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NANOSUSPENSION: A PROMISING DRUG DELIVERY SYSTEM FOR POORLY WATER SOLUBLE DRUG AND ENHANCED BIOAVAILABILITY

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ABSTRACT: Nanosuspension consists of a submicron colloidal dispersion of pharmaceutically active ingredient particles in the liquid phase, which is stabilized by surfactant. Poor water solubility is a major problem for the manufacturing of formulation. The drug particle reduces leads to enhance the surface area as well as bioavailability. Nanosuspension prepared by way of a number of methods. Techniques such as media milling, high-pressure homogenization have been used commercially for producing Nano-suspension. Recently engineering of nanosuspension employs emulsion and microemulsion as a templet. The unique feature of Nanosuspension has enabled its use in different dosage forms and delivered by using various routes such as an oral, pulmonary, ocular, topical, and mucoadhesive hydrogel. The benefits of nanosuspensions are improved drug dispersibility and drug solubilization, improved therapeutic efficacy and reduced toxicity. Therefore, the present review described the achievements of nano-suspensions in the drug delivery system in order to enhance the solubility, stability, and bioavailability of the drugs. This review article describes the preparation methods, characterization, and applications of the nanosuspensions.

INTRODUCTION: Pharmaceutical industries are always looking for new methods in order to obtain adequate oral bioavailability, as most of the biological properties exhibiting NCEs are poorly water-soluble. The increasing frequency of poorly water-soluble NCEs exhibiting therapeutic activity is of major concern to the development of new formulations in the pharmaceutical industry, which leads to low turnout in the development of new molecular entities as drug formulations are poor solubility and poor permeability of the lead compounds.

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Recently, the formulation of such drugs as nanoscale systems (which have a size below 1µm) has quickly grown as a new and novel drug delivery system. The major distinctive of these systems is the quick dissolution rate, which improves bioavailability after oral administration [1]. The present article aims to review the nano-suspensions as an emerging and promising tool for the formulation of poorly soluble drugs.

1.2. Definition: A Pharmaceutical nanosuspension is described as "very finely colloid, biphasic, discrete solid drug particles in an aqueous vehicle, stabilized by way of surfactants, for either parenteral and pulmonary administration, oral and topical use or, with decreased particle size, leading to a better dissolution rate and therefore increased bioavailability". The diameter of the suspended particle is less than 1 µm in size (*i.e.* 0.1nm-1000

nm). The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. An upturn in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity. Nanosize particles can increase dissolution velocity and dissolution velocity because of the vapor pressure effect [2].

1.3. Need of Nanosuspension: To date, More than 40% of drugs are poorly soluble in water, so they show difficulties in formulating them in conventional dosage forms. Also, for class II drugs that are poorly soluble in aqueous and organic media, the problem is more difficult [2]. Preparing nanosuspension is chosen for such compounds that are insoluble in water (but are soluble in oil) with high log P-value. Various methods to resolve problems of low solubility and low bioavailability micronization, solvency, oily solution, salt formation- some other techniques are liposomes, emulsions, microemulsion, solid dispersion, ß-cyclodextrin inclusion complex, *etc*. But, many of these techniques are not universally applicable to all drugs [3]. In these cases, nanosuspensions are preferred. In the case of drugs that are insoluble in both water and inorganic media in its place of using lipidic systems, nanosuspensions are used as a formulation method. It is most appropriate for the compounds with high log P value, high melting point, and high dose. Nanosuspensions can be used to improve 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 rises, and the maximum plasma level is reached faster (*e.g.*, oral or intravenous (IV) administration of the nanosuspension). This is one of the typical advantages that it has over other approaches for increasing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses an important challenge for the formulators. Major issues associated with poorly water-soluble compounds [4].

