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An Overview Of Medication Delivery System Using Nanosuspension- A Review

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Abstract

Nanotechnology is the science that deals with the process that occurs at a molecular level and nano length scale size and it has developed as a great field in medicine. Nano refers to particle size range 1-1000 nm. Nanotechnology is the part of Nanosuspension. They are important carriers in developing novel drug formulations. Many drugs have solubility as a crucial factor for drug effectiveness and independence of route of administration. The nanosuspension contains a sub-micron colloidal dispersion active pharmaceutical ingredients. Particles in the liquid phase are stabilized by surfactants. The production of drugs in the form of nanosuspension has been advanced for drug delivery systems in the form of oral formulation and of non-oral administration, nanosuspension proved to be a better and attractive alternative approach compared to others. conventional formulations. This review narrates the pharmaceutical nanosuspension formulation, preparation, characterization, and pharmaceutical application in drug delivery as well as marketed product

Keywords: - Nanosuspension, drug delivery, colloid

Introduction

A Nanosuspension is a submicron colloidal dispersion of drug particles stabilized by surfactant. A pharmaceutical nanosuspension is defined as a very finely dispersed solid drug particle in the aqueous vehicle for either oral or topical use or parenteral and pulmonary administration particle size distribution in solid particles in nanosuspension is usually one micron with an average particle size ranging between 200 to 600 nm [1] A formulation of nanosized particle can be applied to all drug compounds belonging to pharmaceutical classification system [BCS] classes II and IV to increase their solubility and hence partition into gastrointestinal barrier[2]

Micro ionization is used for class II drugs of (BCS) which are drugs having good permeability and poor solubility. Solubility of poorly soluble drugs can be enhanced by many conventional methods which contain solubilization using cosolvent, micro ionization, salt form, precipitation techniques, oily solution, and surfactant dispersion other techniques like solid dispersion, emulsion, and liposomes but they lack universal application to all drugs. this technique is not useful for those drugs that are not soluble in aqueous and organic solvents.[3] an alternative and promising approach is the production of drug nanoparticles to overcome these

problems. Administration methods for nano suspension parenteral, oral, pulmonary, and 0ccular. Nanosuspension works for targeted medication administration [4] nano suspended particles containing pH value 4 and below which insoluble in watery solution but it is well soluble in water at pH 7[5] This article simplifies that formulating the drug in nanosuspension can improve the oral bioavailability of poorly soluble drugs

Formulation of Nanosuspension [6]

Excipient	Function	Example
Stabilizer	Weight the drug particle thoroughly, prevent Ostwald's ripening and agglomeration of nanosuspension, providing a steric and ionic barrier	1. Polysorbate 2. Povidone 3. Lecithin 4. poloxamers
Cosurfactant	Influence phase behavior when microemulsions are used to formulate nanosuspension	1. Ethanol 2. Bile salts 3. dipotassium 4. isopropanol
Organic solvent	Pharmaceutically acceptable less hazardous solvents for preparation of formulation	1. Methanol 2. chloroform 3. ethyl acetate 4. ethyl formate
Other Additives	According to the requirement of the administration or the properties of the drug moiety	1. buffers 2. salts 3. polyols 4. cosmogenic

Advantages of Nanosuspension [7]

1. it increases the solubility and bioavailability of drugs.
2. They are easily available and cost-effective.
3. Tissue inflammation is avoided
4. Lack of dose-response proportionality
5. It is viable to alter the dose.
6. The physical stability of nanosuspension is more than liposomes.
7. It has rapid dissolution and tissue targeting.
8. Improved drug delivery.
9. In ocular and inhalation drug delivery it has higher bioavailability.
10. Nanosuspension can be formulated into various dosage forms such as capsules, tablets, and injections. And providing flexibility in drug delivery options.

Disadvantages of Nanosuspension [6]

1. Sedimentation caused problems.
2. Physical stability, and compaction cause problems.
3. Dose precision is not achieved.
4. It has limited drug loading capacity.
5. It involves a complex process for the production of nanosuspension.

