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A REVIEW ARTICLE ON NANOSUSPENSION BASES DRUG DELIVERY SYSTEM FOR TOPICAL APPLICATION

Gauri Dilip Rupnawar*1, M.R. Deokar*2

*1Student, Late Laxmibai Phadatare College Of Pharmacy, kalamb, India.

*2Assistant Professor, Late Laxmibai Phadatare College Of Pharmacy, kalamb, India.

ABSTRACT

Nano suspensions have garnered recent attention as a promising strategy for mitigating the bioavailability challenges of Hydrophobic drugs, particularly those characterized by poor solubility in both aqueous and organic environments. Addressing Solubility issues associated with poorly water-soluble drugs has largely resolved the need to enhance drug absorption and bioavailability. As mucosal formulations and topical administration progress in the future, nanosuspension drug delivery, straightforward Formulation techniques, and versatile applications will continue to be subjects of interest. Nanosuspension have undergone extensive Scrutiny in preparation for topical applications, encompassing ocular, pulmonary, and dermal usage. Among the numerous methods Aimed at improving cutaneous application, nanocrystals represent a relatively recent yet profoundly intriguing approach. Despite the Increasing availability of various nanosuspension products, primarily designed for oral administration, only a limited number of studies Have explored skin permeability and drug accumulation in the context of Nano suspensions. Nevertheless, the scant published research Unequivocally underscores the potential of this approach for enhancing cutaneous bioavailability, particularly for active ingredients With low to medium solubility. Nanocrystals exhibit increased skin adhesiveness in addition to heightened saturation solubility and Dissolution rate, thereby augmenting cutaneous distribution. The article provides a comprehensive overview of nanosuspension for Topical application. The methodology employed is robust, with a well-defined experimental design; however, the limited sample size Raises concerns about the generalizability of the findings. While the results demonstrate promising outcomes in terms of enhanced drug Delivery, the discussion falls short of addressing certain limitations. Additionally, the references largely focus on recent studies, but A more diverse inclusion of historical perspectives could offer a more holistic view of the subject.

Keywords: Nanosuspension, Nanotechnology, Topical, Dermal.

I. INTRODUCTION

Over the past two decades, there has been a notable emergence of cutting-edge advancements in the realm of Pharmaceutical research and development. The automation of the drug discovery process, facilitated by technologies Such as high-throughput screening, combinatorial chemistry, and computer-aided drug design, has resulted in the Generation of a substantial array of highly effective drug candidates.1 Regrettably, a considerable proportion of these Promising medications grapple with the challenge of low water solubility, with approximately 40% of drugs in the Developmental pipeline encountering solubility issues.2,3 High-throughput screening techniques have contributed to the Identification of an increasing number of drugs exhibiting limited water solubility.

The constrained solubility of these compounds poses a significant impediment during the initial phases of screening For pharmacological activity, as well as throughout the formulation development and clinical testing processes.4 Preparing one of these substances for preclinical investigations and pharmacological activity assessments is a prerequisite well in advance of their commercialization.5 Consequently, it becomes evident that the adoption of Innovative technical strategies is imperative to augment the bioavailability of drugs characterized by low solubility. The predominant challenge faced by the pharmaceutical industry resides in the development of novel formulation Procedures and drug delivery technologies tailored to effectively address the solubility limitations associated with Therapeutic candidates. These concerns frequently intersect with issues pertaining to low oral bioavailability.6–8 To attain Optimal bioavailability for these medications, it is imperative to ensure their rapid absorption post-oral administration. The Intravenous route represents an additional viable means of administration.9

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Furthermore, various formulation strategies have been devised to address the challenges posed by poorly soluble Medications, often referred to as "particular strategies".10 The effectiveness of these approaches hinges on the specific Chemical characteristics exhibited by molecules, encompassing factors such as their solubility in different organic Solvents and distinctive attributes related to molecular size or configuration, such as molecules designed for incorporation Into cyclodextrin ring structures.2,11 Undoubtedly, a more rational approach would involve the implementation of "universal formulation approach" that can be applied to a wide range of molecules.

