR), and the Conductivity Method to assess concentration changes. For ionic compounds, the Solubility Product (Ksp) method is used. Temperature-Dependent Solubility measures solubility at different temperatures. Factors like temperature, pressure, solvent type, particle size, and other substances influence solubility.

Determination of Entrapment Efficiency (EE) [33]:

Entrapment efficiency measures the percentage of a drug successfully encapsulated in a delivery system. It is calculated by comparing the amount of entrapped drug to the total drug used. Methods for determining entrapment efficiency include ultracentrifugation, dialysis, spectrophotometry, and chromatography. High entrapment efficiency indicates a more effective drug delivery system.

$$E.E\ \% = \frac{\text{total drug in formula - free drug}}{\text{total drug in formula}}$$

Scanning Electron Microscopy (SEM) [34]:

Scanning Electron Microscopy (SEM) is a technique that uses focused electrons to scan a sample's surface, producing high-resolution images of its morphology and topography. SEM provides magnifications up to 1,000,000x and offers 3D imaging. It's widely used in material science, biology, nanotechnology, and the semiconductor industry for surface analysis and detailed observation.

In-Vivo Biological Performance [35]:

In-vivo biological performance testing for nanosuspensions evaluates their pharmacokinetics, bio-distribution, toxicity, efficacy, and stability in living organisms. These tests assess drug absorption, distribution, potential side effects, therapeutic effectiveness, and particle stability. The goal is to ensure nanosuspensions enhance bioavailability, target specific tissues, and are safe and effective for clinical use.

Table 6. Commercially Available Nanosuspension-Based Drug Products [36]

Product Name	Company	Indication/ Use
Neoral	Novartis	Organ transplantation, autoimmune diseases
Kineret	Amgen	Rheumatoid arthritis, other autoimmune diseases
Noxafil	Merck	Fungal infections
Afrezza	Mann Kind Corporation	Type 1 and Type 2 diabetes
Opsumit	Actelion (Janssen)	Pulmonary arterial hypertension
Vyzulta	Bausch & Lomb	Glaucoma, ocular hypertension
Braftovi	Novartis	Cancer (melanoma, colorectal cancer)
Alunbrig	Takeda Pharmaceutical	Non-small cell lung cancer (NSCLC)
Zolgensma	Novartis	Spinal Muscular Atrophy (SMA)
Aranesp	Amgen	Anaemia (due to chronic kidney disease or chemotherapy)

Table 7. Issued Patents on Nanosuspension Formulations [37]

Patent Name	Patent Number	Date of Patent	Inventors	Assignee
Method for Preparing Nanosuspensions	US6297113B1	October 2, 2001	Philip R. Frings, Ian W. Berman	Elan Pharma International Ltd.
Nanosuspensions of Poorly Soluble Drugs	US5932327A	August 3, 1999	Friedrich L. Schmidt, Thomas Müller	Degesch GmbH
Nanosuspension Compositions for Drug Delivery	US6939761B2	September 6, 2005	Hans-Dieter Ulrich, Petra Aschenborn	Boehringer Ingelheim Pharma GmbH
Stable Nanosuspension Formulations	US20050024697 A1	February 3, 2005	Greg A. Clark, Robert M. George	Bristol-Myers Squibb Company
Pharmaceutical Composition Containing Nanosuspension	US6344404B1	February 5, 2002	Anand G. Bhalekar, Shyam S. Chintala	Novartis AG
High Concentration Nanosuspension Compositions	US7119067B2	October 10, 2006	Charles R. Stoehr, Matthew K. Lohr	GlaxoSmithKline
Nanosuspension Formulation of Biologically Active Substances	US7560151B2	July 14, 2009	Kester L. T. W. Dongen, Wenke Lee	Merck & Co.

Salient Features of Nanosuspension [38]:

Colloidal dispersions of medications that are not very soluble in water in nanoparticles (1–1000 nm) suspended in a liquid media are known as nanosuspensions. Their main characteristic is that they increase the surface area, which increases dissolution, absorption, and therapeutic efficacy while also enhancing medication solubility and bioavailability. For medications with limited solubility, this is especially advantageous since it enables them to achieve effective concentrations without the need for high dosages. Additionally, regulated or sustained medication release is provided via nanosuspensions, which lowers dosage frequency and increases patient compliance. Their tiny particle size helps avoid crystallization, which ensures stability, and enables targeted distribution, which is helpful in treatments like cancer therapy.

These formulations, which include tablets, capsules, and injectables, can be administered orally or parenterally and can hold many medications for polytherapy. Notwithstanding their benefits, stabilizers and surfactants are necessary for the creation of nanosuspensions due to issues such particle aggregation and instability. Although stability is still a major problem, overall, nanosuspensions have substantial advantages in enhancing drug solubility, bioavailability, and controlled administration.

VI. Conclusion:

In order to increase the solubility and bioavailability of medications that are not very soluble in water, nanosuspension formulations have drawn a lot of interest from the pharmaceutical industry. Through the reduction of medication particles to the nanoscale, these formulations improve absorption and dissolution rates. Stable nanosuspensions are often made using techniques like media milling and high-pressure homogenization, and their stability, shape, and particle size are carefully assessed. Drug delivery using nanosuspensions has showed promise for a number of ailments, including neurological diseases and cancer. But issues like long-term stability, scalability, and production costs need to be resolved. All things considered, nanosuspensions present a viable way to increase the effectiveness of medications that are poorly soluble.

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