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Nanosuspension as Oral Drug Delivery System: A Review

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S.Nischitha*, J Adlin Jino Nesalin, E.Gopinath, Vineet Chandy

Department of Pharmaceutics, T. John College of Pharmacy, Bangalore, Karnataka, India.

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ABSTRACT

Several potential novel drugs are essentially insoluble in aqueous solvents and even have limited solubility in organic solvents. Since its first development in 1994, the nanosuspension drug delivery system (DDS) has gained popularity as a formulation method for pharmaceuticals that are not easily soluble in water. Nanosuspensions provide a number of excellent advantages for medication distribution since they nanoscale the poorly soluble medicines. Oral administration is the most popular method of drug delivery among all the available delivery methods because of its benefits include pain reduction, simplicity of swallowing, adaptability to a range of drug candidates, low cost of manufacture, high safety, and strong patient compliance. Pharmaceutical nanosuspension DDS products are primarily used for oral delivery in the current market. The purpose of this review is to thoroughly summarize the developments in poorly soluble drug nanosuspension DDS dosage forms for oral delivery.

INTRODUCTION

When compared to other methods for systemic drug delivery via various pharmaceutical products of varied dose forms, oral drug delivery has been recognized for decades and is the most popular route of administration. In the discovery and development of new drug candidates and formulations, oral drug delivery is the most favored method of administration. It is regarded as the most adaptable, practical, patient-acceptable, simple, accurate, cost-effective manufacturing methods, generally improve product shelf life, and frequently used route of drug delivery for systemic action. Regardless of its physical form, such as solid, semisolid, or liquid dosage form, it involves varying contents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal physiology[1].

The oral delivery method also includes the controlled release of the active ingredient most recently. These ideas, particularly controlled release, typically entail regulating medication breakdown in order to improve safety and lengthen the duration of effect. Moreover, the regulated release results in more consistent absorption, enhancing bioavailability and delivery effectiveness[2]. A challenging issue for the pharmaceutical business is the formulation of poorly water-soluble pharmaceuticals, which make up more than 40% of the new drugs created through drug discovery programes[3].Nanotechnology has been introduced to address issues associated with traditional approaches to improving solubility and bioavailability. For drugs that are insoluble in both water and organic solvents, nanosuspension technology has been used[4].

A submicron colloidal dispersion of drug particles or pharmaceutical active substance is known as nanosuspension. The term "pharmaceutical nanosuspension" refers to extremely small, colloid, biphasic, solid, and dispersed drug particles in an aqueous vehicle, stabilized by surfactants and polymers, and prepared by suitable methods for drug delivery applications through various routes of administration, such as oral, parenteral, topical, ocular, and pulmonary routes and the size of the particles must be less than 1 μm[5].The average particle size ranges between 200 and 600 nm, with the particle size distribution of solid particles in nanosuspension typically being less than one micron[6].

In contrast to nanoparticles, nanosuspensions. Solid lipid nanoparticles are lipidic carriers of pharmaceuticals, whereas nanoparticles are often polymeric colloidal carriers of drugs. With the use of without any matrix material, stabilized by polymers and surfactants, and prepared by suitable nanosuspension technology, the drug is kept in the necessary crystalline state with

smaller particles, which increases the pace at which it dissolves and, as a result, improves bioavailability. An increase in surface area and, subsequently, dissolution velocity are associated to an increase in the dissolving rate of micronized particles (particle size <10µm). Due to the vapour pressure effect, nanosized particles can speed up solutions and improve saturation solubility[6].

A nanosuspension not only corrects the poor solubility and bioavailability issue, but it also modifies the drug's pharmacokinetics, enhancing its safety and effectiveness. For drugs that are insoluble in both water and organic media, nanosuspensions are used as a formulation strategy in place of lipidic systems[7].The nanosuspension formulation method is best suited for compounds with a high log P value, a high melting point, and a high dose and the use of nanotechnology to create nanosuspensions of poorly water-soluble drugs provides an opportunity to address the nature of the deficiency associated with this class of drugs. The nanosuspension has shown to improve the absorption and bioavailability, potentially lowering the dose of conventional oral dosage forms[8].

