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NANOSUSPENSIONS: A NOVEL APPROACH TO ENHANCING DRUG SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

Water solubility problems continue to pose a substantial obstacle in pharmaceutical formulation development, which affects close to 40% of new drug candidates. Nanosuspensions present an effective solution for increasing the water solubility and dissolution rate of poorly water-soluble drugs while improving their bioavailability. Nanosuspensions are pharmaceutical formulations that incorporate drug nanoparticles which remain stable in a liquid carrier medium, such as water through the use of surfactants and stabilizers. Researchers have established multiple preparation methods for nanosuspensions which encompass top-down techniques like high-pressure homogenization and media milling together with bottom-up strategies such as nanoprecipitation. The physical and chemical stability of nanosuspensions relies on multiple factors such as particle size and zeta potential along with the selection of stabilizers and additives. Nanosuspensions exhibit adaptability for various drug delivery methods such as oral administration, intravenous delivery, ocular use, pulmonary application, and dermal treatment. Although nanosuspensions bring many benefits they still face obstacles when it comes to perfecting formulation methods as well as enhancing stability over time and increasing production for commercial usage. The review presents an allencompassing examination of nanosuspension principles and preparation methods while addressing stability and pharmaceutical applications to demonstrate how these systems enhance drug bioavailability and therapeutic outcomes.

KEYWORDS: Nanosuspension, Dosage form, Preparation methods.

INTRODUCTION

Significant technological improvements have been made in pharmaceutical research and development over the past 20 years. Numerous extremely effective drug candidates have been produced as a result of the automation of drug discovery made possible by computer-aided drug design, combinatorial chemistry, and high-throughput screening.^[1] Unfortunately, poor water solubility is a problem for many of these potential medications; in fact, approximately 40% of pharmaceuticals under development have solubility issues. The number of medications with poor water solubility has increased as a result of high-throughput screening techniques. These substances, poor solubility poses a significant obstacle to formulation development, clinical trials, and early pharmacological screening. These drugs need to be ready for preclinical research and pharmacological activity assessments prior to being put on the market.^[2]

Therefore, it is obvious that employing innovative technological procedures is vital to boost the bioavailability of poorly soluble medications. In order to address solubility limits in therapeutic candidates which frequently coexist with low oral bioavailability issues the

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pharmaceutical industry's main task is to create sophisticated formulation techniques and drug delivery systems.^[3] It is crucial to guarantee the quick absorption of these drugs after oral administration in order to achieve the best possible bioavailability. Another practical administration method is the intravenous route.^[4]

Furthermore, a number of formulation techniques, referred to as "particular strategies," have been created to get around the problems posed by poorly soluble medications.^[5] The molecules distinct chemical qualities, such as their solubility in a range of organic solvents and particular traits like molecular size or structure such as those made to fit within cyclodextrin ring systems are essential to the effectiveness of these techniques. Adopting a "universal formulation strategy" that works for a wide range of compounds would be a more realistic approach. A common method in pharmaceutical formulations to increase oral bioavailability is micronization, which shrinks drug powder to a size of 1-10 µm. This formulation technique is frequently used to improve pharmaceutical substances absorption.¹

The efficiency of micronization is sometimes diminished

by the poor solubility of routinely used medications. It takes more than merely increasing surface area to improve dissolving rates to overcome the bioavailability issues of Biopharmaceutical Classification System (BCS) Class II medications, which have poor solubility.^[7] Nanonization has been developed as a further development of the micronization concept. To improve the oral bioavailability of medications, nanosystems have advocated using nanocrystals rather than microcrystals since the 1990s. Additionally, pulmonary drug delivery and intravenous administration have made use of waterdispersible nanocrystals, also referred to as nanosuspensions. Drug nanocrystal technology has emerged as a major innovation in the pharmaceutical sector within the past 20 years. One of the main advantages of creating poorly soluble medications is the process that results in "nanosuspensions." Drug nanocrystals are distributed across a liquid media, typically water, to create these nanosuspensions. Drug nanoparticles, typically ranging in size from 100 to 1000 nm, make up the majority of nanosuspensions. To guarantee their stability, a tiny quantity of surface-active substances is applied.^[8]

Advantages of nanosuspension

- a) Useful for poorly water soluble drugs.
- b) Physically more stable than liposome.
- c) Provide ease of manufacture and scale-up for largescale production.
- d) Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- e) Higher bioavailability especially in ocular and inhalational drug delivery. Bioavailability in following order:
- Solution > Suspension > Capsule > Compressed Tablet.
- f) Enhance the solubility and bioavailability of drugs.
- g) Long term physical stability due to the presence of stabilizres.

