

Nanosuspension Technologies for Delivery of Drugs

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Abstract Nanotechnology has emerged as an tremendous field in the medicine. Nano refers as particles size range from 1-100nm. Nanosuspensions are the part of nanotechnology. Many drugs have a poor aqueous solubility. The use of drug nanosuspension is an universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. nanosuspension is defined as very finely colloid, biphasic, dispersed, solid drug particles in an aqueous vehicle, size below 1 μ m, without any matrix material, stabilized by surfactants and polymers, prepared by suitable methods for Drug Delivery applications, through various routes of administration like oral, topical, parenteral, ocular and pulmonary routes. The advantages of Nano suspensions are improved drug dispersibility and drug solubilization, increased therapeutic efficacy and reduced toxicity. Therefore, the present review described about achievements of nanosuspensions in drug delivery system in order to improve the solubility, stability and bioavailability of the drugs. This review article describes the preparation methods, characterization and applications of the nanosuspensions.

Keywords: nanosuspension, bioavailability, poorly soluble drugs, drug delivery, high pressure homogenization

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1. Introduction

A pharmaceutical nanosuspension is defined as "very finely dispersed solid drug particles in an aqueous vehicle, stabilized by surfactants, for either oral and topical use or parenteral and pulmonary administration, with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability". [1] Average particle size is between 200 and 600 nm. [2]

Nano sized particles increase solution velocity saturation solubility because of the vapour pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient result to a much more pronounced increase in the dissolution velocity as compared to a micronized product. More than 40% of drugs are poorly soluble in water, so they show problem in formulating them in conventional dosage form. Also for class II drugs which are poorly soluble in aqueous and organic media, the problem is more complicated. Nanosuspensions helps in solving the problem of bioavailability and poor solubility but other than this it also alters the pharmacokinetic of the drug which leads in improving the drug safety and efficacy. [2] nanosized particle can expand the solution velocity and saturation solubility because of vapor pressure effect. In addition of diffusional distance on the surface of drug, nanoparticle is decreased, thus leading to an increased concentration gradient. The increased in surface area and concentration gradient lead to increase in dissolution velocity as compared to micronized product. Nano means it is the factor of 10^{-9} or

one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom.

2.5 nm = Width of a DNA molecule

1 micron = 1000 nm.

1 nm = 10^{-9} m = 10^{-7} cm = 10^{-6} mm.

Micron = 10^{-6} m = 10^{-4} cm = 10^{-3} mm. [3]

Nanosized particles are stabilized by polymers, surfactants prepared by suitable methods for delivery by various route of administration like topical, parenteral, oral, optical and so on.

1.1. Need of Nanosuspension

The preparing of nanosuspension are preferred for the compound that are insoluble in water with high log P value, in case of drug that are insoluble of both water and organic media instead of lipidic system nanosuspension are used as formulation approach is most suitable for drug with high log P value, high melting point and high dose [1].

2. Advantages of Nanosuspension [4,5]

- It Enhance the solubility and bioavailability of compounds
- Suitable for hydrophilic compounds
- Higher drug loading is possible
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Can be given by any route
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.

- Rapid dissolution & tissue targeting can be achieved by IV route of administration
- Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.
- large-scale production, possible

3. Disadvantages of Nanosuspension

- Physical stability, sedimentation & compaction cause problems.
- It is bulky sufficient care must be taken during handling & transport.
- Improper dose.
- Uniform & accurate dose cannot be achieved. [5]

4. Formulation Consideration

Following agent are used in the preparation of nanosuspension

- Stabilizer
- Organic solvents
- Surfactant
- Co-surfactant
- Other additives.

4.1. Stabilizer

Absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. Functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behavior of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable Nanosuspension Commonly used stabilizers are polysorbate (Tween/Span series), povidone, cellulosic, poloxomers and lecithin. [6]

4.2. Organic Solvents

The acceptability of the organic solvents in the pharmaceutical area, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. The pharmaceutically acceptable and less hazardous water miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. [7]

4.3. Surfactants

Surfactants are incorporated in formulation to improve the dispersion by reducing the interfacial tension.