Nanosuspensions are exceptional due to their simplicity and the benefits they provide over other approaches. They have demonstrated their ability to address the issues related to the administration of pharmaceuticals that are poorly water-soluble and poorly water- and lipid-soluble. This review focuses on the many features of nanosuspensions and how they might work as an effective medication delivery method[9].(schematic representation of method of preparation, dosage form, components and applications of nanosuspension in drug delivery systems is represented in figure 1).

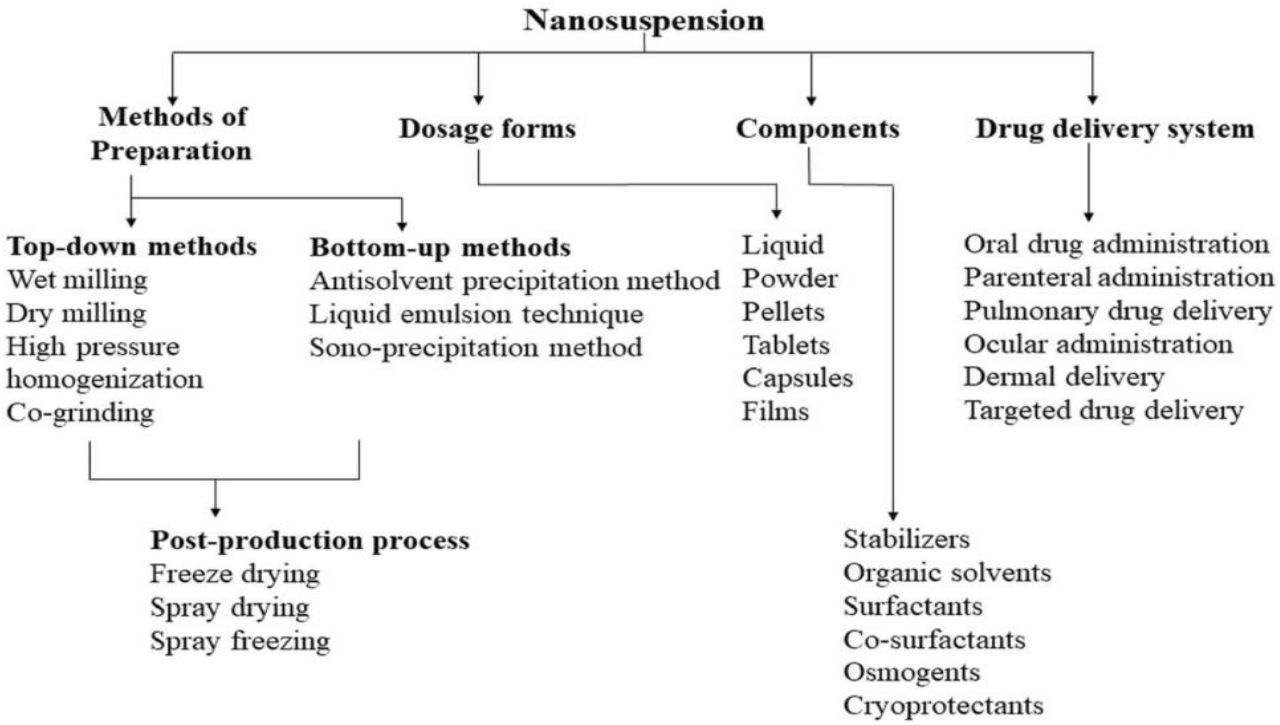

Figure 1: Schematic representation of method of preparation, dosage forms, components and applications of nanosuspension in drug delivery systems.

ADVANTAGES OF NANOSUSPENSION[10,11]

- Decreased particle size, increased drug dissolving rate, increased rate and extent of absorption, enhanced bioavailability of drug, area under the plasma versus time curve, onset time, peak drug level, reduced variability, and decreased impacts of being fed or fasting.
- Compounds that are water insoluble but soluble in oil can be employed in nanosuspensions. In contrast to lipidic systems, nanosuspensions can be used to successfully synthesize molecules that are insoluble in both water and oils.
- Nanoparticles can stick to the gastrointestinal mucosa, extending the drug's contact duration and improving absorption.
- There are numerous ways to administer Nanosuspensions, including oral, parenteral, pulmonary, cutaneous, and ophthalmic. This is a clear benefit.
- Nanosuspensions can provide passive targeting and have greater resistance to hydrolysis, oxidation, and settling. They also have a low incidence of side effects from the excipients.
- By avoiding the need to dissolve the compounds and by keeping the medicine in a desirable crystalline state with a size small enough for pharmacological acceptance, nanosuspensions alleviate the delivery problems for the compounds.