Although all marketed products currently are produced by so-called 'top-down techniques', in which the nanoparticles are found through size reduction into the submicron-range, bottom-up techniques and mostly controlled precipitation methods are methods of interest for the canonization of poorly soluble drugs. In this method, without any harsh conditions and only with simple types of equipment, one could reduce the particle size to a few hundred nanometers range. Therefore, all that method is used for the production of nanosuspension, a careful evaluation of the type and concentration of the stabilizer is a serious stage for the successful production of nanosuspension. Both polymeric and surfactant stabilizers can be used for this purpose. Nano-suspensions differ from Nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid lipid nano-particles (SLN), which are lipidic carriers of the drug. The key modification from conventional formulations of suspensions is that the particle size distribution of the solid particles in nano-suspensions is usually less than 1 μm (*i.e.*, 0.1nm-1000nm), with an average particle size range between 200–600 nm. On the other hand, the particle diameter essential in most good pharmaceutical suspensions is 1 to 50 μm. In nano-suspensions, the overall bioavailability is improved by an increase in surface area and saturation solubility via particle size reduction [5].

1.4. Major Advantages of Nanosuspension [3]

- Its general applicability to the utmost drugs and its simplicity.
- It can be useful for poorly water-soluble drugs.
- It can be given by any route.
- Reduced tissue irritation in the case of subcutaneous/intramuscular administration.
- Rapid dissolution and tissue targeting can be reached by the IV route of administration.
- Oral administration of nanosuspensions provides fast onset, reduced fed/fasted ratio and improved bioavailability.
- The absorption from the absorption window of the drugs can be increased due to a reduction in the particle size.
- In case of ocular administration and inhalation delivery, higher bioavailability and more consistent dosing.

- Drugs with high log P-value can be formulated as nanosuspensions to raise the bioavailability of such drugs.
- Enhancement in biological performance due to high dissolution rate and saturation solubility of the drug.
- Ease of manufacture and little batch-to-batch variation.
- Long term physical stability.
- Nanosuspensions can be incorporated in tablets, pellets, hydrogel, and suppositories are suitable for various routes of administration.
- Increasing the amorphous portion in the particles, most important to a potential change in the crystalline structure and higher solubility.
- The opportunity of surface-modification of nanosuspension for site-specific delivery.
- Possibility of significant production, the pre-requisite for the introduction of a delivery system to the market.

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

2.1. Stabilizer: Stabilizer plays a vital role in the method of nanosuspensions. In the absence of a suitable stabilizer, the excessive floor strength of nanosized particles can induce agglomeration or aggregation of the drug crystals. The most important characteristic of a stabilizer is too moist the drug particles definitely and to forestall Ostwald‟s ripening and agglomeration of nano-suspensions in order to yield a stable bodily formulation with the aid of supplying steric or ionic barriers. The kind and amount of stabilizer have a stated effect on the physical stability and *in-vivo* conduct of nanosuspensions. In some cases, a mixture of stabilizers is required to achieve a stable nanosuspension. The drug-to-stabilizer ratio in the components can also fluctuate from 1:20 to 20:1 and need to be investigated for a unique case. Example: lecithins, PVPK30, PVA, SLS. Cellulosics, two Poloxamers, Polysorbates, Lecithin, and two Povidones [6].

2.2. Organic Solvents: Organic solvents are commonly used in the preparation of nano-suspension if emulsion or microemulsions technologies are used as the template for this. These solvents are very hazardous in physiologic and environmental means; however, nevertheless, some less hazardous water-miscible solvents like methanol, ethanol [7].

2.3. Surfactants: Surfactants are integrated to enhance the dispersion with the aid of reducing the interfacial tension. They also act as wetting or deflocculating agents. Example: Tweens and Spans - broadly used surfactants [6].

2.4. Co-surfactants: The preference of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactants can substantially affect section behavior, the impact of co-surfactant on uptake of the inside section for chosen microemulsion composition and on drug loading ought to be investigated. Example: Transcutol, glycerol, ethanol, and isopropanol bile salts and Dipotassium glycyrrhizinate can be used as co-surfactants [6].

2.5. Other Additives: Nanosuspensions may comprise additives such as buffers, salts, polyols, cosmogenic, and cryoprotectants, depending on both the route of administration or the properties of the drug moiety [3].