Surfactant also act as wetting or deflocculating agents. Tweens and Spans - widely used surfactants in nanosuspension. [1]

4.4. Co-surfactants

The choice of co-surfactant is critical when using microemulsions formulate nanosuspensions. Since co-surfactant can greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsions composition and on drug loading should be investigated. [6] Although the literature describes the use of bile salts and dipotassiumglycyrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions. [8,9]

4.5. Other Additives

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety. [7]

5. Properties of Nanosuspensions

Following are the properties of nanosuspensions

- Physical long term stability
- Internal structure of nanosuspension
- Adhesiveness
- Crystalline State and Particle Morphology
- Increase in Saturation Solubility and Dissolution Velocity of Drug
- Nano Suspension Provide Passive Targeting

5.1. Physical Long-term Stability

Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles. In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles because of that Ostwald ripening is totally absent. [7]

5.2. Internal Structure of Nanosuspensions

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug are exposed to high-pressure homogenization, particles are transformed from crystalline state to amorphous states. The change in state depends upon the hardness of drug, number of homogenization cycles chemical nature of drug and power density applied by homogenizer. [1-10]

5.3. Adhesiveness

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. [1]

5.4. Crystalline State and Particle Morphology

The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. [12] Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high-pressure homogenization [13]. The changes in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis [14] and supplemented by differential scanning calorimetry. [15] In order to get an actual idea of particle morphology, scanning electron microscopy is preferred. [11]

5.5. Increases in Saturation Solubility and Dissolution Velocity of Drug

Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation dissolution velocity increases due to increase in the surface area from micron size to particles of nanometer size. [1]

$$dx/dt = [(D \times A) / h] [C_s - X / V] \quad (1)$$

Where; D is diffusion coefficient,
A is surface area of particle,
dx/dt is the dissolution velocity,
V is volume of dissolution medium and
h is the thickness of the diffusion layer and X is the concentration in surrounding liquid. [16]

5.6. Nano Suspension Provide Passive Targeting

Most of drugs have failed to achieve favorable outcomes because they do not have the ability to reach the target site of action. A significant amount of the administered drug is distributed over the normal tissues or organs that are not involved in the pathological process, often leading to severe side effects. An effective approach to overcome this critical issue to development of targeted drug delivery systems. Versatility the flexibility offered in the modification of surface properties and particle size, and ease of post-production processing of nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories and hydrogels, for various routes of administration, thus proving their versatility. [1]

6. Method of Preparation of Nanosuspension

The following methods are used to prepare nanosuspension

- Media milling

- Homogenization (Dissocubes)
- Homogenization in non-aqueous media (Nanopure)
- Combined precipitation & homogenization (Nanoedge)
- Nanojet technology
- Emulsification-solvent evaporation techniques
- Hydrosol method
- Supercritical fluid method
- Precipitation technique
- Dry-co-grinding.

6.1. Media 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. 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. The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. A planetary ball mill is one example of equipment that can be used to achieve a grind size below 0.1 μm . A Nanosuspension of Zn-Insulin with a mean particle size of 150 nm was prepared using the wet milling technique. Degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles $\geq 5 \mu\text{m}$. [17,18,19,20]

6.1.1. Advantages

- Simple technology
- Low-cost process regarding the milling itself
- Large-scale production possible to some extent

6.1.2. Disadvantages [17]

- Potential erosion from the milling material leading to product contamination.
- Duration of the process not being very production friendly.
- Potential growth of germs in the water phase when milling for a long time.
- Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products. [18,19,20]

6.2. Homogenization Dissocubes

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 result 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. An aqueous suspension of atovaquone was dispersed using an Ultra turrax T25, IKA-Werke GmbH & Co. KG, Staufen, Germany and was further homogenized in a Gaulin Micron Lab 40 highpressure homogenizer. After subjecting to pressures of 1.5×10^7 (two cycles), 5×10^7 (two cycles) and 1.5×10^8 (20 cycles) Pa, a nanosuspension of atovaquone with a mean diameter of 279 ± 7 nm and mean polydispersity index of 0.18 ± 0.001 was obtained. To produce a nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling. [17]

6.2.1. Advantage

- Used for both diluted as well as concentrated suspensions
- Allows aseptic production.

6.3. Homogenization in Non-Aqueous Media (Nanopure)

Nanopure is suspension homogenized in water free media or water mixtures i.e. the drug suspensions in the non-aqueous media were homogenized at 0°C or even below the freezing point & hence are called “deepfreeze” homogenization. The result obtained were comparable to dislocubes & hence can be used effectively for thermolabile substance at milder conditions. [17]

6.4. Combined Precipitation & Homogenization (Nanoedge)

The drug is dissolved in an organic solvent & this solution is mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture the solubility is low & the drug precipitates. Precipitation has also been coupled with high shear processing. The basic principles of Nanoedge are the same as that of precipitation & homogenization. A combination of these techniques results in smaller particle size & better stability in a shorter time. [5]

6.5. Nanojet Technology

Nanojet technology is also called as opposite stream technology. In this technique a stream of suspension in two or more divided parts were passed with high pressure were made to colloid with each other, due to the high shear forces produced during the process leads to results in the reduction of particle size. [21]

6.5.1. Advantages [1]

- Specialized equipment is not necessary.
- Particle size can easily controlled by controlling the size of the emulsion droplet.
- Ease of scale-up if formulation is optimized properly.