Methods of preparation of Nanosuspension.

Nanosuspension technology has been developed as a promising contender for the efficient delivery of hydrophobic drugs. It is applied to poorly soluble drugs that are insoluble in ware and oil. Methods of preparation of nanosuspension are technically simpler alternatives than liposomes and other conventional colloidal drug carriers. It is reported to be more cost-effective.it is a particularly poorly soluble drug and yields physically more stable drugs. [8,9]

There are two methods of preparation for nanosuspension. The conventional method of precipitation is called "bottom-up technology" In this technology drug is dissolved in the solvent, which is added to an on solvent to precipitate the crystal. The "Top-down" technologies are disintegration methods and are preferred over the precipitation method. [8,9]

- ❖ The Top-down process follows an integration approach from large particles, microparticles to nano-sized particles.[8]

Examples are as follows: -

- High-pressure homogenization
- Nano edge
- Nano-pure
- Media milling [Nanocrystals]

The bottom-up process is a conventional method that forms nanoparticles from molecules [8]

Examples are as follows: -

- Solvent anti-solvent method
- Supercritical fluid processes
- Emulsification solvent evaporation technique
- Liquid emulsion as a templet

Examples of top-up process are as follows: -

1.High-pressure homogenization

High-pressure homogenization has been used to prepare nanosuspension of poorly water-soluble drugs. [7,8,9] Before homogenizing three steps are required at high pressure for 10-25 cycles to create the required size nanosuspensions, medications powders are dispersed in a stabilizer solution to form a pre-suspension. This pre-suspension is then harmonized at low pressure per 10-25 cycles until the nanosuspension of the desired size is formed. Different methods are developed based on this principle for the preparation of nanosuspension disso cubes, nano pure, nano edge, and nano jet are developed. [4,8]

A).Hominization in aqueous media [Disso tubes]

This technology was developed by R.H. Muller using a piston gap-type high-pressure homogenizer in 1999[8]. Homogenization involves the forcing of a suspension under pressure through a valve having a narrow aperture. The most commonly used homogenizer in the preparation of nanosuspension is the APV micron LAB 40[2]

PRINCIPLE

This method is based on the cavitation principle. The dispersion present in a 3 cm diameter cylinder is suddenly passed through a very narrow gap of 25µm.

According to Bernoulli's law, the flow volume of liquid in a closed system per cross-section is constant it leads to an increase in dynamic pressure and a decrease of static pressure below the boiling point of water at room temperature due to the reduction in diameter from 3cm-25µm. [10]

- **Advantages: -**
  1. enable for aseptic manufacture of nanosuspension for parenteral delivery.
  2. narrow size distribution of nanoparticulate drugs present in the final product.
  3. scalability is simple, with little batch-to-batch fluctuation.
- **Disadvantage: -**
  1. Preprocessing like micro ionization of drug is required
  2. High-cost instruments are required that increase the cost of dosage form.