3. Properties of Nanosuspension:

3.1. Long-Term Physical Stability: Ostwald ripening is accountable for crystal growth and subsequently, formation of microparticles. Ostwald ripening was brought on through the variations in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentrated area around small particles (higher saturation solubility) to areas around larger particles possessing lower drug attention. This leads to the formation of a supersaturated solution around the large particles and, therefore, to drug crystallization and increase of the large particles. The diffusion process of the drug from the small particles to the large particles leaves a location around the small particles that are now not saturated any more, for this reason leading to the dissolution of the drug from the small particles and eventually completes the disappearance of the small particles [8].

3.2. Internal Structure of Nannosuspension: The high-energy input during the disintegration process causes structural adjustments inside the drug particles. When the drug particles are uncovered to high-pressure homogenization, particles are transformed from a crystalline state to an amorphous state. When the drug particles are exposed to high-pressure homogenization, particles are converted from a crystalline state to amorphous state. The exchange in the state relies upon the hardness of the drug, number of homogenization cycles, chemical nature of the drug, and power density applied by means of the homogenizer [8].

3.3. Adhesiveness: There is a distinct increase in the adhesiveness of ultra-fine powders compared to coarse powders. This adhesiveness of small drug nanoparticles can be exploited for expanded oral delivery of poorly soluble drugs. A considerably excellent report is that of the enlarge in bioavailability for danazol from 5% (as micro suspension) to 82% (as nanosuspension) [5].

3.4. Crystalline State and Morphology: A potential change in the crystalline structure of nanosuspensions, saying increasing the amorphous fraction in the particle or even creating clearly amorphous particles is an attribute of consideration. The application of high pressures at some point of the production of nanosuspensions used to be found to promote the amorphous state [5].

3.5. Increase in Saturation Solubility and Velocity of Drug: The 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 an increase in the surface area from micron size to particles of nanometer size.

$$dx/dt = [(D \times A)/ h] [Cs-X/V] \text{ -----Equation (1)}$$

Where; D is the diffusion coefficient,
dx/dt is the dissolution velocity,
A is the surface region of the particle,
h is the thickness of the diffusion layer,
V is the volume of the dissolution medium, and X is the concentration in the surrounding liquid [9].

3.6. Nanosuspension Provide Versatility: The flexibility provided in the modification of surface properties and particle size and ease of post-production processing of nanosuspensions enable them to be integrated into various dosage forms, such as tablets, pellets, suppositories, and hydrogels, for various routes of administration, as a result proving their versatility.

3.7. Nanosuspension Enhance Bioavailability: Drug with poor solubility, poor permeability or poor solubility in the gastrointestinal tract will lead to poor oral bioavailability. Nanosuspension resolves the trouble of poor bioavailability by solving the trouble of poor solubility, and poor permeability throughout the membranes

4. Preparation Method of Nanosuspension: For manufacturing nanosuspensions, there are two converse methods, "Top-down process technology" and "Bottom-up process technology".

4.1. Top-Down Techniques: The methods in which a nano-size range of particles is acquired through a reduction in the size of large particles [1].

4.1.1. High-Pressure Homogenization: It is the most extensively used technique for preparing nanosuspensions of many poorly aqueous soluble drugs [10]. It includes three steps. First, drug powders are dispersed in a stabilizer solution to form presuspension, and then the presuspension is homogenized in high-pressure homogenizer at low pressure for premilling, and eventually homo-genized at high strain for 10 to 25 cycles until the nanosuspensions of the desired size are formed.. Different techniques are developed based on this principle for preparations of nanosuspensions are [11]

- **A.** Homogenization in aqueous media (Disso cubes)
- **B.** Homogenization in non-aqueous media (Nanopure)
- **C.** Combined precipitation and homo-genization (Nanoedge)
- **D.** Nanojet

A. Homogenization in Aqueous Media (Disso Cubes): This technology was developed through R. H. Muller by means of a piston-gap type high-pressure homogenizer in 1999 [12]. In this method, the suspension containing a drug and surfactant is forced under pressure *via* a Nanosized aperture valve of a high-pressure homogenizer.

