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Narrative Review on Nano Suspensions

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Syed Mustafa, Swarupa Arvapalli, * B.Soumya, D.Swamy.

Joginpally B.R Pharmacy College, Moinabad, Hyderabad.

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ABSTRACT

One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by the biopharmaceutical classification system. A formulation as nanosuspension is an attractive and promising alternative to solve these problems. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in the dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. Preparation of Nanosuspension is simple and applicable to all drugs which are aqueous insoluble. Nanosuspensions are prepared by using the wet mill, a high-pressure homogenizer, emulsion-solvent evaporation, melt emulsification method, and supercritical fluid techniques. Nanosuspension can be prepared by using stabilizers, organic solvents and other additives such as buffers, salts, polyols, cosmogenic and cryoprotectant. Nanosuspensions can be delivered by oral, parenteral, pulmonary and ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels.

INTRODUCTION

More than 40% of the new chemical entities being generated through drug discovery programmes are poorly water-soluble or lipophilic compounds. Formulating a poorly water-soluble drug has always been a challenging problem confronted by the pharmaceutical scientist. The formulation of nanosized particles can be implemented to all drug compounds belonging to the biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition into a gastrointestinal barrier. Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility. There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization solubilization using co-solvents, salt form, surfactant dispersions, precipitation technique, and oily solution. Other techniques are like liposomes, emulsions, microemulsion, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they lack in universal applicability to all drugs. These techniques are not applicable to those drugs which are not soluble in aqueous and organic solvents. Nanotechnology can be used to solve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 µm in size. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., oral or intravenous [IV] administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators.

Advantages of Nanosuspension[(5),(7),(10)]

1. Increase in the dissolution velocity and saturation solubility of the drug
2. Improved biological performance
3. Ease of manufacture and scale-up
4. Long-term physical stability

5. Versatility

6. Increase in the oral absorption

7. Improved dose proportionality.

8. Its general applicability to most drugs & simplicity

9. It can be applied for poorly water-soluble drugs.

10. It can be given by any route.

11. Reduced tissue irritation in case of subcutaneous/intramuscular administration.

12. Rapid dissolution & tissue targeting can be achieved by IV route of administration.

13. Oral administration of nanosuspension provides rapid onset, reduced fed/fasted ratio & improved bioavailability.

14. The absorption form absorption window can be increased, due to a reduction in the particle size.

15. Higher bioavailability & more consistent dosing in case of ocular administration & inhalation delivery.

16. The drug with higher log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs.

17. Improvement in biological performance due to high dissolution rate & saturation solubility of the drugs.

18. Nanosuspensions can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.

19. Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.

20. The possibility of surface-modification of nanosuspension for site-specific delivery.

21. The possibility of large-scale production, the prerequisite for the introduction of the delivery system to the market.

Disadvantages for Nanosuspension Drug delivery system [4],[3]

1. Physical stability, sedimentation & compaction can cause problems.
2. It is bulky sufficient care must be taken during handling & transport.
3. Improper dose.
4. Uniform & accurate dose cannot be achieved.

PREPARATION OF NANOSUSPENSIONS [2],[3],[7]

The most common approach that has been used for preparing nanosuspensions is micronization by colloid or jet milling.[10] This method increases the dissolution rate of the drug but does not have any impact on the saturation solubility and thus cannot improve the bioavailability of drugs.

The principal techniques used in recent years for preparing nanosuspensions can be classified into four basic methods:

1. wet milling,
2. homogenization,
3. emulsification–solvent evaporation
4. supercritical fluid method.

1. Wet Milling

Nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft, and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particle size reduction.

2. Homogenization[3]

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. Dissocubes® was developed by Muller et al. in 1999. In this case, the suspension of the drug is made to pass through a small orifice that results in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the center and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean particle size, and the required homogeneity.

3. Emulsification–solvent evaporation[7]

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

Hydrosol method[6]

This is similar to the emulsification– solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent.[8] Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

4. Supercritical fluid method[8],[11]

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are a rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and precipitation with the compressed anti-solvent process (PCA). The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. Young et al. prepared cyclosporine nanoparticles in the size range of 400-700 nm using this process.

CHARACTERIZATION OF NANOSUSPENSIONS [20],[12]

Nanosuspensions are characterized for appearance, color, odor, assay, related impurities, particle size, zeta potential, crystalline morphology status, dissolution studies and *in-vivo* studies. Among these, the essential characterization techniques were discussed.