- Medicines having a high log P-value can be made into nanosuspensions to increase their bioavailability and improve their biological performance because of their rapid dissolving and saturation solubility.
- Nanosuspensions can be included into tablets, pellets, hydrogel, and suppositories, so they are appropriate for a variety of administration methods and Nanosuspensions have long-term physical stability and versatility.
- Raising the amount of amorphous material in the particles is crucial for potential crystalline structural alteration and increased solubility.
- The possibility of surface modification for site-specific delivery of nanosuspension.

TECHNIQUES FOR PREPARATION OF NANOSUSPENSION

In order to prepare nanosuspension, two methods are used:

- Bottom-up technology and
- Top-down technology.

The bottom-up approach involves dissolving molecules in a solvent and precipitating them using a variety of techniques, including solvent addition, spray freezing, evaporative precipitation, and liquid solvent change process. Top-down procedures are mechanical procedures like homogenization and grinding. Top-down techniques are used more frequently. The mechanical procedures have some downsides, including a need for greater time and energy, the possibility of contaminants, and insufficient control over particle size[12]. (Figure 2)

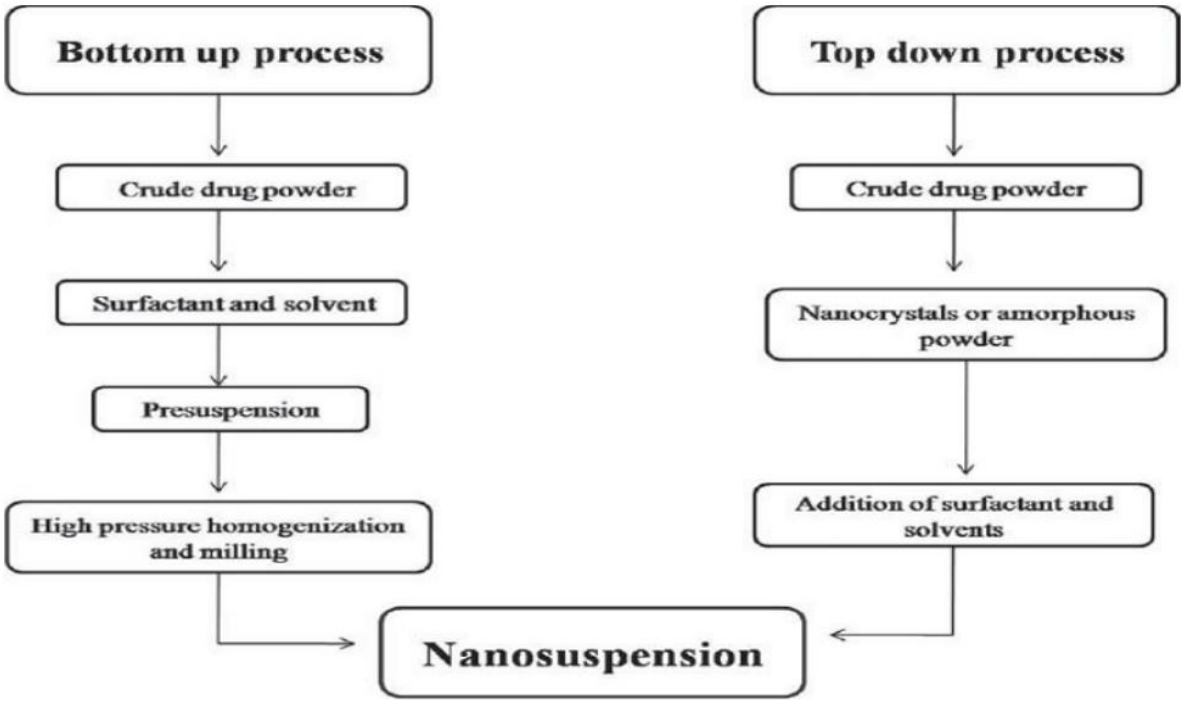

Figure 2: Approaches for preparation of Nanosuspension

1. BOTTOM-UP TECHNOLOGY

a. Nanoprecipitation method (solvent-antisolvent method)