Principle: This method is primarily based on the cavitation principle. The dispersion existing in the 3cm diameter cylinder is suddenly passed through a very narrow gap of 25µm. According to Bernoulli's law, the drift volume of liquid in a closed system per cross-section is constant. It leads to an extension in dynamic pressure and a reduction of static pressure below the boiling point of water at room temperature due to a reduction in diameter from 3cm to 25µm. Then water starts off evolved boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation), and regular air pressure is reached. The particle cavitation forces are sufficiently excessive to convert the drug microparticles into nano-particles.

Advantages:

- It does not cause the erosion of processed materials.
- It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

Disadvantages:

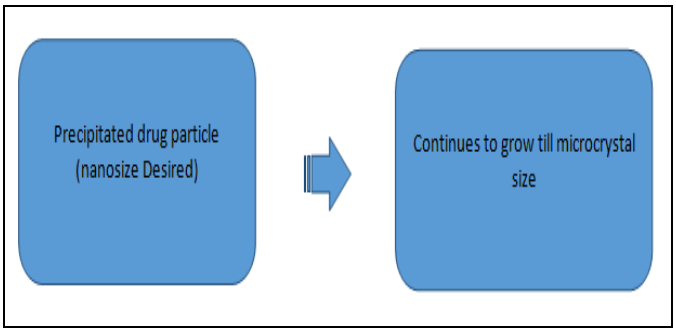
- Pre-processing like micronization of drugs is required.
- High-cost instruments are required that increases the cost of the dosage form.

B. Homogenization in Non-aqueous Media (Nanopure): Nanopure is suspensions homogenized in water-free media or water combinations *i.e.*, the drug suspensions in the non-aqueous media had been homogenized at 0 ºC or even under the freezing point and hence are referred to as "deep-freeze" homogenization. The results obtained had been similar to DissoCubes and hence can be used efficiently for thermolabile substances at milder conditions. The nanocrystals of the drug dispersed in liquid polyethylene glycol (PEG) or a number of oils can be directly filled as drug suspensions into HPMC capsules or gelatin.

Advantages:

- The dispersion medium need not be removed.
- Evaporation is faster and under milder conditions (when water and water-miscible liquids are used).
- This is useful for temperature-sensitive drugs.
- For i.v. injections, isotonic nanosuspensions are obtained by homogenizing in water-glycerol mixtures [1].

C. Combined Precipitation and Homogenization (Nanoedge): The drug is dissolved in an organic solvent, and this solution is blended with a miscible anti-solvent for precipitation. In the water-solvent mixture, the solubility is low, and the drug precipitates. Precipitation has additionally been coupled with high shear processing. This is carried out by a combination of rapid precipitation and high-pressure homogenization. The Nanoedge patented technology *via* Baxter depends on the precipitation of friable substances for fragmentation under conditions of excessive shear and/or thermal energy. Rapid addition of a drug solution to an anti-solvent leads to surprising supersaturation of the blended solution and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may additionally be appreciated at high supersaturation when the solubility of the amorphous state is exceeded [12].



The basic principles of Nanoedge are the same as that of precipitation and homogenization. An aggregate of these strategies outcomes in smaller particle sizes and better stability in a shorter time. The main disadvantage of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology [5].

D. Nanojet: It is also known as opposite stream technology, makes use of a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure due to the high shear forces produced in the course of the method particle size is reduced [13].

The major limitation of this technique is the High numbers of passes (nearly about 75) are required through the microfluidizer, and the product obtained consists of a fairly large fraction of microparticles. A limitation of this process requires large production time [16].

4.1.2. Media Milling (Nanocrystal): This patent-protected technology used to be developed by Liversidge *et al*., (1992). Formerly, the technology was owned by the company Nanosystems; however, recently, it has been acquired by Élan Drug Delivery. In this technique, the nanosuspensions are produced using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft, and a recirculation chamber. The milling chamber charged with polymeric media is the active aspect of the mill. The mill can be operated in a batch or recirculation mode. Crude slurry consisting of drug, water, and stabilizer is fed into the milling chamber and processed into nano-crystalline dispersion, and the milling media or pearls are then rotated at a very high shear rate. The milling technique is carried out beneath controlled temperatures. The standard residence time is generated for a nanometer-sized [8].