1. Mean particle size and particle size distribution:

The mean particle size and particle size distribution affect the saturation solubility, dissolution rate, physical stability, even *in-vivo* behavior of nanosuspensions. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and Coulter counter multisizer PCS can also be used for identifying the width of particle size distribution (polydispersity index, PI). A PI value of 0.1-0.25 indicates a fairly narrow size distribution if PI value greater than 0.5 indicates a very broad distribution The colter-counter gives the absolute no of particles per volume unit for the different size classes and it is more efficient and appropriate technique than LD for quantifying the contamination of nanosuspensions by microparticulate drugs.

2. Surface charge (Zeta potential): [13]

Zeta potential gives information about the surface charge properties and the long-term physical stability of the nanosuspension. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is essential, whereas, in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient.

3. Crystalline state and particle morphology: [13],[15]

The evaluation of the crystalline state and particle morphology helps in understanding the polymorphic or morphological changes that a drug may undergo when subjects to nanosizing. Because of High-pressure homogenization nanosuspension can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms. The changes in the solid state of the drug particles and the extent of the amorphous fraction can be determined by X-ray diffraction analysis and supplemented by DSC. To get an actual idea of particle morphology, scanning electron microscopy is preferred.

4. Saturation solubility and Dissolution velocity:

The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflect the advantages that can be achieved over conventional formulations, especially when designing the sustained release dosage forms based on nanoparticulate drugs. The evaluation of saturation solubility and dissolution velocity helps in determining the *in-vitro* behavior of the formulation.

STABILITY OF NANOSUSPENSIONS [14],[16]

The high surface energy of nanosized particles induces agglomeration of the drug crystals. The main function of the stabilizer is to wet the drug particles thoroughly to prevent Ostwald ripening and agglomeration of the nanosuspension and form a physically stable formulation by providing a steric or an ionic barrier. Typical examples of stabilizers used in nanosuspensions are cellulosic, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral nanosuspensions.

SELECTION CRITERIA OF DRUG FOR NANOSUSPENSIONS [3],[9]

Nanosuspension can be prepared for the API that is having either of the following characteristics: water-insoluble but which are soluble in oil (high log P) or API are insoluble in both water and oils, drugs with a reduced tendency of the crystal to dissolve, regardless of the solvent, API with a very large dose.

FORMULATION OF NANOSUSPENSIONS [17]

Nanosuspension formulation requires basically stabilizer or surfactant, proper solvent system and other ingredients for its preparation.

a. Stabilizers:

The stabilizer is used to wet the surface of solute or drug particle and retard the Ostwald ripening and agglomeration in order to provide high physical stability which further reflects its performance. Commonly used stabilizers are polysorbate (Tween/Span series), povidone, cellulosic, poloxamers and lecithin.

b. Organic solvent:

Organic solvents are generally used in the preparation of nanosuspension if emulsion or microemulsions technologies are used as a template for this. These solvents are very hazardous in physiologic and environmental means but still, some less hazardous water-miscible solvents like methanol, ethanol, chloroform, isopropanol, and partially water-miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol are used over the dichloromethane (reported as a conventional hazardous solvent).

c. Other additives: Uses of other ingredients depends on either the route of administration or physicochemical properties of candidate drug but some additives such as buffers, salts, polyols, cosmogenic and cryoprotectant are normally used.

Drug targeting[18],[19]

Nanosuspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the *in-vivo* behavior. The drug will be uptaken by the mononuclear phagocytic system to allow regional-specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly.[30] Kayser formulated a nanosuspension of Aphidicolin to improve drug targeting against leishmania-infected macrophages. He stated that the drug in the conventional form had an effective concentration (EC 50) of 0.16 mcg/ml whereas the nanosuspension formulation had an enhanced activity with an EC (50) of 0.003 mcg/ml. Scholer et al. showed an improved drug targeting to the brain in the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii using a nanosuspension formulation of Atovaquone.

Mucoadhesion of the nanoparticles Nanoparticles

Orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as “bioadhesion.” From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps

to improve bioavailability but also improves targeting of the parasites persisting in the GIT, e.g., Cryptosporidium parvum. Buparvaquone nanosuspensions have been reported to demonstrate an advantage in TRC- alpha-deficient mice infected with Cryptosporidium parvum oocytes. The bioadhesion can also be improved by including a mucoadhesive polymer in the formulation.