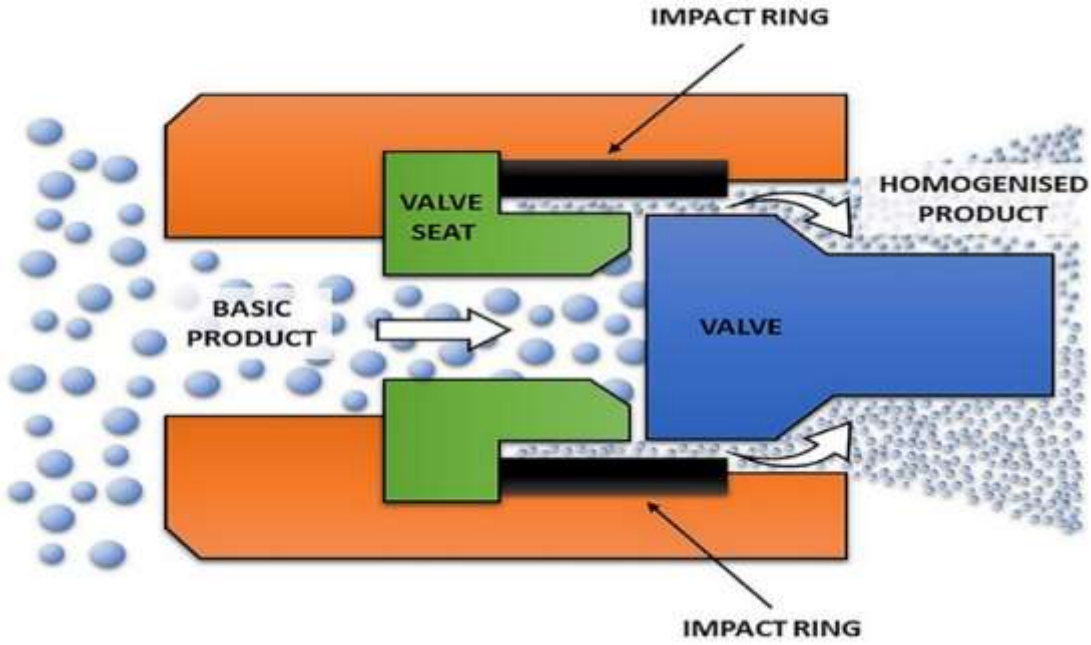


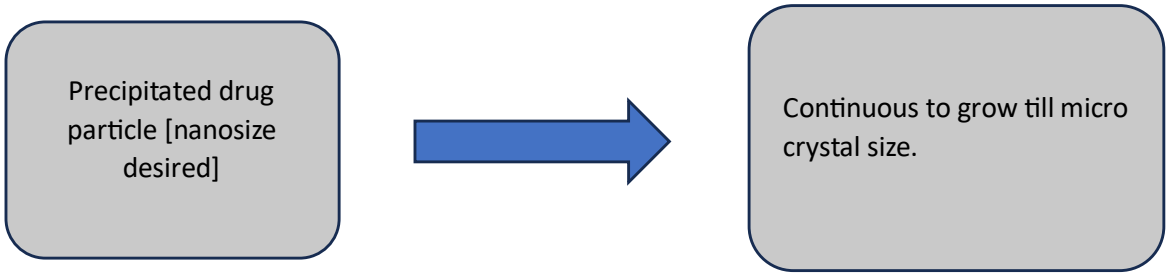
Fig. 1 shematic reprentation of high pressure homoginization

B).Homogenization in a non-aqueous medium [nano pure]

Nano pure is a suspension is suspension homogenized in water free medium or water mixture that is the drug suspension is the non-aqueous medium where homogenized at 0^0C or even below the freezing point and hence is called deep freeze homogenization. the results obtained were comparable to disso cubes and hence can be used effectively for thermolabile substances at milder conditions. The nanocrystals of the drug dispersed in liquid polyethylene glycol [PEG] or various oils can be directly filled as drug suspension into HPMC capsules or gelatin.[11]

C).Nano edge: - [Combined precipitation and hominization.]

The drug dissolved in an organic solvent and this solution is mixed with miscible with an anti-solvent for precipitation [11] . In this technique drug is dissolved in an organic solvent and this solution is mixed with the miscible antisolvent for precipitation. Drug precipitates due to low solubility in the water solvent mixture. Precipitation is coupled with high shear processing which was accomplished by a combination of high-pressure homogenization and rapid precipitation.[12]