Micronization, the process of reducing the size of drug powders within the range of 1 to 10 μm, is a widely employed Technique in pharmaceutical formulations aimed at augmenting the oral bioavailability of drugs. The formulation process Discussed here is commonly employed with the objective of enhancing the oral bioavailability of pharmaceutical Compounds.12,13 The insufficient solubility of frequently used medicines often restricts the effectiveness of micronization. Addressing the unresolved issues related to the bioavailability of drugs categorized under the biopharmaceutical Specification class II, which are characterized by limited solubility, necessitates more than solely increasing the surface Area to enhance dissolution rates.14

Building upon the concept of micronization, nanonization has emerged as a subsequent development. Since the 1990s, the field of nanosystems has advocated for the utilization of nanocrystals, rather than microcrystals, to improve The oral bioavailability of pharmaceuticals. Additionally, nanocrystals that can be dispersed in water, known as Nanosuspension, have found application in intravenous administration and pulmonary delivery of medications.15

Over the past two decades, drug nanocrystal technology has emerged as a prominent advancement in the pharmaceutical industry. One of the key advantages of developing drugs with low solubility lies in the technique it employs, Which results in the creation of "nanosuspensions". These nanosuspensions are essentially the dispersion of drug Nanocrystals within a liquid medium, typically water.16–21 Nanosuspensions primarily comprise drug nanoparticles, Typically ranging in size from 100 to 1000 nm. To maintain stability, these nanoparticles are supported by a small Quantity of surface-active compounds.3,22

The skin serves as a crucial site for the painless and non-invasive administration of therapeutic substances, allowing For the control of their release and circumventing first-pass metabolism. Upon dermal absorption, medications can exert Their effects locally, regionally, or systemically at various target sites.23,24 These considerations have led to the perception That drug delivery through the skin is a compelling yet challenging research area. The principal obstacle is overcoming The skin's remarkable impermeability. The skin is a complex tissue that shields the body from invading pathogens, Withstands chemical and physical assaults, and regulates essential functions such as temperature regulation.25 Its various Anatomically distinct layers consist of the stratum corneum (SC), the accessible epidermis, and the dermis. The primary Physical barrier is situated in the SC, composed of protein-rich dead cells (corneocytes with cornified cytoskeletal Components and corneodesmosomes) and lipid-rich structures (lamellar sheets comprising roughly equimolar amounts of Free fatty acids, cholesterol, and long-chain ceramides).5,26 The nucleated epidermis also contributes to the barrier Through desmosomes, cytoskeletal components, tight junctions, and adherens junctions. Hence, the overall design of the Skin, rather than a specific element, determines its efficacy as a protective barrier. The skin's appendages, including sweat Glands, pilosebaceous units, and hair follicles, emanate from the dermis or subcutaneous fat tissue, introducing significant Discontinuities within this tight framework.27,28

Drugs administered to the skin's surface access the skin through two pathways: the trans-appendageal and transepidermal routes, facilitated by passive diffusion. The skin's appendages provide an alternative route for delivering Medications into the skin, potentially making drug delivery through the stratum corneum (SC) less challenging.29 While this route was previously considered of minimal significance due to its relatively small area, current research on follicular penetration has shed light on the potential importance of hair follicle pathways in the skin penetration Process and the reservoir for topically administered chemicals. Nanosuspensions are colloidal dispersions of nanosized Drug particles in an aqueous vehicle. When applied to dermal surfaces, nanosuspensions offer several potential mechanisms for improved drug delivery:

1. Increased Surface Area: The reduced particle size in nanosuspensions provides a larger surface area for drug contact With the skin, facilitating enhanced absorption.

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2. Improved Penetration: Nanoparticles can penetrate the stratum corneum (the outermost layer of the skin) more Effectively than larger particles. This improved penetration may lead to increased bioavailability of the drug.
3. Targeting Specific Skin Layers: Nanosuspensions can be designed to target specific layers of the skin or even Specific cells, allowing for more controlled and targeted drug delivery.
4. Facilitated Drug Solubility: Nanosuspensions can enhance the solubility of poorly water-soluble drugs, potentially Leading to better absorption through the skin.
5. Interaction with Skin Appendages: Nanoparticles may interact with hair follicles, sweat glands, or other skin Appendages, facilitating localized drug delivery.30,31 As illustrated in Figure 1. Nanosuspensions have found diverse Applications in topical formulations, offering advantages such as improved bioavailability and enhanced drug penetration. While limitations exist, ongoing research and technological advancements continue to address and overcome these Challenges, making nanosuspensions increasingly promising for topical drug delivery. Nanosuspensions in topical drug Delivery aim to address challenges associated with drug solubility, penetration, stability, and controlled release. Various Methods are employed to achieve nanosized particles, each offering specific advantages depending on the characteristics Of the drug and the desired application.

Furthermore, several dermatological conditions, such as acne, alopecia, and various skin tumors, are closely Associated with the sebaceous glands and hair follicles. A molecule can traverse the epidermis through one of two Pathways: transcellularly, by passing through the corneocytes, or intercellularly, by moving through the lipid domains That separate the corneocytes.4,32 Although it is generally accepted that the intercellular route serves as the primary pathway for drug penetration, this route is significantly restricted by the formidable barrier created by the outermost SC Layer.33,34.

