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Nanosuspension As a Technique for Dissolution Enhancement: Review Article

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Abstract

One of the most serious issues with poorly soluble 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 BCS class II by the biopharmaceutical classification system. Formulation as nanosuspension is an appealing and promising solution to these difficulties. Nanosuspension is made up of a pure, weakly water-soluble medication suspended in a dispersion of matrix material. The preparation of nanosuspension is easy and applicable to all medicines that are insoluble in water. 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. This review article discusses nanosuspension preparation methods, characterization, and applications.

التعليق النانوي كطريقة لتعزيز الذوبان: مقالة مراجعة

الخلاصة

أحد من أخطر المشاكل مع الأدوية ضعيفة الذوبان هو التوافر البيولوجي المحدود. الوضع أكثر تعقيدًا إلى حد كبير بالنسبة للأدوية مثل سيناريزين، كيتوبروفين، ودابسون، وهي ضعيفة الذوبان في البيئات المائية وتصنف على أنها ضمن التصنيف الثاني بواسطة نظام تصنيف المستحضرات الصيدلانية الحيوية.

تعتبر الصيغة كتعليق نانوي حلاً جذابًا وواعدًا لهذه الصعوبات. يتكون التعليق النانوي من دواء نقي قابل للذوبان في الماء ومعلق في مشتت مادة المصفوفة. إن تحضير المعلق النانوي سهل وقابل للتطبيق على جميع الأدوية غير القابلة للذوبان في الماء. لا يتغلب التعليق النانوي على مشكلة ضعف الذوبان والتوافر البيولوجي فحسب، بل يغير أيضًا السلوك الحركي للدواء، مما يحسن سلامته وفعاليته. تناقش هذه المقالة طرق تحضير التعليق النانوي والتوصيف والتطبيقات.

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1. 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, with a size less than one micrometer. It is manufactured using appropriate techniques for a variety of delivery 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(Murdande et al., 2015).Nanosuspensions have unique simplicity and some advantages over other approaches (Ganesh et al., 2013). 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 and permeability prevent new molecular entities from being successfully developed as forms of drugs. As a novel and distinctive medication delivery method, the manufacturing of medicines with nanoscale applications (with a size of fewer than one μm) has advanced quickly lately. These approaches' key characteristics are their quick dissolving rates, which enhance availability following oral administration.(Ghasemian et al., 2016).

2. 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 drug crystals during the precipitation step must be regulated by the addition of surfactant(Salazar et al., 2014). 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". (Agarwal & Bajpai, 2014) as illustrated in Fig.1.

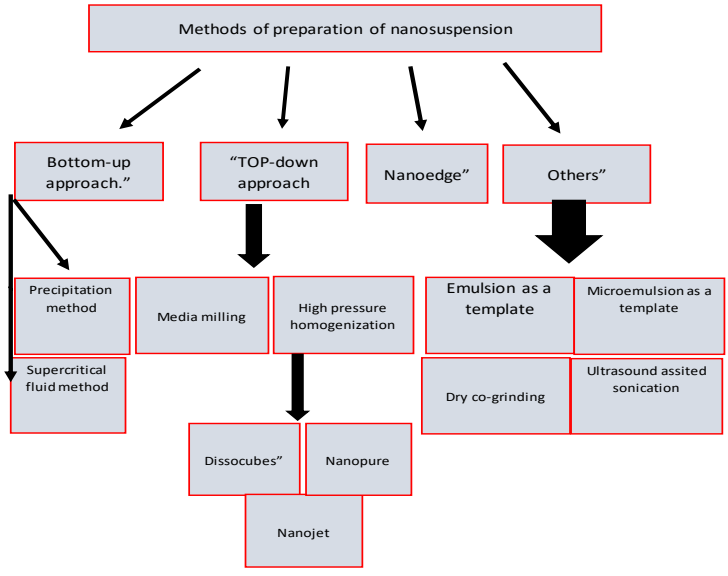

Figure1: Methods of Preparation of Nanosuspension (Thattil Et Al., 2018).

The physicochemical properties of the polymer and the medicine to be loaded determine the most appropriate procedure for nanoparticle formulation.

2.1.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 (I. Khan et al., 2019)[8].

2.2.Bottom-Up Approach

Precipitation method is the general name for the bottom-up procedure, which relies on pieces of drugs precipitating, 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 (Subramani & Ahmed, 2017).

2.3.Precipitation Method

The procedure of precipitation" with the addition of a fluid anti-solvent is simple, 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 Fig.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". (Chun et al., 2013).

