Nanosuspension as a technique for dissolution enhancement.

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ABSTRUCT

One of the most serious issues with poorly soluble class II medicines is their limited bioavailability. The situation is considerably more complicated for medications such as cinnarizine, ketoprofen, and dapsone, which are poorly soluble in aqueous environments and are classified as class II in biopharmaceutical classification system. by the biopharmaceutical classification system. Formulation as nanosuspension is an appealing and promising solution to these difficulties. A nanosuspension comprises a homogeneous dispersion of a polymeric material containing a weakly water-soluble medicine. The preparation of nanosuspension is easy and applicable to most medicines that are insoluble in water. A nanosuspension not only overcomes the problem of poor solubility and bioavailability, but it also changes the pharmacokinetics of the drug, improving its safety and efficacy by reduction in particle size leads to an increase in the dissolving rate of the drug, which in turn enhances the rate and extent of its absorption. Consequently, this results in an increased bioavailability of the drug. This review article discusses nanosuspension preparation methods, characterization, evaluation and applications .

Key words: nanosuspension, top-down approach, bottom-up approach, solubility, bioavailability.

التعليق النانوي كطريقة لتعزيز الذوبان

الخلاصة

من أخطر القضايا المتعلقة بالأدوية غير القابلة للذوبان من الفئة الثانية قلة توافرها الأحيائي. والحالة أكثر تعقيداً بكثير بالنسبة لأدوية مثل سينارازين،كيتوبروفين ودابسون، التي تكون ضعيفة الذوبان في البيئات المائية وتصنف في الفئة الثانية في نظام التصنيف الصيدلاني الأحيائي. وتحضير الادوية كمعلق نانوي هي حل جذاب وواعد لهذه الصعوبات. ويشمل المعلق النانوي تشتتا متجانسا للمادة البوليمرية التي تحتوي على دواء ضعيف الذوبان في الماء. وإعداد المعلق النانوي سهل وينطبق على معظم الأدوية غير القابلة للذوبان في الماء. والمعلق النانوي لا يتغلب على مشكلة ضعف قابلية الذوبان والتوافر الأحيائي فحسب، بل إنه يغير أيضاً الصفات الصيدلية للعقاقير، وتحسين سلامته وفعاليته عن طريق خفض حجم الجسيمات يؤدي إلى زيادة في معدل تحلل العقار، الذي يؤدي بدوره إلى زيادة معدل ومدى امتصاصه. ونتيجة لذلك، يؤدي ذلك إلى زيادة التوافر الأحيائي للعقاقير. تناقش هذه المادة الاستعراضية طرق إعداد الإيقاف النانوي، والتوصيف، والتقييم والتطبيقات.

الكلمات الأساسية : تعليق نانوي ، نهج من أعلى لأسفل ، نهج من أسفل إلى أعلى ، قابلية الذوبان ، التوافر البيولوجي.

INTRODUCTION

A submicron colloidal dispersion of drug particles is known as nanosuspension. A pharmaceutical nanosuspension is described as very small, colloid, biphasic, distributed, solid drug particles in an aqueous medium, stabilized by surfactants and polymers, and with a size less than one micrometer. It is manufactured using appropriate techniques for a variety of administration methods, including oral, topical, parenteral, ophthalmic, and pulmonary. In addition to overcoming the issues of poor solubility and bioavailability, nanosuspension modifies the pharmacokinetics of the medication, increasing drug efficacy and safety, increased surface area and saturation solubility result from drug particle reduction to the nanometer range, which speeds up dissolution[1].Nanosuspensions have unique simplicity and some advantages over other approaches [2]. Additionally, most

biological characteristics exhibiting new chemical entities (NCEs) are weakly water soluble, the pharmaceutical companies are continually looking for innovative approaches to achieve appropriate oral bioavailability. The pharmaceutical business's expansion of new products is seriously concerned about the rising number of new chemical entities that are poorly water-soluble but still show therapeutic effects. This is because the lead compounds' poor solubility prevent new molecular entities from being successfully developed as forms of drugs. In recent times, there has been rapid progress in the manufacturing of medications with nanoscale applications, which represents a novel and distinctive medication delivery technology. These medicines possess a size of less than one micrometer. These approaches' key characteristic is their quick dissolving rates, which enhance availability following oral administration.[3].