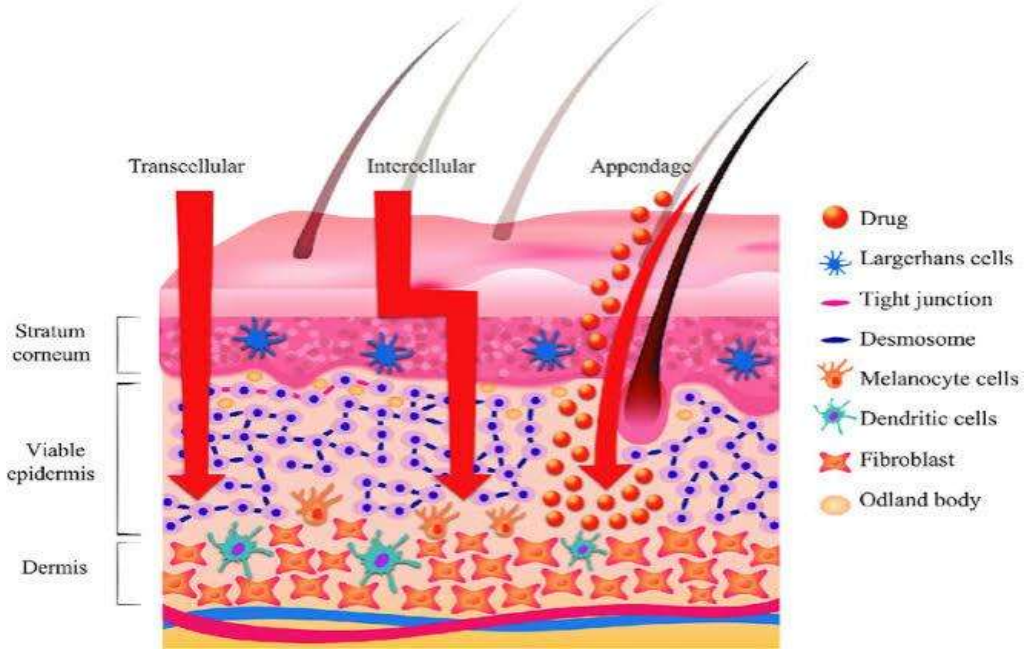

Figure 1: Schematic representation of proposed mechanism of increased dermal penetration of drug nanosuspension

II. METHODS OF PREPARATION OF NANOPARTICLES

1) Media Milling (Nanocrystals)

This method was discovered by Liversidge et al. in 1992 and first patented by "Nanosystems" group, and now This patent transferred to "E lan drug delivery. "Here, the particle size is reduced by the high shear Rate. And the Total process is performed under controlled Temperature. Otherwise, at high shear rate, some temperature Will Build up which will degrade some of the ingredients in The dosage form. This equipment is known as high shear Media milling or Pearl mills (Figure 3).This mill consists of three major columns:

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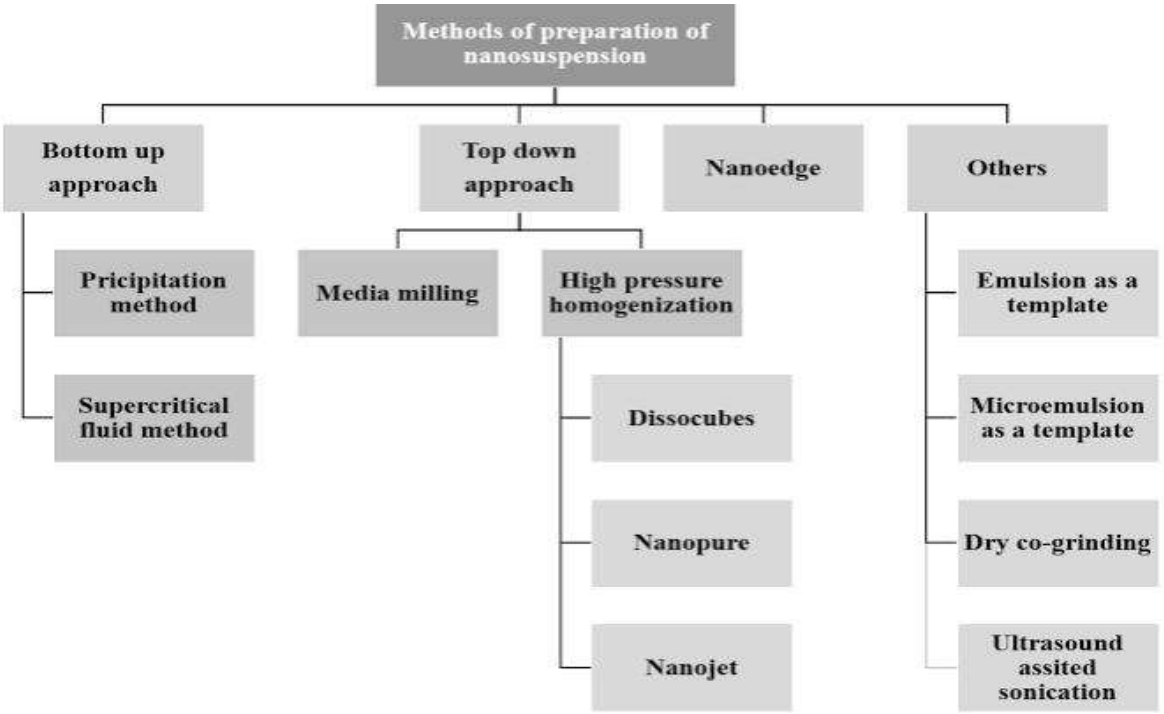
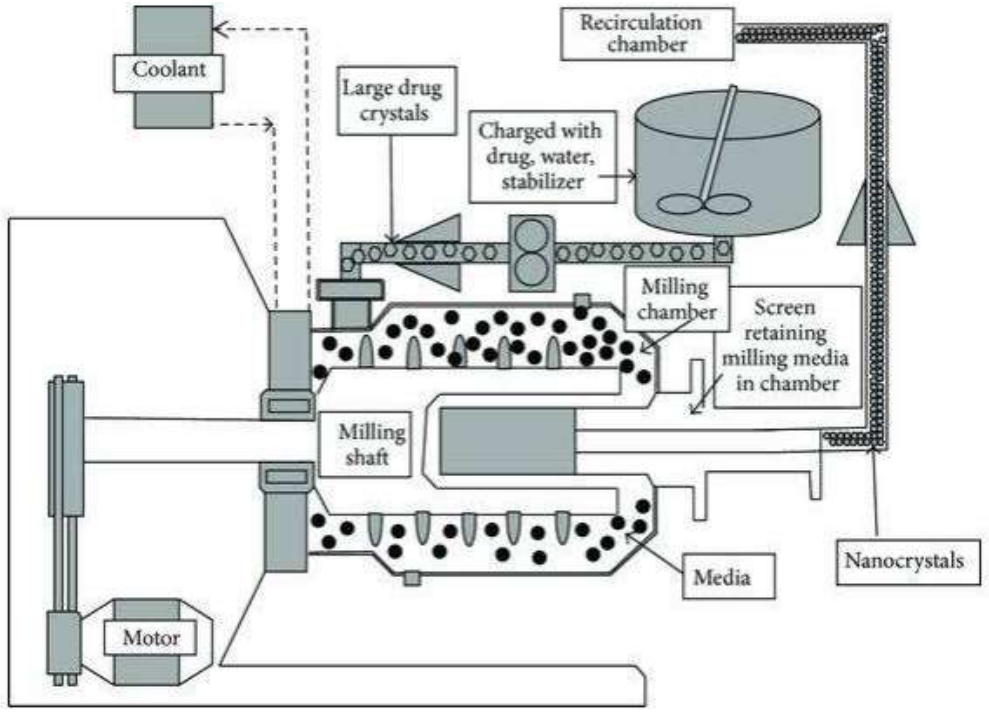
(a) Milling chamber;
(b) Milling shaft
(c) Recirculation chamber.



- **Principle:** Here, the main principle involved in the size Reduction is "impaction". By this shear, the Micro particles Are braked down into nanoparticles. And it is connected to The recirculating chamber so that Continuous production will Be carried out. It is suitable for both batch operation and Continuous operation. By this, we can reduce the particle size Up to <200 nm in 30–60 min only