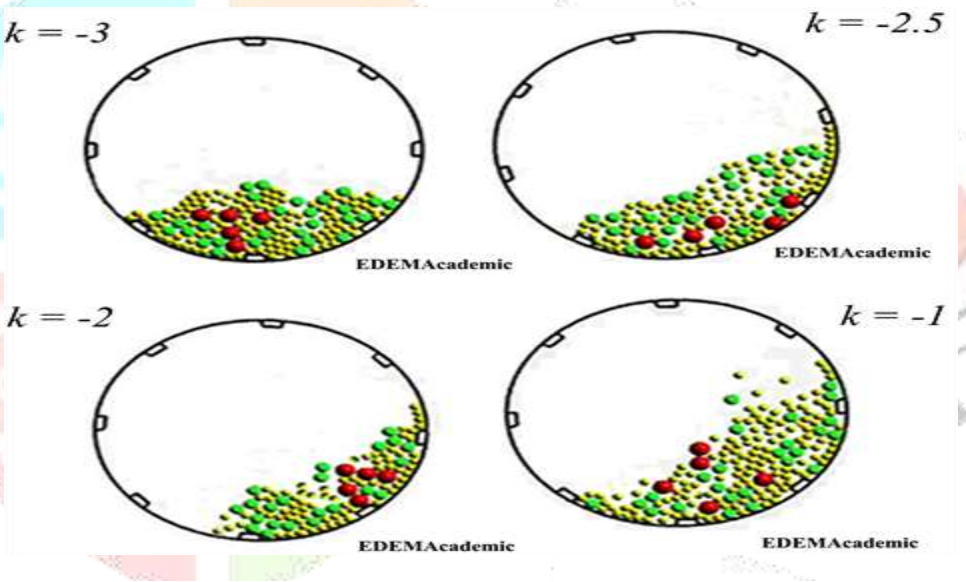


D).Nano jet technology: -

It is used as a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure up to 400 bar at the high velocity of 1000 m/s [7]. The high shear force produced during the process results in particle size reduction. Equipment used for this particle includes the M110L and M110S microfluidizers. The major limitation of this technique is the high number of passes through the microfluidizers [up to 75 passes] and that product obtained contains a relative combination of rapid precipitation and high-pressure homogenization. Rapid addition of the drug solution to an anti-solvent leads to sudden supersaturation of the mixed solution and generation of fine crystalline and amorphous solids. Precipitation in amorphous material may be favored at high supersaturation when the solubility of amorphous state is exceeded.

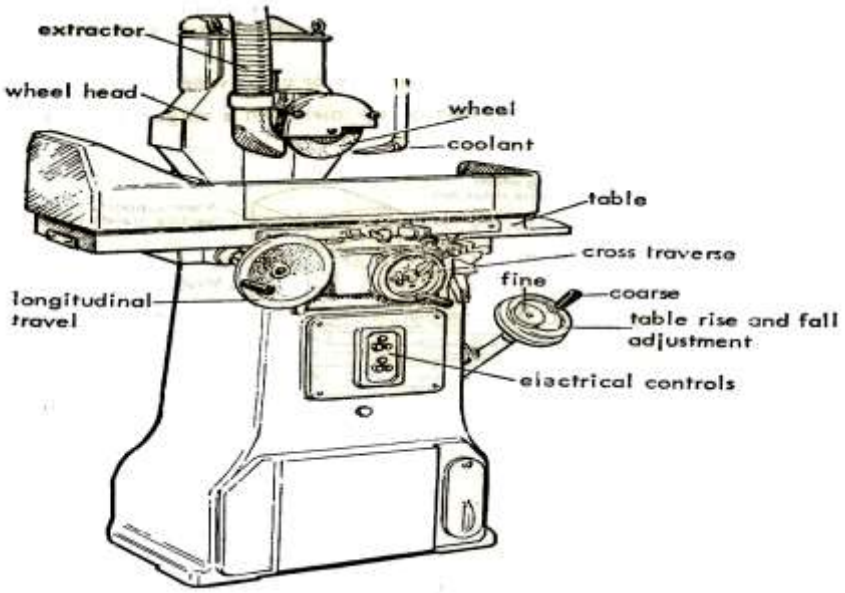
2.Media milling: - [Nanocrystals]