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Disadvantages of nanosuspension

- a) Physical stability, sedimentation and compaction causes problems.
- b) It is bulky sufficient care must be taken during handling and transport.
- c) Uniform and accurate dose cannot be achieved unless suspension are in a proper dose.^[9]

Polymers used to prepare nanosuspension

Polymers are frequently employed in nanosuspension formulations to stabilize drug nanoparticles and avoid aggregation. Some of the commonly used polymers are:

- 1. Hydroxypropyl methylcellulose (HPMC): Stabilizes nanoparticles by avoiding particle growth.
- 2. Polyvinylpyrrolidone (PVP): Increases drug solubility and stability.
- 3. Poloxamers (e.g., Poloxamer188, Poloxamer 407): Surfactant and stabilizer.
- 4. Sodium carboxymethyl cellulose (NaCMC): Avoids nanoparticles from aggregation.
- 5. Eudragit polymers: Employed for controlled release of drugs in nanosuspensions.
- 6. Hydroxypropyl cellulose (HPC): Enhances drug wettability and stability.
- 7. Polyethylene glycol (PEG): Aggregation reduction and drug solubility improvement.
- 8. Chitosan: A biopolymer that renders mucoadhesion and controlled release.
- 9. Gelatin: Used in Biodegradable nanosuspensions for drug delivery
- 10. Xanthan gum: Viscosity increase and stabilizes nanoparticles.
- 11. Carbopol (Carbomer): Offers stabilization and controlled release characteristics.
- 12. Polyvinyl alcohol (PVA): Facilitates nanosuspension stability maintenance.
- 13. Alginate: A biopolymer employed in sustained-release formulations.^[10]

Author	Drug name (Uses)	Method of preparation	Polymer used	Results
Tuomela A, et al. ^[11]	Brinzolamide (Ocular hypertension)	Wet milling	HPMC, <u>Poloxamer</u> F127 and F68, Polysorbate 80	The nanosuspensions exhibited homogeneity and stability. <i>In vitro</i> , they rapidly dissolved and led to a substantial reduction in intraocular pressure values.
Qamar Z, et al. ^[12]	Dexamethason, Prednisolone (Conjunctivitis)	High pressure homogenization (HPH)	Eudragit Chitosan	Nanosuspensions displayed an enhanced drug action intensity and greater drug absorption extent.
Fu tt, et al. ^[13]	Fluticasone propionate (Asthma)	Wet milling combined with high pressure homogenization	HPMC, Poloxamer	The local anti-inflammatory impacts of fluticasone are primarily influenced by its dissolution profile. When administered, nanosuspensions considerably extended the local anti inflammatory effectiveness of fluticasone. This was achieved by diminishing Mucociliary clearance, prolonging the pulmonary absorption duration, and enhancing local retention.

Nagpal S, et al. ^[14]	Glabridin (Psoriasis)	Anti-solvent precipitation combined with high pressure homogenization	Hydroxypropy l cellulose (HPC)	Nanosuspension significantly enhanced the drug penetration flux through rat skin, exhibiting no lag phase in both <i>in vitro</i> and <i>in vivo</i> experiments when compared to the coarse suspension and physical mixture. Following three months of storage at room temperature, the Glabridin nanosuspension exhibited no noticeable aggregates and experienced a minimal Glabridin loss of 5.46%.
Vidlarova L, et al. ^[15]	Curcumin (Anti-acne)	Wet milling combined with high Pressure homogenization	HPMC, Poloxamer	The drug concentration within nanosuspensions can vary from 0.02% for poorly soluble medications to 0.2% for economically feasible pharmaceuticals. The low viscosity of dermal formulations facilitates enhanced skin penetration and targeted accumulation within hair follicles.
Oktay AN, et al. ^[16]	Flurbiprofen (Anti inflammatory and analgesic)	High pressure homogenization (HPH)	PVP	The use of drug nanosuspensions resulted in a 5.3-fold increase in drug saturation solubility. The Design of Experiments (DoE) technique proved to be a valuable tool for the preparation of Flurbiprofen Nanosuspensions.
Romero GB, et al. ^[17]	Cyclosporin A (Antioxidant)	Wet milling	Hydroxypropy l cellulose (HPC)	The nanosuspension formulation has achieved enhanced skin penetration while maintaining higher stability.
Pireddu R, et al. ^[18]	Diclofenac sodium (NSAIDs Anti inflammatory)	Wet milling	HPMC, Hydroxypropy l cellulose (HPC)	Application of nanosuspensions presents a dual effect: the drug's saturation Solubility remains constant, leading to drug accumulation, with no significant alteration in its permeation.
Yingchong Chen, et al. ^[19]	Breviscapine (Anti inflammatory, Antioxidant)	High pressure homogenization (HPH)	Xanthan gum	The rheology results demonstrated that BRE-NS was a non-Newtonian fluid with good spreadability & bioadhesion performance. Moreover, the absolute bioavailability estimated for BRE-NS after intranasal administration was 57.12%.
Casula L, et al. ^[20]	Beclomethasone Dipropionate and curcumin (Bronchial asthma)	Wet milling	Poloxamer 188 (P188)	A notable enhancement of approximately 54-fold in the apparent solubility of curcumin over its raw material was observed. Utilization of multicomponent nanosuspension, coupled with optimized dimensional properties and aerodynamic parameters, suggests that the formulated curcumin should be administered with precision and effectiveness to reach deeper lung regions.