- **Advantages :**

1. Little batch to batch variations.
2. Ease of handling large quantities of drugs.

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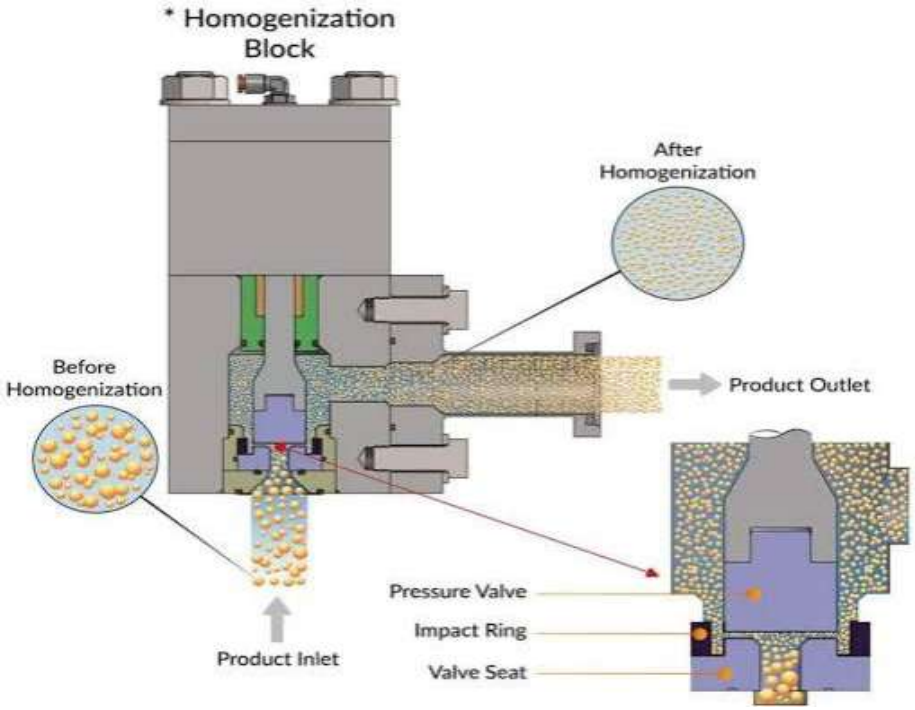
- **Disadvantages:**

1. Generation of residue of milling media.
2. Time consuming process.
3. Prolonged milling may induce the formulation.
4. Scale is not easy due to mill size and weight.

2) High-Pressure Homogenization (Disso cubes).

The process Was developed by R. H. Muller, and first patent was taken By DDS Gmbh. Later, patent was Transferred to Skype Pharmaceuticals. Commonly used homogenizer is the APV Micron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany). And another Type is piston-gap homogenizers. And it is manufactured By Avestin (Avestin Inc., Ottawa, Canada). And another one is Stansted (Stansted Fluid Power Ltd. Stansted, UK).The main principle is high pressure that is 100–1500 bars. By this pressure we can easily convert the micron Size particle, Into Nano size particle. And it initially needs the micron range Particle that is <25 micrometre, so That we have to get the Sample from the jet mill because by using jet mill we can Reduce the particle size up to <25 micrometre (Figure 4).And we can use this equipment for both batch and Continuous operations. Capacity Is also 40 mL to thousand Liters. Here, first, we have to convert the particles into form (after jet milling).

- **Principle:** High shear and high pressure are due to Particle collisions; the particle size will be reduced. Here, We Have to add viscosity enhancers to increase the viscosity of Nanosuspension. In this methods we have to Mainly concentrate on two parameter called pressure and homogenization Cycles (depending on particle Hardness analyzed by particle Size and polydispersibility index) .



- **Advantages:**

1. General applicability to most drugs.
2. For dilute and high concentrated Nanosuspension preparation.
3. Simple technique.
4. Sterile products preparation.
5. Drugs which belongs to BCS class 2 a4.
6. Ease of scale up and little batch to batch variations.

- **Disadvantages:**

1. High number of homogenization cycles.
2. Prerequisites micronized drug particles.
3. Possible contamination of products could occur from metal ions coming off from the walls of homogenizers.

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4. Pre suspension is required.

3) Emulsion as Template:

These emulsions are also Media Milling (Nanocrystals). This method was discovered By Liversidge et al. in 1992 and first patented by "Nanosystems" group, and now this patent transferred To "Élan drug delivery." Here, the particle size is reduced by the high shear rate. And the total process is Performed under controlled temperature. Otherwise, at high shear rate, some temperature will build up Which will degrade some of the ingredients in the dosage form. This equipment is known as high shear

Media milling or pearl mills .This mill consists of three major columns:

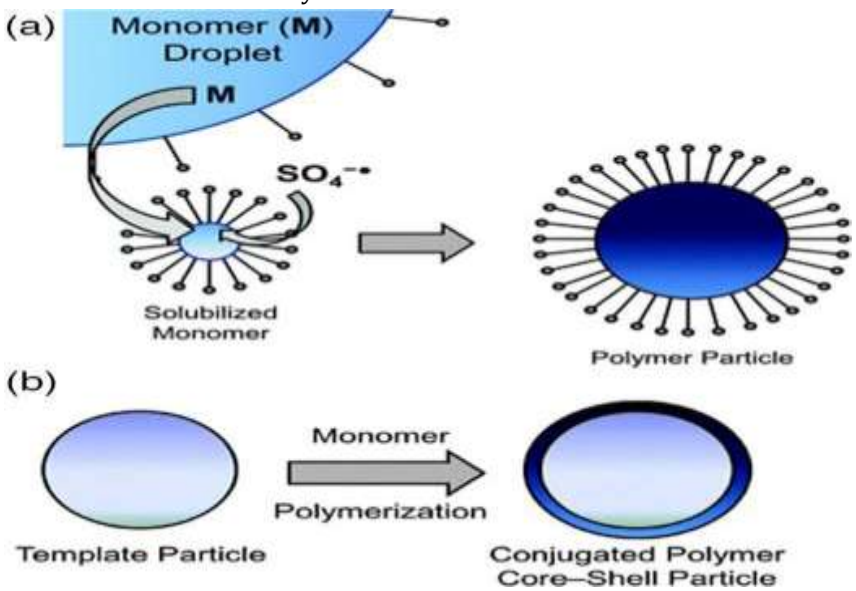
(a) Milling chamber

(b) Milling shaft;

(c) Recirculation chamber.

- **Principle:**

Here, the main principle involved in the size reduction is "impaction". By this shear, the Micro particles are braked down into nanoparticles. And it is connected to the recirculating chamber so that Continuous production will be carried out. It is suitable for both batch operation and continuous operation. By this, we can reduce the particle size up to <200 nm in 30–60 min only



- **Advantages:**

1. High drugs Solublization
2. Long shelf life.
3. Large scale preparation.
4. Low cost.
5. Simple manufacturing method.
6. Some organic solvents like ethyl acetate and ethyl format can used.

- **Disadvantages:**

1. Used organic solvents are much unsuitable as human health cost.
2. Use of high amount of surfactant and stabilize

4) The emulsion as Template: These emulsions are also useful for the preparation of nanosuspensions. The Drugs which were insoluble in volatile organic solvents or partially soluble in water are prepared by this Method. This method is done by two types.

5) Microemulsion as Template: Microemulsion is thermodynamically stable and isotropically clear Dispersion of the two immiscible liquids such as oil and water, and they were stabilized by an interfacial film Of surfactant and co surfactant. In this, firstly, the micro emulsion was prepared the dug solution was mixed To that prepared emulsion and drug loading efficiency was tested.

6) Precipitation method:

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Has been applied for years to prepare submicron particles within the Last decade, especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in the solvent. Then solution is mixed With a miscible ant solvent in the presence of surfactants. Rapid addition of a drug Solution to the antisolvent (usually Water) leads to sudden super saturation of drug in the mixed Solution And generation of ultrafine crystalline or amorphous Drug solids . This process involves two phases: Nuclei Formation and crystal growth. When preparing a Stable suspension with the minimum particle size, a high Nucleation rate but low growth rate is necessary. Both rates Are dependent on temperature: the optimum Temperature for Nucleation might lie below that for crystal growth, which Permits temperature optimization.

- **Advantages :**

1. Simple process.
2. Economical production.
3. Ease of scale up.

- **Disadvantages:**

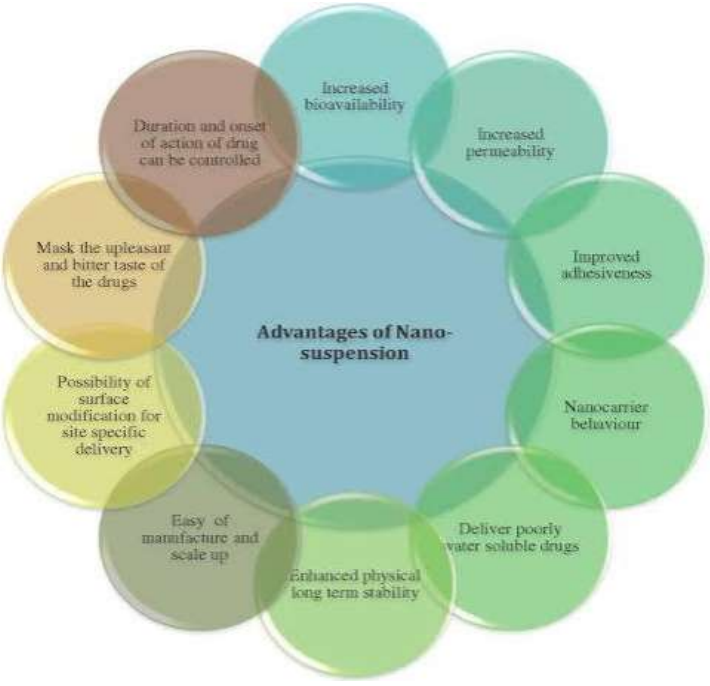
1. Drug has to be soluble at least one solvent and that this solvent is need to be miscible with non solvent.
2. Growing of crystals need to be limited by surfactant addition.