It is mostly utilized for medications that are poorly soluble. In a suitable solvent, first the medication is dissolved. After that, a miscible antisolvent system is combined with this solution in the presence of surfactants. When a drug solution is added quickly to an antisolvent, the drug is abruptly supersaturated and turns into ultrafine drug solids. The two steps of the precipitation process are crystal growth and nuclei production. A high nucleation rate, but a low growth rate, is required when creating a stable suspension with the smallest possible particle size. The temperature affects both rates. The medicine must be soluble in at least one solvent that is miscible with a nonsolvent in order to use this method[13].(Figure 3)

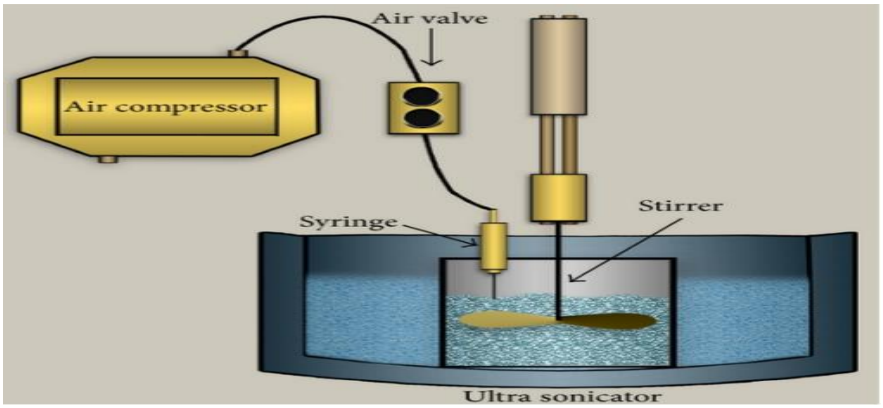

Figure 3: Schematic representation of the precipitation method

2. TOP-DOWN TECHNOLOGY

a. Media milling technique

Using pearl mills or high-shear media mills, nanosuspensions are created. A milling chamber, recirculation chamber, and milling shaft make up this apparatus. Balls or pearls formed of ceramic sintered zirconium oxide or aluminum oxide are used as milling media. Adding water, a medication, and a stabilizer to the milling chamber. The sample is affected by balls rotating at a high shear rate and controlled temperature. Particle size is reduced and nanosized particles are produced as a result of both frictional and impact forces[14].(Figure 4)

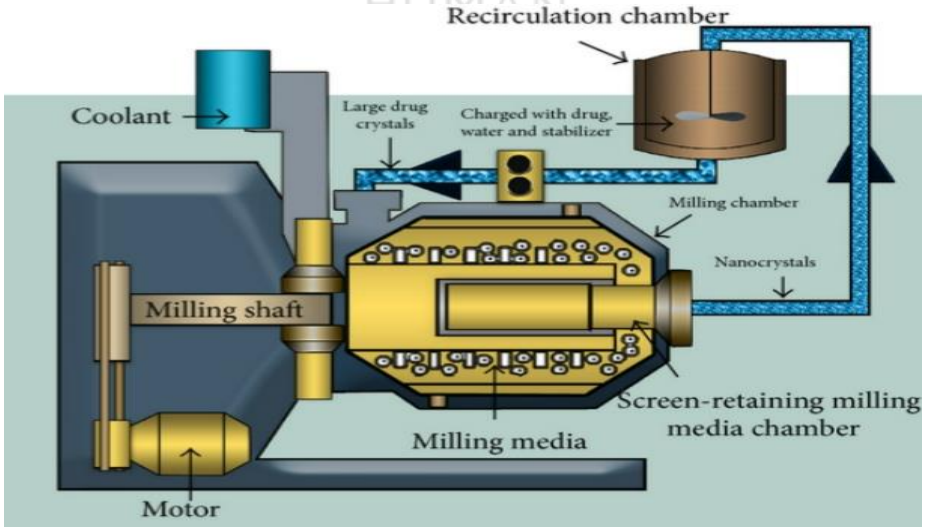

Figure 4: Schematic representation of the media milling process

b. High pressure homogenization technique

When homogenizing, the suspension is forced through a valve with a small aperture while under pressure. Using high-pressure homogenization with a nanosized aperture value, the