Preparation Methods for Nanosuspension

Researchers have created a number of techniques for making nanosuspensions in the pharmaceutical industry. Generally speaking, these strategies can be divided into three groups: top-down methods, bottom-up approaches, and hybrid strategies that incorporate elements of both.^[21] (Fig. 1) In addition to these approaches, various preparation procedures have been successfully established in accordance with advanced investigations, including melt emulsification, emulsification–solvent evaporation, and supercritical fluid technology.^[22]



Fig. 1: Nanosuspension preparation methods (conventional and combination technologies).

Bottom-Up Technology

List and Sucker employed the bottom-up technique, also known as "nanoprecipitation," for the first time in 1987. The bottom-up method depends on precipitating dissolved molecules by adding an insoluble material, which creates nanoparticles. This approach requires the active component to be soluble in at least one solvent, and adequate stabilizers must be used to inhibit particle development following precipitation.^[23] In Fig 2 the characteristics that affect particle size and particle size distribution in NS formulations derived by the bottom-up method are depicted by the fishbone diagram.^[1]



Fig. 2: Schematic representation of the critical parameters of bottom-up technology by the fishbone diagram.

Top-Down Technology

The foundation of top-down technologies is the reduction of big particles to the nanoscale. The low-energy procedure known as media milling and the high-energy process known as high-pressure homogenization are the primary techniques employed.^[24] These techniques are used for items that are already on the market and are more suited for industrial production than bottom-up technologies.^[25]

High-Pressure Homogenization Method

The high-pressure homogenization (HPH) process, which involves applying a suspension to the drug crystals to disperse it after pressing it out of voids or cracks, depends on excessive shear pressures and maybe cavitation. Microfluidization and piston-gap homogenization are the two homogenization concepts that are used, along with the type of homogenizer that is employed in accordance with these principles. Based on the jet-stream principle, microfluidization involves the coarse suspension accelerating and passing through the homogenizing chamber, particularly when high-speed collision, shear, and cavitation forces are present. As a result of these forces, the particle size decreases.^[26] The fishbone diagram in Fig 3 illustrates the parameters that influence particle size and distribution in nanosuspension formulations made using the high-pressure homogenization process.

Active pharmaceutical ingradient (API)



Fig. 3: Schematic representation of the critical parameters of the high-pressure homogenization method by the fishbone diagram.

Wet Media Milling Method

Liversidge et al. discovered the media milling process in 1992.^[27] Although jet mills and colloid mills are also utilized, ball mills are the most popular type of grinding device used to create nanosuspensions. There are three ways to express the ball mill method: pearl milling, wet media milling, and bead milling. This method involves placing the material and stabilizer solution within a chamber and using balls (beads) to grind it mechanically. A milling chamber, milling beads, an appropriate stabilizer, and a dispersion medium typically distilled water are all need for the wet media milling process. This coarse suspension is added to the milling chamber after the active ingredient has been distributed throughout the dispersion medium. Dispersion medium and milling beads typically occupy one-third of the chamber, with the remaining one-third being left empty to allow for the necessary milling space. This chamber is filled with

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beads (zirconium, stainless steel, etc.) that are appropriate for the process, of the appropriate size (various bead diameters), and of the necessary quantity (number of beads in milliliters or weight). The device's rotation speed is then changed, and the milling process starts with the milling time. Wear from the milling chamber or the impact of the beads is the most frequent issue with this technique. It is necessary to use a chamber made of a material such as stainless steel or porcelain and beads made of porcelain, glass, agate, zirconium oxide, or chrome.^[28] In Fig 4, the parameters that affect particle size and distribution in NS formulations obtained by the wet milling method are shown by the fishbone diagram.



Fig. 4: Schematic representation of the critical parameters of the wet milling method by the fishbone diagram.