PROPERTIES OF NANOSUSPENSIONS[8],[10]

Physical Long-term stability: Another special feature of nanosuspensions is the absence of Ostwald ripening, which is suggestive of their long-term physical stability. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. Ostwald ripening is caused by the differences in dissolution pressure/saturation solubility between small and large particles. **The internal structure of Nanosuspensions:** The high-energy input during the disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenization, particles are transformed from crystalline state to amorphous state. The change in the state depends upon the hardness of drug, number of homogenization cycles chemical nature of drug and power density applied by a homogenizer.

Adhesiveness;[5] There is a distinct increase in adhesiveness of ultra-fine powders compared to coarse powders. This adhesiveness of small drug nanoparticles can be exploited for improved oral delivery of poorly soluble drugs. Crystalline state and morphology: A potential change in the crystalline structure of nanosuspensions saying increasing the amorphous fraction in the particle even creating completely amorphous particles is a characteristic of consideration. The application of high pressures during the production of nanosuspensions was found to promote the amorphous state. Increase in Saturation Solubility and Dissolution Velocity of drug: Dissolution of the drug is increased due to an increase in the surface area of the drug particles from micrometers to the nanometer size. According to the Noyes-Whitney equation, dissolution velocity increases due to the increase in the surface area from micron size to particles of nanometer size.

$$dx/dt = [(D \times A)/ h] [Cs-X/V]$$

Where D is diffusion coefficient, A is the surface area of the particle, dx/dt is the dissolution velocity, V is the volume of dissolution medium and, h is the thickness of the diffusion layer and X is the concentration in surrounding liquid.

APPLICATION OF NANOSUSPENSIONS: [4],[9]

Nanosuspensions have various pharmaceutical and biopharmaceutical application a few of them highlighted here are:

1. Formulating the drug as nanosuspensions increases the saturable concentration, dissolution rate as well as bioavailability of the drug.

2. Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. For delivery of such drugs, approaches such as suspensions and ointments have been recommended.

3. These nanosuspensions are having application in different routes of administrations like oral, parenteral, topical, ophthalmic, mucoadhesive, pulmonary and targeted drug delivery.

Parenteral administration; From the formulation perspective, nanosuspensions meet almost all the requirements of an ideal drug delivery system for the parenteral route. Since the drug particles are directly nanosized, it becomes easy to process almost all drugs for parenteral administration. Hence, nanosuspensions enable significant improvement in the parenterally tolerable dose of the drug, leading to a reduction in the cost of the therapy and also improved therapeutic performance. The maximum tolerable dose of paclitaxel nanosuspension was found to be three times higher than the currently marketed Taxol, which uses Cremophore EL and ethanol to solubilize the drug. Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitoneal to intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 μm to avoid capillary blockage. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs.

Oral administration;[3],[7] The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution rate limited

absorption is believed to possess slow and/or highly variable oral bioavailability. Danazol is poorly bioavailable gonadotropin inhibitor, showed a drastic improvement in bioavailability when administered as a nanosuspension as compared to the commercial danazol macro suspension Danocrine. Danazol nanosuspension led to an absolute bioavailability of 82.3%, whereas the marketed danazol suspension Danocrine was 5.2% bioavailable.11 Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood as well as the increased dissolution velocity of the drug. Aqueous nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as a tablet or hard gelatin capsule with pellets. The aqueous nanosuspension can be used directly in the granulation process or as a wetting agent for preparing the extrusion mass pellets. A similar process has been reported for incorporating solid lipid nanoparticles into pellets. Granulates can also be produced by spray drying of nanosuspensions.

Ophthalmic drug delivery;[5] Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water-soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids controls its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. One example of a nanosuspension intended for ophthalmic controlled delivery was developed as a polymeric nanosuspension of ibuprofen. This nanosuspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone, and dexamethasone enhance rate, drug absorption and increase the duration of drug action. To achieve sustained release of the drug for a stipulated time period, nanosuspensions can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts. The bioerodible, as well as water-soluble/permeable polymers possessing ocular tolerability61, could be used to sustain the release of the medication. The polymeric nanosuspension of flurbiprofen has been successfully formulated using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100.62-64 The polymeric nanosuspensions have been characterized for

drug loading, particle size, zeta potential, *in-vitro* drug release, ocular tolerability, and *in-vivo* biological performance. The designed polymeric nanosuspensions revealed superior *in-vivo* performance over the existing marketed formulations and could sustain drug release for 24 h. The scope of this strategy could be extended by using various polymers with ocular tolerability.