surfactant and medication are focused under pressure in this approach. The underlying principle is based on aqueous phase cavitations. Drug microparticles can become nanoparticles thanks to a high enough particle cavitation force. It is crucial to create a presuspension of the micronized drug in a surfactant solution using high-speed stirrers before putting the drug through the homogenization process[15].(Figure 5)

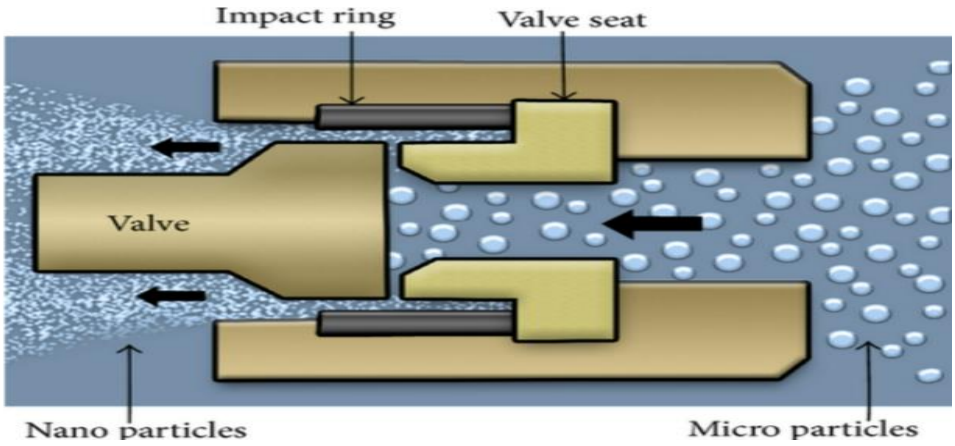

Figure 5: Schematic representation of the High-pressure homogenization process

- Nanopure (Homogenization in nonaqueous media)

In a water-free medium or a water mixture, it is homogenized. The mercury will be zero degrees Celsius or even below freezing. Thus, it is called deep-freeze homogenization. Thermo labile chemicals can be handled the best with this procedure.

• Dissocubes (Homogenization in aqueous media)

In this method, a pressure plunger pump forces the suspension through a small valve at a high pressure. The static pressure will drop below the boiling point of water when the suspension is allowed to pass through the orifice, causing the water to boil and create gas bubbles. Bubbles will implode when the pressure returns to normal after it leaves the orifice. As a result, nearby particles will rush to the surface, resulting in a size reduction.

• Nanoedge (Combined precipitation and homogenization)

The homogenization method or the precipitation approach will be comparable to this method. It is thought that combining these two approaches improves stability and bioavailability. The suspension created using this technique will undergo another homogenization step to minimize particle size and stop crystal formation. The nano edge technology also

incorporates an evaporation method for more effective nanosuspension synthesis, leading to improved starting materials that are solvent-free.

• Nanojet

Nanojet has mostly employed technology. In order to minimize particle size, nanojet technology primarily employs high pressure of force to pass a suspension that has been divided into at least two parts and is impacting with one another as a result of the high shear forces produced throughout the process[15].

c. Emulsification solvent evaporation technique

In this method, the drug is first prepared as a solution, which is then emulsified in a different liquid that isn't the drug's solvent. Drug precipitation occurs as a result of solvent evaporation. By generating strong shear forces using a high-speed stirrer, one may control crystal formation and particle aggregation. Globule size and stabilizer concentration are important variables to take into account when using the emulsification process[16].(Figure 6)