This method was first developed by Liversidge et al. Nanosuspension is formulated by high-shear media mills and pearl mills [13]. The media mill consists of a milling chamber, a milling shaft, and a recirculation chamber. The active component of the mill is the milling chamber with polymeric media. The mill can be operated in batch or recirculation mode.[11] the media mill is a structure of glass, zirconium oxide, or highly cross-linked polystyrene resin. The milling chamber is charged with milling medium, water, drug, and stabilizer. The milling media are then rotated at a very high shear rate. The typical residence time generated for a nanometer-sized dispersion with a mean diameter of < 200 nm is 32-60 minutes [11]



Principle[11,14]: -

The high energy and shear forces caused as a result of the impaction of the milling media with the drug provides energy input to break the microparticulate drug into nanosized particles. The media milling process can successfully proceed with micronized and non-micro ionized drug crystals. Once the formulation and the process improved very little batch-to-batch variation was observed in the quality of the dispersion.



- **Advantages: -**

1. Scalability is simple and there is little batch-to-batch fluctuation.
2. Poorly soluble drugs in both aqueous and organic environments can be easily synthesized into nanosuspensions.

- **Disadvantages: -**

1. This technique is time-consuming.
2. Scale-up is not easy due to mean size and weight.

Examples of bottom-up process are as follows: -

1.Solvent antisolvent method: -[Precipitation technique][10]

This method used for many years for the preparation of submicron particles.it is used for poorly soluble drugs. Firstly, the drug is dissolved in an appropriate solvent then this solution is mixed with the miscible antisolvent system in the presence of a surfactant. If the rapid addition of drug solution in the antisolvent leads to sudden supersaturation of the drug in the mixed solution forms ultra-fine drug solids. There are two phases involved in this method nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but a low growth rate is required. Both rates are depending on temperature. The drug needs to be soluble in at least one solvent which is miscible with non-solvent

2.**Supercritical fluid process [10,15]: -**

This method is used to produce nanoparticles from drug solutions. This method involves the various method various methods that aim to a rapid expansion of the supercritical solution process [RESS], Supercritical antisolvent process, and precipitation with the compressed antisolvent process [PCA]. The RESS involves an expansion of the drug solution in supercritical fluid through a nozzle which leads to loss of solvent power of the supercritical fluid resulting in the precipitation of the drug as fine particles. In the PCA method, the drug solution is broken down into a chamber containing compressed carbon dioxide. As the solvent is removed the solution gets supersaturation and thus precipitates as fine crystals. This process is used as a supercritical fluid in which the drug is poorly soluble and a solvent for the drug that is also miscible with supercritical fluid.

3.Emulsification solvent evaporation technique: -

The emulsification solvent evaporation technique is concerned with preparing a solution for the drug followed by its emulsification in another liquid that is non-solvent for the drug. The solvent leads to the precipitation of the drug for evaporation.

4.Emulsion as a templet [13,14.]: -

this emulsion is also used for the preparation of the nanosuspension. The use of emulsion as templates is applicable for those drugs that are insoluble in either volatile organic solvent or partially water-miscible solvent. There are two ways to produce drug nanosuspension by emulsification method. In the first method, an organic solvent loaded with a drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion the organic phase is evaporated under reduced pressure so the drug particles precipitate instantaneously to form nanosuspension and stabilized by surfactants. Originally organic solvents such as methylene chloride and chloroform were used. Relatively safer solvents such as ethyl acetate and ethyl formate are used.