6.5.2. Disadvantages [1]

- Compounds that are poorly soluble in both aqueous and organic media cannot be formulated by this method.
- Safety concerns because of the use of hazardous solvents in the method.
- Need for diultrafiltration for purification of the drug nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required.

6.6. Emulsification-Solvent Evaporation Techniques

This method 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. [5]

6.7. Hydrosol Method

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. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size. [22]

6.8. Supercritical Fluid Method

The organic solvents used in the preparation of conventional methods as solvent extraction evaporation, solvent diffusion and organic phase separation methods are hazardous to environment and physiological systems. To rectify the problem occurred through the conventional method supercritical fluid technology has been investigated for the preparation of biodegradable micro and nanoparticles, because supercritical fluids are environmentally safe. The most common techniques using supercritical fluids are supercritical anti-solvent (SAS), precipitation with compressed anti-solvent process (PCS) and rapid expansion of supercritical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid (SC CO_2), to dissolve the solute to be micronized; at the process condition, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles. Dexamethasone phosphate drug nanoparticles (for microencapsulation) and griseofulvin nanoparticles were prepared by using SAS method. RESS differs from the SAS process in that its solute is dissolved in a supercritical fluid and then the solution is rapidly expanded through a small nozzle into a region lower pressure, thus the solvent power of supercritical fluid dramatically decreases and solute eventual. [1]

6.9. Precipitation Technique

In this method, the drug is first dissolved in a water miscible organic solvent which is then added to an aqueous surfactant solution.

The solubility of the drug in the water-solvent mixture becomes low as a result of which it precipitates. This method has also been coupled with High Pressure Homogenization or HPH in order to yield good results. The NanoEdge process which is a patented technology by Baxter International is based on such a technology. When the drug solution is added rapidly to the anti-solvent, there occurs a sudden super saturation of the mixed solution and ultimately results in the production of sub-micron colloidal particles. Precipitation is often favored at high super saturation when the solubility of the amorphous phase is exceeded. [23]

6.10. Dry-Co-Grinding

Dry-co grinding can be carried out easily and economically and can be conducted without organic solvents. Physicochemical properties and dissolution of poorly water soluble drugs are improved by Co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. [24]

6.10.1. Advantages

- Easy process and no organic solvent required.
- Require short grinding time.
- Increase dissolution of poorly water soluble drug

7. Evaluation Parameter

- Mean Particle Size and Particle Size Distribution
- Particle Charge (Zeta Potential)
- Crystal Morphology
- Saturation Solubility and Dissolution Velocity
- Surface Hydrophilicity
- Adhesion Properties
- Interaction With Body Proteins.

7.1. Mean Particle Size and Particle Size Distribution

The mean particle size and the span of particle size distribution (polydispersity index, PI) are two important characteristic parameters because they 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 even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of Nano suspensions and should be as low as possible for the long-term stability of Nano suspensions. A PI value of 0.1– 0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution.[11]

7.2. Particle Charge (Zeta Potential)

Zeta potential gives certain information about the surface charge properties and further the long term physical stability of the nanosuspension. [11] Particle

charge determines the stability of Nano suspension. For electrostatically stabilized Nano suspension a minimum zeta potential of $\pm 30\text{mV}$ and for combined steric and electrostatic stabilization it should be a minimum of $\pm 20\text{mV}$. [1]

7.3. Crystal Morphology

To characterize the polymorphic changes due to the impact of high-pressure homogenization in the crystalline structure of the drug, techniques like X-ray diffraction analysis in combination with differential scanning calorimetric or differential thermal analysis can be utilized. The change in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and supplemented by differential scanning calorimetry. In order to get actual idea of particle morphology, scanning electron microscopy is preferred. [11]

7.4. Saturation Solubility and Dissolution Velocity

The nanosuspension have an important advantage over the other techniques, that it can increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility. [4]

7.5. pH

The pH value of aqueous formulation should be taken at a given temperature and only after settling equilibrium has been reached, to minimize “pH drift” and electrode surface coating with suspended particles. Electrolyte should not be added to the external phase of the formulation to stabilize the pH. [17] Prepared nanosuspension was taken in 10ml beaker and pH was measured using pH meter.