Principle: The high energy and shear forces created as a result of the impaction of the milling media with the drug provide the energy enter to break the microparticulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide, or highly cross-linked polystyrene resin. The technique can be performed in either batch or recirculation mode. In batch mode, the time required to acquire dispersions with unimodal distribution profiles and mean diameters <200nm is 30–60 min [9].

Advantages:

- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions.
- Ease of scale-up and little batch-to-batch variation
- Narrow size distribution of the final nano-sized product.
- Flexibility in handling the drug volume ranging from 1 to 400mg/mL, enabling formulation of very dilute as well as highly concentrated nanosuspensions [8].

Disadvantages:

- Generation of residues of milling media, which may be introduced in the final product as a result of erosion.
- The media milling technique is time consuming.
- Some fractions of particles are in the micrometer range.
- Scale-up is not easy due to mill size and weight.

4.2. Bottom-Up Techniques: It is the method in which the nano size is bought by growing the size of particles from molecular range to the nano range [1]. The traditional strategies of precipitation (‘Hydrosol’) are known as Bottom-Up technology. Using a precipitation method, the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent. In the water-solvent blend, the solubility is low, and the drug precipitates. The basic challenge is that throughout the precipitation procedure development of the crystals needs to be controlled via the addition of surfactant to avoid the formation of microparticles.

Advantage:

- The use of simple and low-cost types of equipment.

Disadvantages:

- The drug wants to be soluble in at least one solvent, and the solvent wants to be miscible with non-solvent.
- Moreover, it is no longer applicable to the drugs, which are poorly soluble in both aqueous and non-aqueous media.

4.2.1. Emulsification - Solvent Evaporation Technique: [14] This technique involves preparing a solution of drug accompanied via its emulsification in every other liquid that is non-solvent for drug, evaporation of the solvent lead to the precipitation of drug. Crystal growth and particle aggregation can be controlled through growing excessive shear pressure using a high-speed stirrer.

4.2.2. Supercritical Fluid Process: This approach utilizes solubilization and nanosizing technologies through the supercritical fluid technique for particle size reduction. Supercritical fluids (SCF) are non-condensable dense fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). This technique allows the micronization of drug particles to the submicron levels. Recent advances in the SCF technique are to create the nanoparticulate suspension of particle size of 5 to 2000nm in diameter. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure required for these approaches avoid the utility of this technology in the pharmaceutical industry [15].

4.2.3. Emulsion as Templates: [17]Apart from the use of emulsions as a drug delivery vehicle, they can additionally be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in both volatile organic solvent or a partly water-miscible solvent. An organic solvent or combination of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate immediately to form a nanosuspension stabilized via surfactants. Since one particle is formed in each emulsion droplet, it is feasible to manage the particle size of the nanosuspension via controlling the size of the emulsion

4.2.4. Microemulsion as Templates: [9] Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by using an interfacial film of surfactant and co-surfactant. The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug with the aid of intimate mixing. The suitable dilution of the microemulsion yields the drug nanosuspension with the aid of the mechanism described earlier.

If all the components that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension.

5. Characterisation of Nanosuspension: Nano-suspensions are characterized for appearance, color, odor, assay, related impurities, particle size, zeta potential, crystalline status, dissolution studies, and *in-vivo* studies.