METHODS OF PREPARATION" OF NANOSUSPENSIONS

Primarily there are 2 main approaches for preparing nanosuspensions. The traditional ways of precipitation Hydrosols" are referred to as "Bottom-up technology" which involves dissolving the medication in a solvent, which is then mixed with a non-solvent to precipitate the crystals. To avoid the development of microparticles, the growth of the drug crystals during the precipitation step must be regulated by the addition of surfactant[4].

The Top-Down Methodologies" include Media milling, high pressure homogenization' in non-aqueous mediums, high pressure homogenization" in an aqueous medium, and a mix of high-pressure homogenization " and precipitation". [5] As illustrated in figure (1). The physicochemical properties of the polymer and the medicine to be loaded determine the most appropriate procedure for nanoparticle formulation.

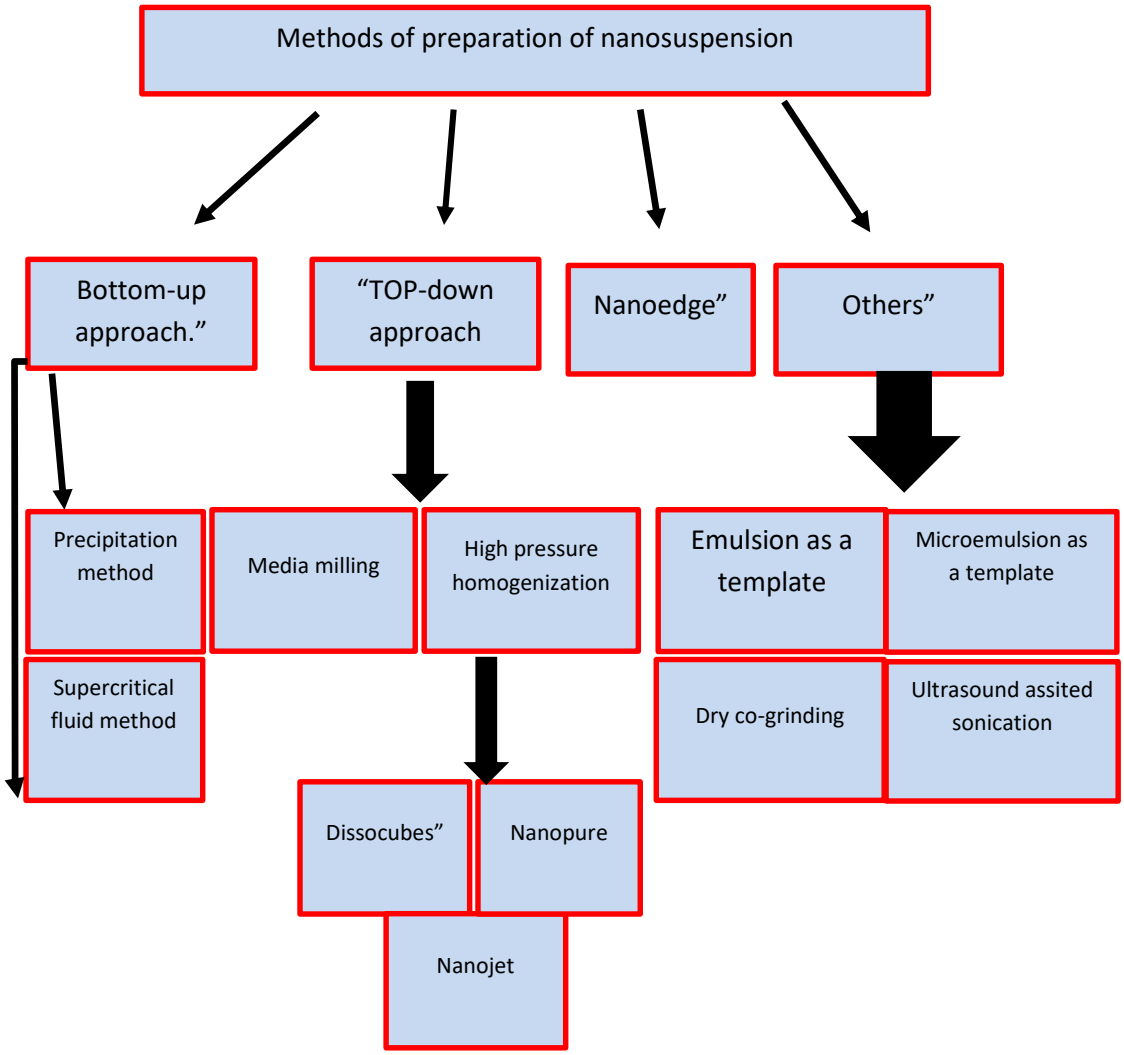

Figure (1): Methods of preparation of nanosuspension [6].