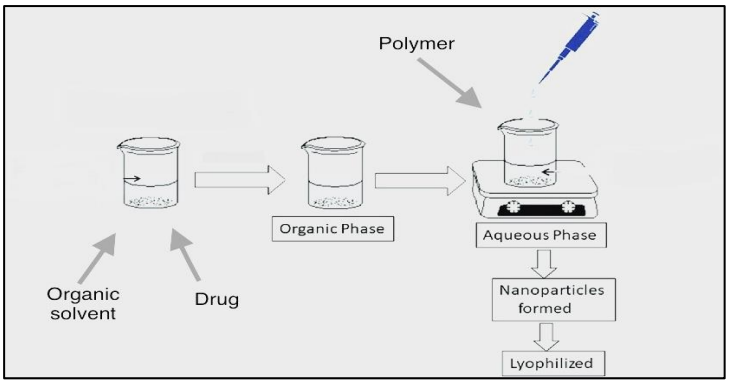

Figure2: Anti-Solvent (Precipitation Method)(Dahiya Et Al., 2018)

3. Evaporation -Precipitation Techniques

Evaporative precipitation into aqueous solution (EPAS) and evaporative precipitation of nanosuspension (EPN) are two different forms of evaporative precipitation procedure (Kaur & Kaur, 2014). 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 (Chang et al., 2015).

3.1. Advantages of Nanosuspension

Following are the primary benefits of nanosuspension" technology:

• Facilitates manufacturing and produced on a massive scale. • thanks to the incorporation of stabilizers", it offers ongoing physical stability".

• When nanosuspensions" are administered by mouth, the onset time, fed-fasted" ratio, which is also and bioavailability "are all accelerated.

• Fast local targeting" and degradation are made possible by IV delivery.

• The two intriguing unique qualities of nanosuspensions" are a rise in saturating solubility" and, thus a consequence, a boost in the drug's dissolution rates.

• Increase in adhesiveness, leading to increased bioavailability(Azimullah et al., 2019)

3.2.Formulation Materials of Nanosuspensions

1. 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 steric reactive" ionic obstacles. The type and number 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.(D. Patel et al., 2020). Surfactants that are among the most widely utilized physical stabilizers". They are chemical agents that can alter the surface and interfacial properties (Wu et al., 2020). Indirectly, these substances can prevent coagulation or aggregation by preserving particle charge and altering the particle's outermost layer (Xie et al., 2020). Polyelectrolytes have been used to alter surface characteristics and the interactions between particles and their surroundings at the nanoparticle-liquid interface (Tan et al., 2017).

2. 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" sector, 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.(Shah et al., 2015).

3. 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", can be used in the creation of microemulsions" without risk.(SPawar et al., 2017)

4. Other Additives

Design concerns of Nanosuspensions" can include additives" such as buffers", salt", polyols", osmogents", even cryoprotectants", based on the method through which they are given or the properties of the medication molecule.(Tejas et al., 2022).

5. 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 (Goel et al., 2019), the mean particle size and the span of the particle size distribution (polydispersity index, PDI) are two crucial characteristics.

2. Surface charge" zeta potential"

Surface charge characteristics of nanosuspensions "surface and their long-term physical stability are both revealed by "zeta potential". Nanosuspension's zeta potential is controlled by both the stabilizer and the medication itself (Zhang et al., 2017).

3. State of crystallinity" and morphology " of the particles.

Another method for determining how much an amorphous" drug's physical" state changes is the X-Ray Diffraction "XRD". Through the use of the technique of differential scanning calorimetry "DSC", the structure of crystals is identified. Given that drug nanoparticles are converted into amorphous" form when nanosuspensions" are manufactured, it is imperative to estimate the amount of amorphous" drug generated during the development of nanosuspensions".(Zainab E. Jassim & Nawal A. Rajab, 2018).

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 saturation solubility of the medication in various physiological buffers and at various temperatures should be evaluated(Aukunuru et al., 2014).

6. Applications for 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 (Jayaprakash et al., 2016).

2. Parenteral 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". (Mane et al., 2014). 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 (Komal R. Nikam et al., 2013)

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" is an example of a medication that is manufactured as a nanosuspension" and administered orally. It is used as a cyanide" antidote. (Wang et al., 2017)

4. Ocular drug delivery

Drugs with poor intravascular 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 (M. S. Khan et al., 2013).

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. (Li et al., 2018)

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 (D. J. Patel & Patel, 2013)

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 bio adhesivity", 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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