5.1. *In-vitro* Evaluation:

5.1.1. Mean Particle Size and Size Distribution: Various parameters of nanosuspensions like saturation solubility, dissolution velocity, physical stability, dissolution velocity, physical stability, and biological performance depend on the mean particle size and particle size distribution. Mean particle size and particle width (poly-dispersity index) can be decided through Photon Correlation Spectroscopy (PCS), laser diffraction, and colter current multi-sizer. The Poly-dispersity index (PI) be low for the long-term stability of the nanosuspensions. PI value of 0.1–0.25 shows a narrow size distribution, whereas a PI value larger than 0.5 suggests a very broad distribution. Due to the low measuring range (3nm to 3 μm) of PCS, the determination of the contamination of the nanosuspension (by drugs having a particle size greater than 3 μm) is difficult. So, to observe and quantify the microparticles that may have been generated in the course of the production process, laser diffractometry (LD) analysis should be carried out in addition to PCS analysis. Particles ranging from 0.05–80 μm and in certain units, particle sizes up to 2000 μm can be measured via using LD.

Particle size analysis *via* the Coulter counter method is vital (in addition to PCS and LD) for nanosuspensions that are meant for intravenous administration. Coulter counter is a more efficient and appropriate method than LD analysis as it gives the absolute number of particles per volume unit for the different size classes. It quantifies the contamination of nanosuspensions through micro-particulate drugs [1].

5.1.2. Particle Charge (Zeta Potential): Zeta potential determines the stability of the nanosuspension. Both the stabilizer and the drug govern the zeta potential of a nanosuspension. Zeta potential of minimal ±30mV is required for electrostatically stabilized nanosuspension, and

±20mV is required in case of electrostatic and steric stabilization.

5.1.3. Crystalline State and Particle Morphology: It is necessary to know the crystal morphology of the drug in the nanosuspension. Polymorphic or morphological modifications in a drug that appears during nano-sizing can be determined *via* the information of crystalline state and particle morphology. The amorphous state of the drug formed during the preparation of nanosuspension is determined *via* X-ray diffraction analysis. It gives information about the adjustments in the physical state of the drug particles as well as the extent of the amorphous fraction. Differential scanning calorimetry can be used additionally. Scanning electron microscopy is additionally used to get exact information about particle morphology. The effect of high-pressure homogenization on the crystalline structure of the drug is estimated *via* X- ray diffraction analysis in aggregate with differential scanning calorimetry. Techniques like scanning electron microscopy (SEM), atomic force microscopy (AFM), or transmission electron microscopy (TEM) are preferred for determining the exact size and morphology of nanoparticles in suspension.

5.1.4. Saturation Solubility and Dissolution Velocity: The dissolution velocity and the saturation solubility are enhanced through the formula of nanosuspensions. Reduction in particle size results from the increased dissolution pressure and hence the solubility. Change in surface tension takes place as the solubility will increase (due to particle size reduction), which leads to increased saturation solubility. Different physiological solutions at different pH and different temperatures are used to carry out the determination of the saturation solubility and dissolution velocity according to the techniques suggested in the pharmacopeia. *In-vivo* overall performance (blood profiles, plasma peaks, and bioavailability) of the formulation is assessed by using these parameters. An increase in saturation solubility can be explained by using the Ostwald Freundlich equation [19]. Determination of the dissolution velocity of nanosuspensions gives information about the advantages of nanosuspension over conventional formulations, especially in sustained-release dosage forms

The Ostwald-Freundlich equation is:

$$C(r) = C(\infty) \exp (2\gamma M / r\rho RT) \text{ ------Equation (1)}$$

Where C(r) and C(∞) are the solubilities of a particle of radius r and of infinite size. γ, M, and ρ are interfacial tension at the particle surface, the molecular weight of the solute, and the density of the particle, respectively [18].

5.1.5. Stability: Nanosuspensions Stability depends on the particle size of the suspended particles. The reduction in the particle size to the nano range will increase the surface energy of the particles, and the tendency of the particles to agglomerate increases. Therefore the stabilizers are used to reduce the chances of Ostwald ripening and to improve the stability of the suspension by means of providing a steric or ionic barrier. Stabilizers like cellulosic, Poloxamers, Polysorbates, lecithin, polyoleate, and Povidones are generally used in the nanosuspensions. Lecithin is desired in the improvement of parental nanosuspensions. Nano-suspensions can be stored at different stress conditions like distinctive temperatures (15, 25, 35 45°C), thermal cycling, and mechanical shaking and alternate in their mean particle size can be accompanied for three months.