Fig. 5: Schematic representation of the nanosuspension preparation methods.^[21]

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Combination Technology

In addition to these two technologies (bottom-up and top-down), it is possible to use several techniques together in the preparation of NSs and to obtain NSs with desired properties by making some modifications. These studies also provide an evaluation of the advantages of the above mentioned methods. With combined methods, it is possible to prepare NSs of the obtained formulation using bottom-up technology and then top-down technology or vice versa.^[29]

Factors Affecting the Stability and Efficacy of Nanosuspension

Stabilizers

A stabilizers main function is to guarantee that the drug particles are thoroughly moist in order to stop Ostwald's ripening and the agglomeration of nanosuspensions, which improves the formulation's physical stability. This is accomplished by acting as an ionic or steric barrier.^[30] The kind and amount of stabilizer used significantly affects the nanosuspensions *in vivo* behavior and physical stability. The development of nanosuspensions has made use of a variety of stabilizers, such as lecithins, povidones, cellulosics, polysorbates, and poloxamers. Lecithin has been the go to stabilizer in the search for a nanosuspension that can tolerate autoclaving and be administered parenterally.^[31]

Organic Solvents

Organic solvents are required in the formulation of the nanosuspension when emulsions or microemulsions are used as templates. Methanol, ethanol, chloroform, and isopropanol are examples of water-miscible solvents that are less dangerous and pharmaceutically acceptable in certain situations. Ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, and benzyl alcohol are examples of partially water-miscible solvents that are also preferred in the formulation process over traditional dangerous solvents like dichloromethane.^[32]

Co-Surfactants

The choice of an appropriate co-surfactant becomes crucial when creating nanosuspensions using microemulsion technique. This is due to the fact that the selection of co-surfactants can have a substantial impact on drug loading and internal phase uptake within a particular microemulsion composition, which in turn can affect the phase behavior. While bile salts and dipotassium glycyrrhizinate are frequently mentioned in literature references as possible co-surfactants, additional solubilizers, including transcutol, glycofurol, ethanol, and isopropanol, can be used in the creation of microemulsions without posing any unnecessary dangers.^[33]

Other Additives

A variety of additives, including buffers, salts, polyols, osmotic agents, and cryoprotectants, can be added to nanosuspensions. In order to improve the stability and effectiveness of the nanosuspension, the previously

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mentioned additions serve a variety of purposes. Salts add to system stability by supplying ionic strength, whereas buffers play a critical role in maintaining exact pH levels. Conversely, polyols serve as stabilizers, stopping the aggregation of particles. In order to guarantee compatibility with cellular structures, osmotic agents are responsible for controlling the osmolarity of the solution. Lastly, cryoprotectants are used to protect the nanosuspension while it is being frozen and thawed.^[34-35]

Post Production Processing

When the drug candidate is extremely susceptible to hydrolysis or chemical degradation, post-production preparation is essential for nanosuspensions. It is also required if some administration routes create limitations or if the most effective stabilizer is unable to guarantee long-term stability. In light of these factors, methods like lyophilization or spray drying can be used to create a dry powder that contains medication particles at the nanoscale.^[36]

Parameters Evaluated Reflecting Characteristics of Nanosuspension

Color, Odor, and Taste

Prior to commencing the formulation process of oral dosage forms, it is imperative to account for particular considerations. Particle size, crystal structure, and subsequent alterations in particle dissolution can all potentially lead to flavor discrepancies, particularly in the case of active ingredients. Changes in taste, odor, and color may also serve as indicators of chemical instability.^[37]

Particle Size and Its Distribution

The physiochemical properties of the formulation, including saturation solubility, dissolving rate, and physical stability, are largely determined by the particle size distribution. A number of techniques, such as photon correlation spectroscopy (PCS), laser diffraction (LD), and the Coulter Counter Multisizer, are available to evaluate the particle size distribution. The LD technique has a measuring range of 0.05 to 80 µm, whereas PCS has a range of 3 nm to 3 μ m. It is important to note that the Coulter Counter Multisizer delivers a precise count of individual particles, while the LD method produces a relative size distribution. Larger particles may result in capillary obstructions and embolisms, hence it is crucial that particles used for intravenous (IV) therapy are smaller than 5 µm, since the smallest capillaries have dimensions of 5-6 µm.[38]

Zeta Potential

The zeta potential serves as an indicator of suspension stability. In cases where stability relies solely on electrostatic repulsion, a zeta potential of ± 30 mV is requisite for maintaining stability. However, when a combination of electrostatic and steric stabilization is employed, a zeta potential of ± 20 mV would suffice.^[39]

Crystal Morphology

To clarify the polymorphic changes brought about by high-pressure homogenization in the drug's crystal structure, techniques like X-ray diffraction analysis combined with differential scanning calorimetry or differential thermal analysis can be used. Nanosuspensions may experience changes in their crystalline structure as a result of the high-pressure homogenization process, either taking on different polymorphic patterns or changing into an amorphous form.^[40]

Solubility and Dissolution Rate

By improving both dissolving rate and saturation solubility at the same time, nanosuspensions provide a notable benefit over alternative techniques. These two important factors must be determined using different physiological solutions. Evaluations of saturation solubility and dissolution rate are useful for forecasting the compositions behavior *in vitro*. Particle size decrease causes the rate of dissolution to rise, which raises the dissolution pressure.^[41]