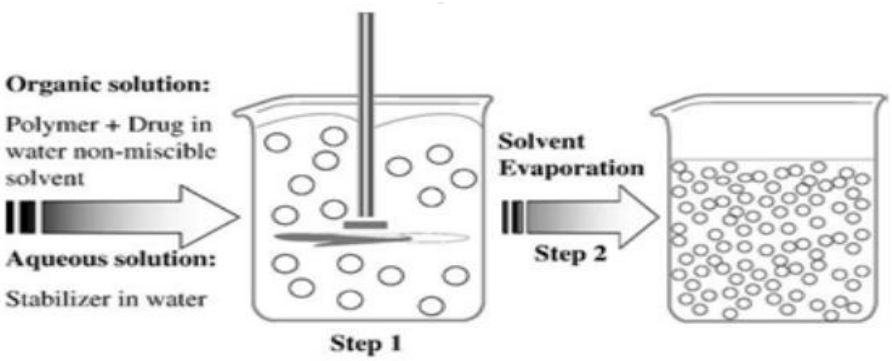

Figure 6: Schematic representation of the solvent-evaporation technique

d. Melt emulsification method

In this procedure, the medication is mixed with the stabilizer's aqueous solution, heated above the drug's melting point, and homogenized to create an emulsion. The sample holder was covered in heating tape that had a temperature controller attached during this procedure, and the emulsion's temperature was kept above the drug's melting point. The emulsion was next slowly cooled to room temperature or placed in an ice bath. The fundamental benefit of this approach is that no organic solvents are ever used in the manufacturing process[17].

e. Supercritical fluid process

Using dense noncondensable fluid and the supercritical fluid technique, particle size is reduced. This fluid has a critical temperature and critical pressure that are higher than those values. Using its methods, medication particles can be micronized down to a certain particle size, which is frequently submicron. The ability to produce nanoparticulates has been established using this approach. Particles with a diameter of between 5 and 2000 nm experience nanosuspension. The industry's use of technology is limited by the poorly soluble drugs and surfactants in supercritical CO2 and the high-pressure requirements for these operations[18].

f. Dry co-grinding

After dispersing in liquid media, soluble copolymers and polymers like PVP, PEG, and HPMC are used to dry grind poorly soluble drugs to create nanosuspensions. Due to an increase in surface polarity and the conversion of the medication from crystalline to amorphous, co-grinding improved the physicochemical characteristics and dissolving of the poorly soluble substance. It is simple to perform dry co-grinding without an organic solvent. The particle size is decreased[19].

Formulation of nanosuspensions [20]

Stabilizers or surfactants, the appropriate solvent system, and other chemicals are essential for the creation of nanosuspension formulation.

a) Stabilizers

Stabilizers are used to moisten the surface of solute or drug particles and delay Ostwald ripening and agglomeration in order to give great physical stability, which further enhances performance.

Stabilizers such polysorbate (Tween/Span series), povidone, cellulosics, poloxomers, and lecithin are frequently utilized.

b) Organic solvent

Organic solvents are usually used for the manufacturing of nanosuspension using emulsion or microemulsion technologies as a template. These solvents are extremely dangerous for both human health and the environment, but they can still be substituted for dichloromethane (which is known to be a hazardous solvent) with less dangerous water-soluble solvents like

methanol, ethanol, chloroform, isopropanol, and partially water-soluble solvents like ethyl acetate, ethyl formate, butyl lactate, triacetine, propylene carbonate, and benzyl alcohol.

c) Other additives

Several substances may be utilized depending on the route of administration or the physicochemical characteristics of the potential medicine, although some additives, such as buffers, salts, polyols, osmogent, and cryoprotectants, are frequently used.

Post-production processing

Nanosuspensions require post-production processing when the drug candidate is extremely susceptible to hydrolytic cleavage or chemical degradation. Processing might also be required if there are restrictions on acceptable routes or if even the best stabilizer is unable to keep the nanosuspension stable for a prolonged length of time. Considering these factors, it is possible to produce a dry powder of drug particles that are nanoscale in size using techniques like lyophilization or spray drying. In these unit activities, a logical decision must be made while taking into consideration the characteristics of the drug and the economy. In general, spray drying is more practical and less costly than lyophilization. The impact of post-production processing on the nanosuspension's particle size and the moisture content of dried nanosized drugs must be taken into account[21].