Top-down approach

The high-energy "formation-disintegration" procedure is top-down process. By using procedures like high pressure homogenization and the milling technique, the drug particles are shrunk down to smaller sizes. The top-down approach is more practical than other procedures since it is universal and industrial [7], [8]

Bottom-up approach

Precipitation method is the general name for the bottom-up procedure, which is dependent on the precipitation of medication particles, medication from an extremely concentrated solution. This method includes dissolving the medication in an organic solvent first, and then allowing it to precipitate while a stabilizer was present. Precipitation processes have been successfully employed for a long time to create inorganic nano-ranged size particles, and extensive research on organic drug nanoparticles was conducted utilizing bottom-up techniques two decades ago [9].

- Precipitation method

The procedure of precipitation" with the addition of an anti-solvent is simple and low-cost. The medicine is first mostly dissolved in an organic solvent that is mixed with water, then the proper anti-solvent is applied, as in figure (2).

Mostly water, that contains an appropriate stabilizer, and the drug is then precipitated right away. Drugs can be dissolved using a variety of organic solvents that are water soluble, such as acetone, ethanol, methanol, isopropanol, and N-methyl pyrrolidone. Co-solvents can also be employed, including propylene glycol, polyethylene glycol, and buffer systems (in a certain pH range). The anti-solvent is frequently a stabilizer(s) in aqueous solution. Under certain conditions, miscible organic solvents can be used for neither the solvent" nor the anti-solvent". [10].

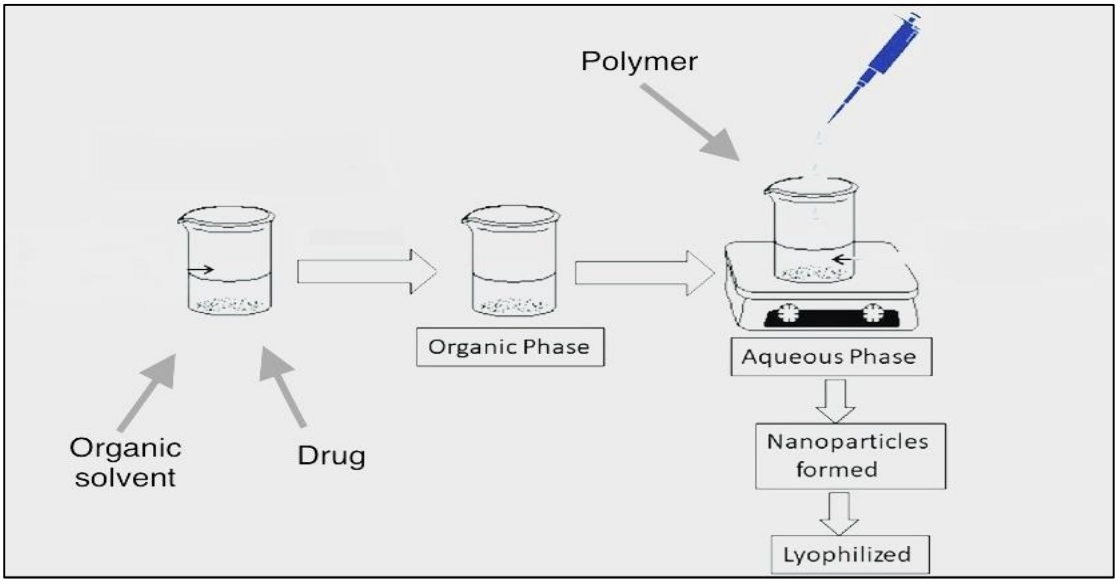

Figure (2): Anti-solvent (precipitation method)[11]

- Evaporation precipitation techniques

Evaporative precipitation into aqueous solution (EPAS) and evaporative precipitation of nanosuspension (EPN) are two different forms of evaporative precipitation procedure [12]. In EPAS, the medication and the organic solvent are combined with heating to create an organic solution that is sprayed into a heated aqueous solution through a fine nozzle. A suspension of colloidal" particles, controlled by a combination of small-molecular weight polymeric" surfactants, was used for precipitating the drug, which was next either spray" dried or ultra-rapidly frozen. The manufacture of products with a high rate of dissolution is a benefit of the EPAS process. The medication powder is quickly added to an anti-solvent after being dissolved in a solvent as part of

the EPN process. A nanosuspension is created by vaporizing the solvent and anti-solvent, which is subsequently dried under vacuum. EPN has the advantages of being affordable, simple to use, and produced on a massive scale [13].