Density

The formulations specific gravity or density is a crucial factor to take into account. A drop in density over time frequently signifies the existence of trapped air in the formulations structure. In order to determine density precisely at a given temperature, it is recommended to use a uniformly well-mixed formulation and precision hydrometers.^[42]

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To prevent "pH drift" and the accumulation of suspended particles on electrode surfaces, the pH of an aqueous formulation should be measured at a controlled temperature only after equilibrium is reached following settling. To ensure pH stability, electrolytes should not be added to the external phase of the formulation.^[8]

Droplet Size

The light scattering method or electron microscopy can be used to evaluate the droplet size distribution of colloidal systems utilized for drug delivery and formulation in the pharmaceutical and other sectors, such as microemulsion vesicles and nanosuspensions. A neon laser with a wavelength of 632 nm is used in a spectrophotometer to measure dynamic light scattering.^[43]

Viscosity

A Brookfield-type rotating viscometer can be used to measure the viscosity of lipid-based formulations with varying compositions at varied shear rates and temperatures. Not all nanosuspensions, meanwhile, are lipid-based. A variety of stabilizers and carriers, including as polymers, surfactants, and other non-lipidbased substances, can be used to create nanosuspensions. One kind of formulation used to produce stable and efficient nanosized therapeutic particles is lipid-based

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nanosuspensions. The samples must be submerged in a thermal bath that keeps the instruments sample chamber at 37° C in order to perform this measurement.^[44]

Physical Stability

The primary role of the stabilizer is to ensure comprehensive coverage of the drug particles, thereby preventing Ostwald ripening and agglomeration in the nanosuspension and ultimately offering a physically stable formulation by serving as either a steric or ionic barrier. Stabilizers such as cellulosics, poloxamers, polysorbates, lecithin, polyoleates, and povidones are frequently utilized in nanosuspensions. When developing parenteral nanosuspensions, lecithin may be a suitable choice.^[29]

Biological Performance

Establishing an in vitro/in vivo correlation and closely monitoring the drugs in vivo performance are essential elements of several drug delivery systems, regardless of the route and mode of administration selected. However, because intravenous formulations circumvent many of the characteristics that make IVIVC significant for oral formulations and enter the systemic circulation directly and quickly, they might not be as readily applicable to IVIVC principles. This is especially true for medications that are injected because organ distribution has a significant impact on how well they work in vivo. The drug's surface characteristics, including its hydrophobicity and interactions with plasma proteins, determine its distribution. Nanosuspensions are used to take these considerations into consideration.^[7] It is well known that the kind and quantity of protein that is absorbed following an intravenous injection of nanoparticles is determined by how well they interact with bloodstream proteins, which has a big impact on where the particles end up in the body. Thus, it is essential to use appropriate techniques to evaluate surface characteristics and protein interactions in order to understand their activity in vivo.^[45]

Applications of Nanosuspensions

Nanosuspensions have been extensively researched for use in topical applications, including ocular, pulmonary, and dermal treatments, as outlined below.

Nanosuspension for Ocular Drug Delivery

Topical ocular medication delivery is the most widely adopted method for addressing both external and internal ocular conditions. The choice of approach depends on whether drugs are required to be retained at the 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.^[46]

Topical Pulmonary Applications of Nanosuspensions

Local and systemic distribution of pulmonary

medications offers a non-invasive alternative for lung care. Aerosols produced by nebulizers and inhalers can be given directly to a person's lungs. The most common method of treating a variety of respiratory conditions is the local administration of therapeutic medications to the lungs. Compared to alternative modes of administration, it provides the benefits of higher local drug concentrations and increased selectivity.^[47]

On the other hand, the pulmonary route has garnered increasing attention as a possible method for systemic drug delivery because of its abundant vascularization, weak epithelial barrier, and vast alveolar surface area, all of which promote drug absorption. Furthermore, pulmonary injection bypasses the gastrointestinal tract's first-pass metabolism, enabling direct systemic circulation entrance and possibly enhancing patient compliance. However, a number of variables, including aerosol particle size, shape, and geometry, surface adhesion characteristics, and the rate and mechanism of respiratory system clearance, are critical to the efficacy of this delivery strategy.^[33,48]

Topical Dermal Applications of Nanosuspensions

Drug nanocrystals are generally regarded as a welltolerated and safe dosage form for a variety of delivery routes. Two important factors make nanocrystalline formulations more effective in oral medication delivery: higher intestinal wall bioadhesion and improved solubility and dissolution rates. As a result, when a medicine in the form of nanocrystals is taken orally, a significant concentration gradient is created between the blood vessels and the gastrointestinal system, which increases absorption and bioavailability. Apart from commercially available goods, a lot of research is still being done on creating novel formulations that use nanosuspension technology improve to oral bioavailability.^[2] Carrier-free nanocrystals of 100% pure drug may be advantageous in ocular delivery because they lessen eye irritation, which in turn lessens tearing and drainage of the implanted dosage.