ORAL ADMINISTRATION OF NANOSUSPENSION

Oral suspension allows for liquid medication, which is recommended in the geriatric and pediatric age groups while ensuring chemical stability. Additional benefits include disguising the bitterness of medications, increasing the time they take to work, boosting the aqueous solubility of drugs that aren't very water soluble, and improving drug dissolution and bioavailability. Moreover, suspension is the preferred option if the medicine is insoluble in water and other solvents are prohibited.

Because of the increased surface area and subsequent increase in saturation solubility, drug nanosizing can result in a significant improvement in dissolution rate. This causes an increase in dissolution velocity and concentration gradient across the gastrointestinal tract, resulting in increased absorption and significant bioavailability. Thus, nanosuspensions are most beneficial for drug candidates in Biopharmaceutical Classification System classes II and IV (BCS)[22].

The formulation of nanosized particles can be applied to all the drug compounds belonging to BCS classes II and IV to increase their solubility and, as a result, partition into the gastrointestinal barrier. The medications belonging to BCS classes II and IV have solubility. For BCS class II medications, micronization is employed, and there are numerous more traditional techniques for making pharmaceuticals that are weakly soluble more soluble[23].

The reduction in particle size increases the rate of dissolution; however, the enormous surface free energy possessed by nanoparticles can sometimes result in reduced drug uptake. The aqueous solubility of the drug was increased, and bioavailability was significantly improved after oral administration of amphotericin B nanosuspension[24].

- Transformation of liquid nanosuspensions into intermediate solid powder

➢ Powders

Before processing, many medications or chemicals are also available in powder form. A good redispersant should quickly break up agglomerates created during drying so that the original particle size is quickly restored. Before the drying stage, redispersants must be applied to the the nanosuspensions. Sucrose, trehalose, maltodextrin, lactose, and mannitol are common redispersants utilized. Mannitol is also employed as a cryoprotectant during lyophilization. When compared to coarse powder and marketed product (Norvir®), ritonavir nanosuspension in rats showed a significantly higher rise in Cmax and AUC0t values[25].

➢ Pellets

The advantages of pellets as multiparticulate dosage forms include regulated drug release, release independent of gastric emptying rate, reduced possibility of dose dumping, little local irritation, adaptability to multiple release profiles, capacity to combine various medications, and patient compliance. The fluid bed coating process was used to spray the dried indomethacin nanosuspensions onto pellets. Drug nanosuspensions and dried pellets with nanosuspensions both showed similar dissolving characteristics[26]. Ketoprofen nanosuspension-containing pellets for up to 24-hour sustained medication release have been described[27].

➢ Tablets

Pharmaceutical tablets are solid unit dose forms that typically include medicinal ingredients compressed with the help of appropriate pharmaceutical excipients. Granules were created

using freeze drying or spray drying procedures in the majority of the investigations. These techniques convert nanosuspension into dry powder, which can then be crushed or moulded into tablets. By immediately freezing drying the nanosuspension in a blister pack, it is also possible to transform nanosuspension into tablets[28].

The preparation of naproxen tablets involved compressing the granules made from nano dispersion with mannitol as a bulking and stabilizing agent and a disintegrating agent. Under sink and non-sink circumstances, it was discovered that the dissolution of the nano dispersion was complete in 1 minute[29].

- Capsules

It was discovered that the oral administration of Novartis compound A and itraconazole nanosuspension in beagle dogs and rats, respectively, increased bioavailability[30,31]. The bioavailability of glimepiride nanocrystal-loaded capsules was shown to be much higher than that of the commercial formulation in both *in vitro* dissolution tests and *in vivo* investigations in rats[32].

- Oral films

Oral films, also known as orodispersible films, have significant advantages over other oral dosage forms because they quickly dissolve in the mouth, quickly traverse the oral mucosa, and skip hepatic metabolism, increasing the drug's bioavailability.

Recently, a mucoadhesive film based on nanosuspension was created with a layer containing carvedilol that was sandwiched between the backing and mucoadhesive layers. Using PEG400 as a plasticizer, nanosuspension was added to hydrogel made from HPMC and Carbopol 934P. When compared to commercial tablets, in vivo investigations on rabbits showed a considerable increase in the relative bioavailability[33].