Advantages of nanosuspension"

Following are the primary benefits of nanosuspension" technology:

[14,15]

1. The reduction in particle size leads to various benefits, including an increase in the dissolution rate of the drug, an enhanced rate and extent of drug absorption, and an improved bioavailability. Additionally, it results in a larger area under the plasma concentration-time curve, a shorter onset time, a higher peak drug level, reduced variability, and diminished differences between drug absorption in fed and fasted states. The penetrating power of topical nanosuspension preparations experiences a significant boost as a result of particle size reduction.
2. Nanosuspensions are a viable option for the formulation of chemicals that exhibit poor water solubility but possess solubility in oil. In contrast, nanosuspensions can serve as an alternative to lipidic systems, effectively enabling the formulation of molecules that exhibit insolubility in both aqueous and oily media.
3. Nanoparticles have the ability to attach to the gastrointestinal mucosa, resulting in an extended duration of medication interaction and subsequently improving its absorption.
4. One notable benefit of nanosuspension is in its versatility in terms of administration methods, which encompass oral, parenteral, pulmonary, cutaneous, and ocular routes.
5. The utilization of nanosuspensions containing nanoparticles presents several benefits compared to traditional ocular dosage forms. These advantages include a decrease in the required dosage, sustained drug release over an extended duration, diminished systemic toxicity, improved drug absorption due to prolonged nanoparticle residence on the corneal surface, higher drug concentrations in infected tissue, suitability for poorly water-soluble drugs, and better patient tolerance towards smaller particles. Consequently, nanoparticles exhibit promising potential as drug carriers for ophthalmic applications.
6. The use of excipients in nanosuspensions results in a minimal occurrence of negative effects.
7. Nanosuspensions address the challenges associated with delivering compounds by eliminating the requirement for dissolution and by preserving the medicine in a desired crystalline form that meets the standards of the pharmaceutical industry in terms of size.
8. There is an observed enhancement in resistance to hydrolysis and oxidation, as well as an improvement in physical stability against settling.
9. The reduction of administration quantities is crucial for the intramuscular, subcutaneous, and ocular routes of drug delivery.
10. Nanosuspensions have the potential to offer passive targeting.

FORMULATION MATERIALS OF NANOSUSPENSIONS.

- Stabilizer

The nanosuspensions are thermodynamically unstable and are going to lower their total free energy by aggregating the particle to one another. Stabilizers are essential in the creation of nanosuspensions. To create a stable physical formulation, stabilizers work to thoroughly wet particles of medication and prevent Ostwald's ripening" and aggregation of nanosuspensions" by forming stericoreactive" ionic obstacles. The type and amount of stabilizers utilized greatly affect the in vivo behavior" and physical stability" of nanosuspensions. To produce an ideal nanosuspension, various stabilizers may be required in specific cases.[16]. ethylene oxide (EO), a hydrophilic compound, and propylene oxide (PO), a hydrophobic compound, are combined to create poloxamers, an amphiphilic block copolymer [17]. Poloxamers come in a variety of grades (124, 188, 237, 338, and 407) that were created by utilizing different lengths of polymer blocks. They exhibit a wide range of uses