The use of anti-inflammatory drugs as nanocrystals for ophthalmic applications is presently being investigated by a number of researchers. Drug nanocrystals are also present in the aqueous phase of cosmetic skin preparations like sunscreen and anti-aging therapies, as well as pharmaceutical skin preparations like antiinflammatory lotions or gels.[45] When traditional formulation techniques don't work as well, dermal nanocrystals can be used in cosmetic products. When drug nanocrystals are used, the concentration gradient between the formulation and the skin is improved. saturation solubility "supersaturated" Higher in formulations improves the skin's ability to absorb medications. Positively charged polymers can act as stabilizing agents to improve the stability of drug nanocrystals. The stratum corneum, a layer of the skin, has a negative charge, which further enhances the attraction of drug particles to the skin.^[49]

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Oral Administration

Drugs that are nanosized have higher oral absorption and hence, bioavailability. Drug nanoparticles capacity to stick to the mucosa and their enhanced saturation solubility, which raises the concentration gradient between the blood and the gastrointestinal tract lumen, are the causes of improved bioavailability. Direct use of aqueous nanosuspensions is possible in both liquid and dry dosage forms, including tablets and hard gelatin capsules containing pellets. Nanosuspensions can also be spray-dried to create granulates.^[50]

Parenteral Drug Delivery

Creating items that are delivered intravenously is one of the key uses of nanosuspension technology. IV administration offers a number of benefits, including the ability to administer poorly soluble medications without the need for higher concentrations of harmful cosolvents, enhance the therapeutic effect of medications that are available as traditional oral formulations, and target the medication to macrophages and the pathogenic microorganisms that reside within them. In order to overcome the limited efficacy of traditional solubilization strategies, such as the use of surfactants and cyclodextrins to boost bioavailability, injectable nanosuspensions of the weakly soluble medication tarazepide have been developed.^[51]

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 he established using wet milling, high pressure (HPH). homogenization The application of nanosuspensions in oral, ocular and pulmonary drug delivery systems have been extensively researched during the last few decades. Further, utilization of nanosuspensions in other drug delivery systems such as brain, topical, buccal, nasal and transdermal routes are under extensive investigation. Though nanosuspension has received serious consideration from pharmaceutical scientists, the exact mechanisms of stabilization, solidifications and redispersibility of dried nanosuspension are yet to be explored.

REFERENCE

- Pinar SG, Oktay AN, Karaküçük AE, Çelebi N. Formulation strategies of nanosuspensions for various administration routes. Pharmaceutics, May 17, 2023; 15(5): 1520.
- 2. Aldeeb MM, Wilar G, Suhandi C, Elamin KM, Wathoni N. Nanosuspension-based drug delivery systems for topical applications. International Journal of Nanomedicine, Dec. 31, 2024; 825-44.

- 3. Ahmadi Tehrani A, Omranpoor MM, Vatanara A, Seyedabadi M, Ramezani V. Formation of nanosuspensions in bottom-up approach: theories and optimization. DARU Journal of Pharmaceutical Sciences, Jun. 1, 2019; 27: 451-73.
- Nabavi M, Nazarpour V, Alibak AH, Bagherzadeh A, Alizadeh SM. Smart tracking of the influence of alumina nanoparticles on the thermal coefficient of nanosuspensions: application of LS-SVM methodology. Applied Nanoscience, Jul. 2021; 11(7): 2113-28.
- Ma Y, Cong Z, Gao P, Wang Y. Nanosuspensions technology as a master key for nature products drug delivery and in vivo fate. European Journal of Pharmaceutical Sciences, Jun. 1, 2023; 185: 106425.
- Guner G, Seetharaman N, Elashri S, Mehaj M, Bilgili E. Analysis of heat generation during the production of drug nanosuspensions in a wet stirred media mill. International Journal of Pharmaceutics, Aug. 25, 2022; 624: 122020.
- Liu T, Müller RH, Möschwitzer JP. Production of drug nanosuspensions: effect of drug physical properties on nanosizing efficiency. Drug development and industrial pharmacy, Feb. 1, 2018; 44(2): 233-42.
- Du Y, Yuan X. Coupled hybrid nanoparticles for improved dispersion stability of nanosuspensions: a review. Journal of Nanoparticle Research, Sep. 2020; 22(9): 261.
- Pradeep, Kamal, Kumari B. Versatility of nanosuspension formulation in various drug delivery systems. Advance Pharmaceutical Journal, 2020; 5(2): 36-46.
- Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomaterials research, Jan. 15, 2020; 24(1): 3.
- 11. Tuomela A, Liu P, Puranen J, et al. Brinzolamide nanocrystal formulations for ophthalmic delivery: reduction of elevated intraocular pressure in vivo. Int J Pharm., 2014; 467(1-2): 34-41.
- Qamar Z, Qizilbash FF, Iqubal MK, et al. Nanobased drug delivery system: recent strategies for the treatment of ocular disease and future perspective. Recent Pat Drug Deliv Formul, 2019; 13(4): 246-254.
- 13. Fu TT, Cong ZQ, Zhao Y, et al. Fluticasone propionate nanosuspensions for sustained nebulization delivery: an in vitro and in vivo evaluation. Int J Pharm., 2019; 572: 118839.
- Nagpal S, Kumari P, Saini K, Kakkar V. Pain Management with Topical Aceclofenac Nanosuspension In-Vitro/In-Vivo and Proof of Concept Studies. Curr Drug Ther., 2022; 17(4): 289-304.
- Vidlarova L, Romero GB, Hanus J, Stepanek F, Müller RH. Nanocrystals for dermal penetration enhancement - Effect of concentration and underlying mechanisms using curcumin as model. Eur J Pharm Biopharm, 2016; 104: 216-225.