7.6. Osmolarity

Osmolarity of nanosuspension can be measured by using Osmometer. Intravenous dosage form should be isoosmolar with the blood so the nanosuspension formulation checked for osmolarity. Practically osmolarity was measured using osmometer and theoretically it was calculated using following formula

Osmolarity (mOsmol) = weight in gm/lit. No. of species * 1000/molecular weight*100 [30]

7.7. Surface Hydrophilicity

Surface hydrophilicity / hydrophobicity is considered as one of the important parameters affecting the in vivo organ distribution after i.v. injection. The surface hydrophobicity determines the interaction with cells prior to phagocytosis and; in addition, it is a relevant parameter for the adsorption of plasma proteins the key factor for organ distribution. To avoid artifacts, the surface hydrophobicity needs to be determined in the original environment of the drug nanoparticles, which means in

aqueous dispersion medium. A suitable technique is hydrophobic interaction chromatography (HIC), previously employed to determine the surface hydrophobicity of bacteria, and then transferred to the characterization of nanoparticulate drug carriers. [1]

7.8. Adhesion Properties

In vivo bioadhesive study is performed where Male Wistar rats can be used. In general, each animal receives a single oral dose of 1ml aqueous suspension containing 10 mg of the nanoparticles loaded with the drug (approximately 45 mg particles/kg body Weight). The animal is sacrificed by cervical dislocation at 1 and 3 h post administration. The abdominal cavity is opened and the stomach, small intestine and cecum is removed, opened lengthwise along the mesentery and rinsed with phosphate saline buffer (pH 7.4). Further, the stomach, small intestine and cecum is cut into segments of 2 cm length and digested in suitable alkali for 24 h. Drug extracted from the digested samples by addition 2ml methanol, vortexed for 1 min and centrifuged. Aliquot (1 ml) of the supernatants is assayed for the drug by spectrofluorimetry to estimate the fraction of adhered nanoparticle to the mucosa. For calculations, standard curve of the drug can also be prepared.

7.9. Interaction with Body Proteins [1]

In vitro interaction between nanoparticles and mucin can be studied by incubation of mucin and nanoparticles (1:4 weight ratio) either in acidic or in neutral medium. The incubation is carried out under stirring at temperature of 37°C. The dispersions are then centrifuged and 150µl of each supernatant is placed in a test plate. Micro BCA Protein Assay Reagent Kit (150µl) is then added to the supernatants and the plate, is incubated for 2 hrs at 37°C. According to this procedure, the absorbance of mucin can be measured by colorimeters at λ_{max} of the drug. The amount of the mucin adsorbed to the nanoparticles can be determined as a difference between its initial concentration and the concentration found in the dispersion after incubation and centrifugation. The calculations can be made on the basis of mucin standard curves.

8. Pharmaceutical Applications of Nanosuspensions in Drug Delivery

- Oral Drug Delivery
- Parental Drug Delivery
- Ophthalmic Delivery
- Pulmonary Drug Delivery
- Targeted Drug Delivery
- Topical
- Mucoadhesion of The Nanoparticles
- Bioavailability Enhancement.

8.1. Oral Drug Delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. Orally

administered antibiotics such as atovaquone and bupravaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The oral administration of naproxen nanoparticles lead to an area under the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with just 44.7 mg-h/l for Naprosyn suspensions and 32.7 mg-h/l for anaprox tablets. Oral administration of the gonadotropin inhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2%. A nanosuspension of Amphotericin B developed by a significant improvement in its oral absorption in comparison with the conventional commercial formulation. [11]

8.2. Parental Drug Delivery

Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, Nano suspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden. Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal clofazimine in Mycobacterium avium-infected female mice. [22]

8.3. Ophthalmic Delivery

Certain drugs have poor solubility in lachrymal fluid. If it is formulated as nanoparticles its saturation solubility and bioavailability will increase. Mainly applied for hydrophobic drugs. It increases the residence time in cul de sac. The best example of nanosuspension is ibuprofen. The anti inflammatory activity of ibuprofen increased compared with the aqueous preparation [25,26]

8.4. Pulmonary Drug Delivery

Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Aqueous Nano suspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in lungs. The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. [6]

8.5. Targeted Drug Delivery

Targeted drug delivery can be used for the anti-mycobacterial, fungal or leishmanial drugs to macrophages if the infectious pathogen is persisting intracellular. The further plan of action for targeted drug delivery system is by using various surface coatings for active or passive targeting., atovaquone nanosuspension concentration in brain, lungs, sera, liver is high and has improved therapeutic efficacy against toxoplasma encephalitis in murine mold infected with toxoplasma gondii. [27]

8.6. Topical Drug Delivery

Drug nanoparticles can be incorporated into creams & water free ointments. The nanocrystalline forms leads to an increased saturation solubility of drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin [5].

8.7. Mucoadhesion of the Nanoparticles

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 Nano suspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT. [28]

8.8. Bioavailability Enhancement

Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation. The therapeutic effect was significantly enhanced, which indicated higher bioavailability. [29].

9. Conclusion

Nanosuspensions appear to be a unique and yet commercially viable approach to combating such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production techniques such as media milling and high pressure homogenization have been successfully for large-scale production of Nano suspensions. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of Nano suspensions for various routes. The applications of Nano suspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized. Poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds and leads to employment of novel formulation technologies. The use of drug nanocrystals is universal formulation approach to increase the therapeutic performance of these drugs in any route of administration.

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