Different concentrations of small molecule surfactants (like sodium lauryl sulfate (SLS) and do fax 2A1 (DF)) and polymeric stabilizer (like Hydroxypropyl methylcellulose (HPMC)) can be evaluated to determine the effect of stabilizer type and micellar solubilized drug on Ostwald ripening [19].

5.1.6 pH: The pH of the nanosuspension can be easily measured by means of the use of a pH meter [20].

5.1.7. Osmolarity: Practically, the Osmolarity of nanosuspension can be measured by way of using Osmometer [20].

5.1.8 Drug Content: The drug content material of nanosuspension formulation can be carried out with the aid of extracting the nanosuspension in the appropriate solvent mixture, like Methanol: THF (1:1) mixture, shaken well and then centrifuged. The supernatants can be separated and diluted with the same solvent combination, and the absorbance can be measured at appropriate λmax. The drug

content then can be calculated the usage of the calibration curve [20].

5.2. *In-vivo* Evaluation: [1] Particular drug and route of administration require the specific *in-vivo* evaluation of the nanosuspensions. Generally, the formulations are administered with the aid of the required route, and the plasma drug concentrations are decided *via* HPLC-UV visible spectrophotometry. Surface hydrophilicity/hydrophobicity (which determines interaction with cells prior to phagocytosis), adhesion properties, and the interaction with body proteins are normally evaluated *via in-vivo* parameters. The monitoring of the *in-vivo* overall performance of the Nanosuspensions and the establishment of the relationship between *in-vitro* release and in-vivo absorption are required in order to prepare a successful preparation. Irrespective of the route of the administration and the delivery systems. The rate of dissolution influences the *in-vivo* biological overall performance of oral nanosuspensions. The size of nanoparticle and surface properties of the particles determines the organ distribution for intravenously injected nanosuspensions. The *in-vivo* organ distribution conduct of the nanosuspension is affected by means of hydrophilicity/ hydrophobicity and interactions of particles with plasma proteins. Surface hydrophobicity is determined with the aid of hydrophobic interaction chromatography, and absorption of protein is determined by 2-D PAGE quantitatively and qualitatively after intravenous injection of nanosuspensions of the drug in animals.

6. Application of Nanosuspension: Nanosuspensions have a wide range of applications, especially in the case of low solubility and low bioavailability drugs. They are stated below.

6.1. Oral Drug Delivery: Because of the several benefits, the oral route is the preferable route for many of the drugs specified in the case of orally administering antibiotics such as atovaquone and buparvaquone. By making it in nano size, its solubility and bioavailability will increase. The oral administration of naproxen nanoparticles leads to an area below the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with naproxen nanosuspension and naproxen tablets [16]. In the case of danazol (gonadotrophin inhibitor), nanosuspension has an absolute bioavailability of 82.3 and the traditional dispersion only 5.2% [21].

6.2. Parentral Drug Delivery: Nanotechnology is additionally used in the parenteral drug delivery system. The advantage of this technique is it need only much less amount of toxic cosolvent for poorly soluble drugs. This will uplift the therapeutic effect of the drug compared with the conventional oral formulation and targeting the drug to the macrophages. The drug clofazimine is given as iv the concentration in the liver, spleen, and lungs reached an excessive level *i.e.*; higher than minimum inhibitory concentration, for most of the mycobacterium avium strains. Tarazepide is formulated as nanosuspension in order to overcome the use of surfactants and cyclodextrins to improve the bioavailability [22].