Pulmonary drug delivery; Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Currently, such drugs are delivered as suspension aerosols or as dry powders by means of dry powder inhalers. The drugs used in suspension aerosols and dry powder inhalers are often jet milled and have particle sizes of microns. Because of the microparticulate nature and wide particle size distribution of the drug moiety present in suspension aerosols and dry powder inhalers, some disadvantages are encountered: like limited diffusion and dissolution of the drug at the site of action, rapid clearance of the drug from the lungs, less residence time for the drugs, unwanted deposition of the drug particles in pharynx and mouth. The ability of nanosuspensions to offer quick onset of action initially and then controlled the release of the active moiety is highly beneficial and is required by most pulmonary diseases. Moreover, as nanosuspensions generally contain a very low fraction of microparticulate drug, they prevent unwanted deposition of particles in the mouth and pharynx, leading to decreased local and systemic side-effects of the drug. Additionally, because of the nanoparticulate nature and uniform size distribution of nanosuspensions, it is very likely that in each aerosol droplet at least one drug nanoparticle is contained, leading to even distribution of the drug in the lungs as compared to the microparticulate form of the drug. In conventional suspension aerosols, many droplets are drug-free and others are highly loaded with the drug, leading to uneven delivery and distribution of the drug in the lungs. Nanosuspensions could be used in all available types of the nebulizer. However, the extent of influence exerted by the nebulizer type as well as the nebulization process on the particle size of nanosuspensions should be ascertained.

Bioavailability enhancement;[19].[23] A drug with poor solubility or permeability in the gastrointestinal tract leads to poor oral bioavailability. Nanosuspension resolves the problem of poor bioavailability by solving the problem of poor solubility, and poor permeability across the membranes. Dissolution rate was increased in diclofenac when formulated in nanosuspension form from 25 to 50 % in SGF and H2O while in case of SIF it was increased from 10 to 35 % as compared to coarse suspension. Bioavailability of poorly soluble, a COX-

2 inhibitor, celecoxib was improved using a nanosuspension formulation. The crystalline nanosized celecoxib alone or in tablet showed a dramatic increase of dissolution rate and extent compared to a micronized tablet. Spironolactone and budesonide are poorly soluble drugs. The higher flux contributes to the higher bioavailability of nanosuspension formulation. The bioavailability of poorly soluble fenofibrate following oral administration was increased compared to the suspensions of micronized fenofibrate.

Target drug delivery;[22] Nanosuspensions can also be used for targeted delivery as their surface properties and *in-vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale-up and commercial product enable the development of commercially viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of buparvaquone. Similarly, conditions such as pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes. Nanosuspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the *in-vivo* behavior. The drug will be uptaken by the mononuclear phagocytic system to allow regional-specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly.

Topical formulations;[20] Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.

Mucoadhesion of the nanoparticles;[21] Nanosuspension containing drug nanoparticles orally diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT. The oral

route, since it avoids the pain and discomfort associated with injections and is more attractive from a marketing and patient compliance perspective. Finally, the major advantage of nanocrystals for oral delivery is generally regarded as being on the increased specific surface area of the particles. However, EMEND® and TriglideTM are formulated as nanosuspension to reduce fed/fasted variability.

CONCLUSION

Nanosuspensions of pure drug offer a method to formulate poorly soluble drug and enhance the bioavailability of several drugs. It has many formulations and therapeutic advantages, Nanosuspensions are a distinctive and commercially feasible approach to solve the problems of a hydrophobic drug such as poor solubility and poor bioavailability. For large-scale production of nanosuspensions, media milling and high-pressure homogenization technology have been successfully used. The characteristics, like the improvement of dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of postproduction processing, have widened the applications of nanosuspensions for various routes of administration. Applications of nanosuspensions in parenteral, oral routes, pulmonary and ocular delivery have been realized. However, their applications in buccal, nasal and topical delivery are still awaiting exploration.

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