in drug administration due to their numerous effects, such as solubility change, stability enhancement, and decreased protein binding. They have been widely employed to stabilize nanocrystals, acting as a physical barrier on the surface of the particle to prevent particle interaction and subsequent particle aggregation [18] A synthetic polymer mostly made of linear 1-vinyl-2-pyrrolidinone, polyvinyl pyrrolidone (PVP) is a homopolymer of 1-ethenyl-2-pyrrolidinone. Acetylene and pyrrolidone react to create vinyl pyrrolidone, which is then polymerized to create PVP. Depending on the degree of polymerization, several types of polymers with various molecular weights may be produced. It is categorized by how viscous an aqueous solution is compared to water, expressed as a K value in the range of 10-120. It is being used for a diverse range of purposes, such as a stabilizer in suspensions [19]. Hydroxypropyl methylcellulose (HPMC) it is a cellulose derivative that is water soluble. It is a biocompatible, hydrophilic, and biodegradable polymer. It is a safe, inexpensive, and often utilized in the creation of nanoparticles. Its characteristics include being tasteless and odorless. Its color ranges from white to slightly off-white. Depending on the desired characteristics and the marketable usage, the grade of substitution (DS) of commercial HPMC, with these methoxy and hydroxypropoxy groups will vary. The molecule's unique traits of being cold-water soluble and exhibiting reversible gelation when heated and re-cooled are due to these additional groups [20]. Surfactants that are among the most widely utilized physical stabilizers. They are chemical agents that can alter the surface and interfacial properties [21]. Indirectly, these substances can prevent coagulation or aggregation by preserving particle charge and altering the particle's outermost layer [22], most common surfactant that use in nanosuspension preparation are sodium cholate (SC) and sodium lauryl sulphate (SLS), Polyelectrolytes have been used to alter surface characteristics and the interactions between particles and their surroundings at the nanoparticle-liquid interface [23].

- Organic solvents

When creating nanosuspensions, organic solvents might be required if an emulsion or microemulsion is utilized as a model. Due to the early phases of development of these processes, full details on formulating issues have not yet become accessible. The acceptance of organic solvents in the pharmaceutical field their possible toxic effects, and the ease with which they may be eliminated from the final product all need to be taken into consideration when producing nanosuspensions using emulsions or microemulsions as models.[24].

- Co-surfactants

When utilizing microemulsions to create nanosuspensions, the choice of co-surfactant is crucial. The impact of co-surfactant" on inner phase acquisition and drug load specifically in microemulsion" preparations ought to be investigated since it has a significant impact on phase characteristics. Although the salts of bile and dipotassium glycyrrhizinate are mentioned in the scientific literature as co-surfactants", additional solubilizers, including transcutol, glycofurol, ethanol, and isopropanol, are able to be used in the creation of microemulsions" without risk.[25]

4. *Other additives".*

Design concerns of Nanosuspensions can include additives such as buffers, salts, polyols, osmogents, even cryoprotectants, based on the method through which they are given or the properties of the medication molecule.[26].

CHARACTERIZATION OF NANOSUSPENSIONS"

The most significant characterization methods were covered among these:

1. Mean particle size" and distribution of particle sizes".

Because they have an impact on the saturation solubility, dissolving rate, physical stability, and even in vivo behavior of nanosuspensions [27], the mean particle size and the span of the particle size distribution (polydispersity index, PDI) are two crucial characteristics. Photon correlation spectroscopy (PCS) is a technique that was introduced by B. W. Müller and R. H. Müller in 1984. It has the capability to swiftly and precisely determine the average particle size of nanosuspensions[15]. Furthermore, it is

recommended to do laser diffractometry (LD) analysis alongside PCS analysis for nanosuspensions. This will enable the detection and quantification of any drug microparticles that may have been formed during the production process.

2. Surface charge" zeta potential"

Surface charge characteristics of nanosuspensions surface and their long-term physical stability are both revealed by "zeta potential". A nanosuspension's zeta potential is controlled by both the stabilizer and the medication itself [28]. The Zetasizer Nano program generates a frequency spectrum, which is then used to compute the electrophoretic mobility and subsequently determine the zeta potential. For the detector to accurately measure the dispersed light, it is necessary for the intensity of the observed light to fall within a predetermined range.

3. State of crystallinity and morphology of the particles.

The evaluation of the crystalline state and particle shape collectively contributes to the comprehension of potential polymorphism or morphological alterations that a pharmaceutical substance may suffer while undergoing nanosizing. Furthermore, the preparation of nanosuspensions has the potential to manufacture drug particles in an amorphous state. Therefore, it is imperative to conduct a thorough investigation into the magnitude of amorphous drug nanoparticles that are formed during the manufacturing process of nanosuspensions. X-ray diffraction analysis, along with differential scanning calorimetry, can be employed to ascertain the alterations in the physical state of the drug particles and the magnitude of the amorphous portion. Scanning electron microscopy is the ideal method for obtaining a comprehensive understanding of particle morphology [29].