Techniques for characterization of nanosuspension

The performance of dissolution is also changed by the solid state of nanoparticles, which has an impact on particle size, particle size distribution, and zeta potential in nanodrug delivery systems. Hence, predicting the *in vitro* and *in vivo* effectiveness of nanodrug delivery systems heavily relies on nanoparticle characterization.

- The mean particle size and distribution,
- particle charge (zeta potential)

- crystalline state and particle morphology

all these have a significant impact on the *in vivo* pharmacokinetic performance and biological function of nanosuspension[34].

APPLICATIONS OF NANOSUSPENSION

❖ Nanosuspension through oral route

The main issue with oral drug administration is poor solubility, inadequate dissolution, and insufficient effectiveness. Oral nanosuspensions are specifically utilized to boost the absorption rate and bioavailability of poorly soluble medicines due to their smaller particle size and significantly higher surface to volume ratio[34].

❖ Bioavailability Enhancement

The drug's poor oral bioavailability could be brought about by the digestive tract's poor solubility, permeability, or stability in the gastrointestinal tract (GIT). By addressing both the issues of poor solubility and poor permeability across the membrane, nanosuspensions are able to address the issue of poor bioavailability[35].

❖ Spray drying and lyophilization of Nanosuspension

The solidified form is preferable over aqueous nanosuspensions due to the large reduction in aggregation and other instability issues. As a result, solidifying prepared nanosuspensions is a typical process. The powder is subsequently transformed into alternative dosage forms, such as sterile powder for injection, nebulized for pulmonary delivery, tablets, and capsules for oral administration[36].

❖ Nanosuspension provide passive targeting

The medicine administered is disseminated over normal tissues or organs that are not involved in the disease process in a substantial proportion, frequently resulting in severe side effects. a successful strategy to solve this important problem in the creation of targeted medicine delivery systems. The versatility of nanosuspensions is demonstrated by their ability to be incorporated into a variety of dosage forms, including tablets, pellets, suppositories, and hydrogels, for various routes of administration. This is made possible by the flexibility offered in the modification of surface properties and particle size, as well as the ease of post-production processing[37].

❖ Mucoadhesion Of the Nanoparticles

Orally administered nanoparticles in the form of a suspension permeate into the liquid medium and quickly come into contact with the mucosal surface. The bio adhesion process immobilizes the particles at the intestinal surface. The initial step before particle absorption is the direct contact of the particles with the intestinal cells through a bio adhesive phase, which improves bioavailability and targeting of the parasites that are still present in the GIT[8].

❖ Other routes of administration

The most convenient way to administer nanosuspension is via the oral route. Other than oral route drug targeting, mucoadhesion of nanoparticles, parenteral, pulmonary, ocular, and transdermal delivery methods are all possible for administration of nanosuspension. These strategies increase the solubility and permeability of pharmaceuticals, hence enhancing bioavailability.

CONCLUSION

The optimal formulation choice for rigid hydrophobic drugs constrained by high log P, molecular weight, melting point, and dose is nanosuspension. It is possible to effectively create and scale up nanosuspensions using conventional size reduction techniques like wet milling and homogenization as well as formulation methodologies like precipitation, emulsion-solvent evaporation, solvent diffusion, and microemulsion techniques. Because of the significant enhancement in saturation and intrinsic solubility, noteworthy mucoadhesivity, and flexibility for surface modification in drug targeting, the application of this novel formulation has been greatly extended. For formulation scientists, nanosuspension has the ability to be a useful tool for addressing a range of formulation and drug delivery issues associated with different drug entities. Research on the use of nanosuspensions in pulmonary, ocular, and oral drug delivery systems has been conducted extensively over the past few decades. Numerous studies are being conducted on the application of nanosuspensions in additional drug transport systems, including the brain, transdermal, topical, buccal, and nasal routes. Pharmaceutical experts have given the technology a lot of thought, but the precise processes underlying the stability, solidification, and redispersibility of dried nanosuspensions have not yet been completely elucidated.

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