7) Dry Cogrinding.- Recently, nanosuspensions can be Obtained by dry milling techniques. Successful work in Preparing stable nanosuspensions using dry grinding of Poorly soluble drugs with soluble polymers and Copolymers After dispersing in a liquid media has been reported. Colloidal particle formation of many poorly Water soluble Drugs like like griseofulvin, glibenclamide and nifedipine Obtained by grinding with Polyvinylpyrrolidone (PVP) and impact ring Valve seat Valve Nano particles Micro particles [16]. Many soluble polymers And copolymers such as PVP, polyethylene glycol (PEG), Hydroxypropyl Methylcellulose (HPMC), and cyclodextrin Derivatives have been used. Physicochemical properties and Dissolution of poorly water-soluble drugs were improved by Cogrinding because of an improvement in the Surface polarity And transformation from a crystalline to an amorphous drug. Dry cogrinding can be carried out Easily and economically And can be conducted without organic solvents. The cogrindIng technique can reduce Particles to the submicron level and A stable amorphous solid can be obtained.

- **Advantages:**

1) Easy process.
2) No organic solvents
3) Requiring short grinding time generation of residue of milling media.

- **Advantages of Nanosuspension:**



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- **Factors affecting Nanosuspension:**

Stabilizer:

The primary role of a stabilizer is to ensure the thorough wetting of drug particles in order to prevent Ostwald's ripening and the Agglomeration of nanosuspensions, thereby promoting the physical stability of the formulation. This is achieved by serving as A steric or ionic hindrance.7,13,22 The type and quantity of stabilizer employed have a substantial impact on both the physical Stability and in vivo behavior the nanosuspension. Various stabilizers, including lecithins, povidones, cellulosics, polylosorbate, And poloxamers, have been used in nanosuspension development thus far. In the quest for creating a nanosuspension suitable for Parenteral administration and capable of withstanding autoclaving, lecithin has emerged as the preferred stabilizer.16, 47

Organic Solvents

When emulsions or microemulsions are utilized as templates, organic solvents become necessary in the nanosuspension Formulation. In such cases, it is advisable to opt for pharmaceutically acceptable, less hazardous, water-miscible solvents Like methanol, ethanol, chloroform, and isopropanol. Partially water-miscible solvents such as ethyl acetate, ethylFormate, butyl lactate, triacetin, propylene carbonate, and benzyl alcohol are also preferred over conventional hazardous Solvents like dichloromethane in the formulation process.31, 48

Co-Surfactants

When developing nanosuspensions with the aid of microemulsions, the selection of a suitable co-surfactant becomes A critical consideration. This is because the choice of co-surfactants can significantly affect the internal phase uptake and Drug loading within a specific microemulsions composition, ultimately impacting the phase behavior. Although literature References often mention bile salts and dipotassium glycyrrhizinate as potential co-surfactants, other solubilizers, such as Transcutol, glycofurol, ethanol, and isopropanol, can be employed in the formulation of microemulsions without Introducing any undue risks.19,28

Other Additives

Nanosuspensions can incorporate various additives, which encompass buffers, salts, polyols, osmotic agents, and Cryoprotectants. These aforementioned additives fulfill multiple roles aimed at enhancing the stability and efficacy of The nanosuspension.

Buffers assume a crucial role in the maintenance of precise pH levels, while salts contribute to system stability by Providing ionic strength. Polyols, on the other hand, act as stabilizers, preventing particle aggregation. Osmotic agents Are tasked with regulating the solution's osmolality to ensure compatibility with cellular structures. Finally, Cryoprotectants are employed to safeguard the nanosuspension during freezing and thawing procedures.48,49

Post-Production Processing

Post-production processing becomes essential in nanosuspensions when the drug candidate is highly susceptible to Hydrolytic cleavage or chemical degradation. Additionally, processing may be warranted if even the most effective Stabilizer fails to maintain the nanosuspension's stability over an extended period, or if certain routes of administration Pose limitations.6,17,40 Given these considerations, techniques such as lyophilization or spray drying can be employed to generate a dry Powder comprising nanoscale drug particles. When opting for either of these unit operations, a judicious decision must be Made, taking into account the drug's characteristics and cost-effectiveness. In general, spray drying proves to be a more Cost-effective and practical choice compared to lyophilization.24,30

Topical Applications of Nanosuspensions:

Nanosuspensions have been widely studied in preparation of topical applications, either for ocular, pulmonary, or dermal Uses, as summarized below:

Nanosuspension for Ocular Drug Delivery

Topical ocular medication delivery is the most widely adopted method for addressing both external and internal ocular Conditions.53–55 The choice of approach depends on whether drugs are required to be retained at the

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cornea and/or Conjunctiva (eg, for conditions such as conjunctivitis, blepharitis, or keratitis sicca) or whether they need to traverse these Barriers to access the internal eye tissues (eg, for conditions like glaucoma or uveitis), based on the specific target sites For various ocular diseases (Table 1).