4. SATURATION SOLUBILITY AND DISSOLUTION VELOCITY

In comparison to other methods, nanosuspensions have the key advantage of being able to improve both dissolution velocity and saturation solubility. The examination of the saturation solubility, rather than the augmentation of saturation solubility, continues to be a significant parameter of interest. It is imperative to evaluate the saturation solubility and dissolution velocity of drug nanosuspensions in various physiological buffers and at different temperatures using the methodologies outlined in the pharmacopoeia. The examination of the rate at which nanosuspensions dissolve demonstrates the potential benefits that can be attained compared to traditional formulations, particularly in the development of sustained release dosage forms utilizing nanoparticulate medicines [30].

Applications of nanosuspensions".

1. Oral drug delivery

Due to its many well-known benefits, the preferred route of medication administration is orally. Antibiotics taken orally, like atovaquone and buparvaquone", very clearly illustrate this issue. When such medications are nanosized, their oral absorption and subsequently, bioavailability can rise dramatically, Danazole", a gonadotrophin inhibitor, has an absolute bioavailability of 82.3% in nanosuspension, compared to 5.2% in traditional dispersion, after oral administration [31].

2. IV drug delivery

One of the main applications of nanosuspension" nanotechnology is the preparation of medications for delivery via vein. The capacity to provide drugs that are poorly soluble" absent a requirement for risky co-solvents", improvement of the curative effectiveness of treatments accessible through conventional oral forms, and drug targeting" of macrophages" are only a few advantages of intravenous (IV) administration. Nanosuspensions" of the very poorly soluble drug tarazepide" have been developed in order to conquer the challenges found when applying conventional solubilization" tactics, such as usage of surfactants", cyclodextrins", etc., in order to enhance bioavailability". [32]. Example on drug prepared as nanosuspension and given via parenteral route is Paclitaxel use as anticancer, it has been found better responses in treating tumors [33]

3. Pulmonary" drug delivery".

Medications with poor pulmonary drainage solubility might adapt well to administration using nanosuspensions". Aqueous" nanosuspensions for inhalation can be nebulized using manual or ultrasonic nebulizers. Aerosol droplets tend to contain a minimum of one medication particle due to their small size, which leads to a more uniform dispersion of the drug across the lungs. Fast

diffusion" and breakdown at the drug's region of action are made possible by the nanoparticulate structure of the molecule. Disodium alpha-ketoglutarate as an example of a medication that is manufactured as a nanosuspension" and administered orally. It is used as a cyanide antidote. [34]

4. Ocular drug delivery

Drugs with poor intraocular solubility may benefit from nanosuspensions. Hydrophobic medications are best delivered via nanosuspensions because of their intrinsic propensity to increase drug saturation solubility. Additionally, the drug's nanoparticulate structure enables it to stay in the body longer and provide sustained drug release, Pilocarpine nitrate nanosuspensions were created in order to increase intraocular drug availability and decrease the frequency of drug administration [35].

5. Targeted drug delivery

Because their surface characteristics and in-vivo behavior may be easily changed by changing either the stabilizer or the milieu, nanosuspensions can be employed for targeted distribution. Building stealth nanosuspensions which is comparable to stealth" liposomes" using multiple coatings on the surface for either passive" or active" attacking of the location of interest will be the next generation of targeted drug delivery systems. Meloxicam nanosuspensions are more bioavailable and safer, which could significantly improve inflammation targeting. [36]

6. Muco-adhesion" of Nanoparticles

Orally administered nanoparticles that are in suspension form diffuse into the liquid medium and quickly meet the mucosal surface. The initial stage prior to particle absorption is the direct interaction of the particles with the intestinal cells through a bio adhesive phase, mucoadhesive nanosuspension containing famotidine nanocrystals could produce added value by allowing a reduction in ulcer index compared to famotidine suspension [37]

CONCLUSION

Nanosuspensions are a unique and economically viable solution to the issues associated with hydrophobic drugs, such as their poor solubility and bioavailability. Media milling and high-pressure homogenization technology have been successfully employed for the mass manufacture of nanosuspensions. Due to prominent characteristics like higher dissolution velocity, greater saturation solubility, enhanced bioadhesivity, versatility in modifying the surface, and ease of postproduction preparation, the usage of nanosuspensions for different ways of administration has risen. Although they still need to be explored, nanosuspensions are used in orally and parenteral routes, where they have a sufficiently proven track record of use. Their topical, nasal, and buccal delivery techniques, however, are still not finished.

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