I

- Oktay AN, Karakucuk A, Ilbasmis-Tamer S, Celebi N. Dermal flurbiprofen nanosuspensions: optimization with design of experiment approach and in vitro evaluation. Eur J Pharm Sci., 2018; 122: 254-263.
- Romero GB, Arntjen A, Keck CM, Muller RH. Amorphous cyclosporin A nanoparticles for enhanced dermal bioavailability. Int J Pharm., 2016; 498(1-2): 217-224.
- Pireddu R, Sinico C, Ennas G, et al. Novel nanosized formulations of two diclofenac acid polymorphs to improve topical bioavailability. Eur J Pharm Sci., 2015; 77: 208-215.
- 19. Yingchong Chen, et al. Nose-to-Brain Delivery by Nanosuspensions-Based in situ Gel for Breviscapine. International Journal of Nanomedicine, 2020; 15: 10435–10451.
- 20. Casula L, Lai F, Pini E, et al. Pulmonary delivery of curcumin and beclomethasone dipropionate in a multicomponent nanosuspension for the treatment of bronchial asthma. Pharmaceutics, 2021; 13(8): 1300.
- 21. Guner G, Yilmaz D, Bilgili E. Kinetic and microhydrodynamic modeling of fenofibrate nanosuspension production in a wet stirred media mill. Pharmaceutics, Jul. 10, 2021; 13(7): 1055.
- 22. Ran Q, Wang M, Kuang W, Ouyang J, Han D, Gao Z, Gong J. Advances of combinative nanocrystal preparation technology for improving the insoluble drug solubility and bioavailability. Crystals, Aug. 25, 2022; 12(9): 1200.
- 23. Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly watersoluble drugs. Asian journal of pharmaceutical sciences, Feb. 1, 2015; 10(1): 13-23.
- Zhang, J.; Xie, Z.; Zhang, N.; Zhong, J. Nanosuspension Drug Delivery System: Preparation, Characterization, Postproduction Processing, Dosage Form, and Application; Elsevier Inc.: Amsterdam, The Netherlands, 2017; 413–443.
- 25. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. European journal of pharmaceutics and biopharmaceutics, Jan. 1, 2006; 62(1): 3-16.
- 26. Oktay AN, Ilbasmis-Tamer S, Karakucuk A, Celebi N. Screening of stabilizing agents to optimize flurbiprofen nanosuspensions using experimental design. Journal of drug delivery science and technology, Jun. 1, 2020; 57: 101690.
- Liversidge, G.G, Cundy, K.C, Bishop, J.F, Czekai, D.A. Surface Modified Drug Nanoparticles. Google Patents US5145684A, 8 September 1992.
- 28. Guner G, Yilmaz D, Yao HF, Clancy DJ, Bilgili E. Predicting the temperature evolution during nanomilling of drug suspensions via a semitheoretical lumped-parameter model. Pharmaceutics, Dec. 18, 2022; 14(12): 2840.
- 29. Hassan AS, Soliman GM. Rutin nanocrystals with enhanced anti-inflammatory activity: Preparation and ex vivo/in vivo evaluation in an inflammatory

rat model. Pharmaceutics, Dec. 6, 2022; 14(12): 2727.