Despite the numerous biological processes and physical barriers within the eye, it is well-documented that the ocular Bioavailability of administered drugs is low, at approximately 5%.60–69 This is due to the constant drainage of fluids, the Blink reflex, and the activity of metabolic enzymes, all of which can rapidly degrade drug molecules. Consequently, after Application, the drug remains in the precorneal region for only a brief duration. For drugs intended to reach the inner eye, they must traverse two primary barriers that envelop the eyeball: the cornea and the conjunctiva. The choice of a specific Approach depends on the physicochemical properties of the drug, the desired release profile, and the safety considerations For ocular administration. It is essential to carefully evaluate the trade-offs between improved drug delivery and potential Adverse effects to select the most appropriate strategy for a given therapeutic agent.66,70,71

Preparation Method	Drug	Pharmacological Uses	Type of Study	Results	References
Wet milling	Brinzolamide	Ocular hypertension	In vivo	The nanosuspensions (NSs) exhibited homogeneity and stability. In vitro, they rapidly dissolved and led to a substantial reduction in intraocular pressure values.	[56]
	Loteprednol Etabonate	Anti-inflammatory	In vivo	An elevated concentration of loteprednol etabonate (LE) was noted in ocular tissues and fluids, along with an enhanced pharmacokinetic profile, exemplified by a threefold increase in the maximum concentration (Cmax) in rabbit ocular tissues, when compared to the Lotemax 0.5% suspension.	[57]
	Ciclosporin A	Keratoconjunctivitis	In vivo	The utilization of nanosuspension with a PVA stabilizer resulted in reduced eye irritation in comparison to the commercial product Restasis.	[58]
High pressure homogenization (HPH)	Dexamethasone, Hydrocortisone and prednisolone	Conjunctiva	In vivo	Nanosuspensions (NSs) displayed an enhanced drug action intensity and greater drug absorption extent.	[71]

Topical Pulmonary Applications of Nanosuspensions

Pulmonary medication delivery, both locally and systemically, provides a non-invasive option for lung treatment (Table 2). Inhalers and nebulizers produce aerosols that can be directly administered to the lungs in individuals.72 The Local application of therapeutic drugs to the lungs is the predominant approach for managing various respiratory Disorders. It offers the advantages of greater selectivity and higher local drug concentrations compared to other routes Of administration.17,73

In contrast, the pulmonary route has gained increasing attention as a potential method for systemic drug delivery due To the extensive alveolar surface area, the delicate epithelial barrier, and the significant vascularization conducive to drug Absorption.75–78 Furthermore, drugs administered via the pulmonary route bypass the first-pass metabolism of the Gastrointestinal tract, enter the systemic circulation, and may eliminate barriers associated with patient Compliance.5,19,79 However, the effectiveness of drug delivery through this route depends significantly on factors such As aerosol particle size, particle shape and geometry, surface adhesive properties, and the mechanism and rate of removal From the respiratory system.80–86

One critical feature of the drug formulation is the aerodynamic diameter of the aerosol, which characterizes its Aerodynamic behavior, taking into account size, density, and shape. Optimizing this parameter is essential for effective Pulmonary administration. It's important to note that the success of nanosuspensions in pulmonary delivery depends on Various factors, including the specific drug properties, patient characteristics, and the intended therapeutic outcomes. Each approach has its advantages and limitations, and the choice of strategy should be tailored to the unique requirements Of the drug being delivered.16,87,88

III. CONCLUSION

Nanosuspensions present a promising and economically viable strategy for addressing the challenges associated with Delivering hydrophobic drugs, especially those characterized by limited solubility in both aqueous and organic solvents. These challenges predominantly pertain to enhancing drug absorption and bioavailability in the context of poorly water-soluble drugs. The latest nanosuspension manufacturing process can be established using wet milling, high pressure Homogenization (HPH), smart crystal, and nanoedge methods. Furthermore, the integration of drug nanoparticles into Water-free ointments and creams holds the potential to augment their saturation solubility, thus facilitating improved drug Absorption through the skin. The ongoing advancements in mucosal formulations and topical administration are expected To maintain interest in nanosuspension drug delivery, characterized by simplified formulation techniques and a broad Spectrum of potential applications.

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