TABLE 1: ADVANTAGES OF NANOSUSPENSIONS OVER CONVENTIONAL FORMULATIONS [24]

Route of administration	Disadvantages of conventional formulations	Benefits of Nanosuspensions
Oral	Slow onset of action/ poor absorption	Rapid onset of action/ improved solubility so improved bioavailability
Ocular	Lacrimal wash off/ low bioavailability	Higher bioavailability/ dose consistency
Intravenous	Poor dissolution/ nonspecific action	Rapid dissolution/ tissue targeting
Inhalations	Low bioavailability due to low solubility	Rapid dissolution/ high bioavailability/
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation

6.3. Pulmonary Drug Delivery: In pulmonary drug delivery, we are using nanopreperations for the drugs which have poor solubility in pulmonary secretions. For lung delivery, it is nebulized by means of the mechanical or ultrasonic nebulizer. Uniform distribution of the drug is possible, and every droplet contains at least a single drug particle. Nano sizing improves the diffusion and dissolution of the drug. It enhances the adhesiveness of the drug to the mucosal surface and extended residence time at the site of absorption. Nanosuspensions have the onset of action quickly at the start, and then controlled release of active moiety occur, which is required for most of the pulmonary nanosuspensions has the speedy onset of action in the beginning and then controlled the release of active moiety occur which is required for most of the pulmonary disease [24]. *e.g.* budenoside.

6.4. Occular Drug Delivery: Certain drugs have poor solubility in the lachrymal fluid. If it is formulated as nanoparticles, its saturation solubility and bioavailability will increase. Mainly utilized to hydrophobic drugs. It increases the residence time in cul de sac. A great example of nanosuspension is ibuprofen. The anti-inflammatory activity of ibuprofen increased compared with the aqueous preparation [23].

6.5. Targeted Drug Delivery: Nanosuspensions also used for targeting their surface properties and altering the stabilizer can easily alter the *in-vivo* behavior. The drug will be uptaken *via* the mononuclear phagocytic system to allow regional specific drug delivery. This can be used for targeting antimycobacterial, fungal drugs to the macrophages. Atovaquone is used as targeting nanosuspension to the brain [25].

6.6. Mucoadhesion of Nanoparticle: If the nano-suspension is orally administered, it diffuses into the liquid medium and adheres to the mucosal surface before absorption. It improves the bioavailability and targeting to the parasite persisting the git.eg; buparvaquone against *Cryptosporidium parvum* [26].

TABLE 2: CURRENT MARKETED FORMULATIONS USING NANOSUSPENSIONS TECHNOLOGY [27, 28]

Drug	Product	Company/ Individual	Uses
Megestrol Acetate	MEGACE® ES	PAR Pharmaceutical	Appetite stimulant
Tizanidine Hydrochloride	LA.Zanaflex CapsulesTM	Acorda	To treat spasticity
Morphine Sulphate	Avinza®	King Pharmaceutical	To treat moderate to severe pain that lasts for more than a few days
Dexmethylphenidate Hydrochloride	Focalin®XR	Novartis	Treatment of Attention Deficit Hyperactivity Disorder
Sirolimus	RAPAMUNE®	Wyeth	Immunosuppressant
Fenofibrate	TriCor®	Abbott	Treatment of hypercholesterolemia
Aprepitant	EMEND®	Merck	Antiemetic
Fenofibrate	Triglide™	First Horizon Pharmaceutical	Treatment of Hypercholesterolemia
Methylphenidate Hydrochloride	Ritalin®	Novartis	Treatment of Attention Deficit Hyperactivity Disorder

CONCLUSION: Nanosuspensions seems to be a unique and yet commercially feasible method to combating such as poor bioavailability that is related to the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production strategies such as media milling and high-pressure homogenization has been efficaciously for large-scale production of nanosuspensions. The advances in production methodologies the usage of emulsions or microemulsions as templates have provided still easier processes for manufacturing however, with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesive, versatility in surface modification and ease of post-production processing, have widened the applications of nanosuspensions for various routes.

The applications of nanosuspensions in parental and oral routes have been very well-investigated and applications in pulmonary and ocular delivery have been realized. However, their applications in topical, buccal, and nasal delivery are still looking ahead to exploration. Poor aqueous solubility is rapidly becoming the main hurdle for formulation scientists working on oral delivery of drugs compounds and leads to the employment of novel formulation technologies. The use of drug nano-crystals is a conventional formulation approach to increase the overall therapeutic performance of these drugs in any route of administration.

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