- Guan W, Ma Y, Ding S, Liu Y, Song Z, Liu X, Tang L, Wang Y. The technology for improving stability of nanosuspensions in drug delivery. Journal of Nanoparticle Research, Jan. 2022; 24(1): 14.
- 31. Zuo W, Qu W, Li N, Yu R, Hou Y, Liu Y, Gou G, Yang J. Fabrication of multicomponent amorphous bufadienolides nanosuspension with wet milling improves dissolution and stability. Artificial cells, nanomedicine, and biotechnology, Oct. 3, 2018; 46(7): 1513-22.
- 32. Dos Santos AM, Meneguin AB, Fonseca-Santos B, et al. The role of stabilizers and mechanical processes on physico-chemical and antiinflammatory properties of methotrexate nanosuspensions. Journal of Drug Delivery Science and Technology, Jun. 1, 2020; 57: 101638.
- Khandbahale SV. A review-Nanosuspension technology in drug delivery system. Asian Journal of Pharmaceutical Research, 2019; 9(2): 130-8.
- Stahr PL, Keck CM. Preservation of rutin nanosuspensions without the use of preservatives. Beilstein journal of nanotechnology, Sep. 19, 2019; 10(1): 1902-13.
- 35. Arora D, Khurana B, Rath G, Nanda S, Goyal AK. Recent advances in nanosuspension technology for drug delivery. Current pharmaceutical design, Jun. 1, 2018; 24(21): 2403-15.
- 36. Jin SM, Lee SN, Kim JE, et al. Overcoming chemoimmunotherapy-induced immunosuppression by assemblable and depot forming immune modulating nanosuspension. Advanced Science, Oct. 2021; 8(19): 2102043.
- Guan W, Ma Y, Ding S, et al. The technology for improving stability of nanosuspensions in drug delivery. Journal of Nanoparticle Research, Jan. 2022; 24(1): 14.
- Arora D, Khurana B, Rath G, Nanda S, Goyal AK. Recent advances in nanosuspension technology for drug delivery. Current pharmaceutical design, Jun. 1, 2018; 24(21): 2403-15.
- 39. Ali AM, Warsi MH, Abourehab MA, Ali AA. Preparation and transformation of solid glass solutions of clotrimazole to nanosuspensions with improved physicochemical and antifungal properties. Journal of Pharmaceutical Innovation, Dec. 2022; 17(4): 1420-33.
- Goel S, Sachdeva M, Agarwal V. Nanosuspension technology: recent patents on drug delivery and their characterizations. Recent patents on drug delivery & formulation, Jun. 1, 2019; 13(2): 91-104.
- Galinovskiy AL, Htet KM, Provatorov AS. Ultra-Jet as a Tool for Dispersing Nanosuspensions. Polymer Science, Series D., Apr. 2020; 13: 209-13.
- 42. Chakravorty R. Nanosuspension as an emerging Nanotechnology and Techniques for its Development. Research Journal of Pharmacy and Technology, 2022; 15(1): 489-93.

I

- 43. Chinthaginjala H, Abdul H, Reddy AP, Kodi K, Manchikanti SP, Pasam D. Nanosuspension as Promising and Potential Drug Delivery: A Review. 2020. Int J Life Sci. Pharm Res., 2020; 11(1): P59-66.
- 44. Perrin L, Pajor-Swierzy A, Magdassi S, Kamyshny A, Ortega F, Rubio RG. Evaporation of nanosuspensions on substrates with different hydrophobicity. ACS Applied Materials & Interfaces, Jan. 24, 2018; 10(3): 3082-93.
- 45. Azimullah S, Sudhakar CK, Kumar P, et al. Nanosuspensions as a promising approach to enhance bioavailability of poorly soluble drugs: An update. J. Drug Deliv. Ther., Mar. 20, 2019; 9(2): 574-82.
- Kurhe SA, Katkar K, Bakkam A, Mokal S, Mane A, Jain A. Ocular Nanosuspension a Novel Approach– Review. Res J Pharm Dos Forms Technol, 2023; 15(1): 45–50.
- Casula L, Lai F, Pini E, et al. Pulmonary delivery of curcumin and beclomethasone dipropionate in a multicomponent nanosuspension for the treatment of bronchial asthma. Pharmaceutics, Aug. 20, 2021; 13(8): 1300.
- Bhattacharjee A, Thomas S, Palit P. Nebulizer spray delivery of phytopharmaceutical nanosuspension via oral and nasal route: a challenging approach to fight against COVID-19. In Applications of Multifunctional Nanomaterials. Elsevier, 2023; 437-457.
- 49. Manca ML, Lai F, Pireddu R, et al. Impact of nanosizing on dermal delivery and antioxidant activity of quercetin nanocrystals. Journal of drug delivery science and technology, Feb. 1, 2020; 55: 101482.
- 50. Mathew M, Krishnakumar K, Dineshkumar B, Nair SK. Antibiotics nanosuspension: A review. J Drug Deliv Ther., 2017; 7: 128-31.
- 51. Mishra S. Nanosuspension in advanced drug delivery. Int J Adv Pharm Sci., 2017; 1: 56-65.