Formulation consideration

Following agents are used in the preparation of nanosuspension

1. Stabilizer
2. Organic solvent
3. Surfactant
4. Co-surfactant
5. Other additives

1] stabilizer

It plays important role in the formulation of nanosuspension. Absence of a stabilizer the high surface energy of nano sized particles can reduce the maturation and agglomeration of the drug particles. The function of the stabilizer are to wet drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of nanosuspensions to yield physically stable formulation by providing stericor ionic barriers.[16]

The physical stability and in-vivo performance of nanosuspension is controlled by the quantity of stabilizer. The commonly used stabilizer in nanosuspension is polysorbate, poloxomers, povidone, lecithin, and tellulosics.[20]

2] Organic solvent:-

Organic solvents is used inside the additives of nanosuspension if emulsions are used as templet. Due to their less toxic effect the water miscible solvent like methanol, ethanol, isopropranol and solvents that are particularly miscible with water like ethyl formate, propylene carbonate are prefferd in formulation over the conventional hazardous solvents such as dichlomethane.[20,21]

3] Surfactant:-

Surfactants are compressed in formulation to improve dispersion by reducing the intrafacial tension. It also act as a wetting of deflocculating agent. The widely used surfactants are Tweens and Spans. [16]

4] Cosurfactant:-

The selection of co-surfactant is criticle when using microemulsion formulate nanosuspension. Because co-surfactant which has proof of an effect on phase behaviour, the effect of co-surfacatnt on uptake of internal phase for selected microemulsion composition and the drug loading shuld be investigated. Even through the literature using bile salts and dipottasium glycerrhizinate as a co-surfacatant.the safely used cosurfactants in the formulation of microemulsion as various solubilizer such as glycofuranol, transcutol and ethanol.[22]

5] Other:-

Nanosuspension may additionally moreover contains of additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration and their properties of drug moiety.[21]

Ideal properties of nanosuspension[16]

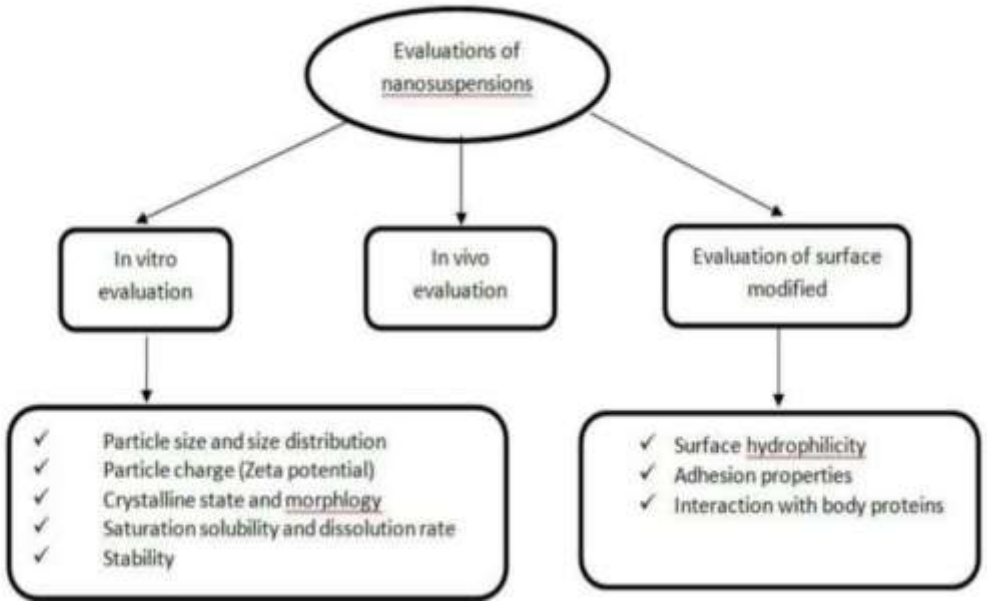
The ideal properties of nanosuspension are as follows

1. Long-term physical stability
2. Adhesiveness
3. Increase in saturation solubility and dissolution velocity of the drug
4. It gives a passive target
5. Internal structure of nanosuspension.

Evaluation parameter of nanosuspension

The various involved in characterization of nanosuspension with different parameters like Size of particle, particle size distribution and also zeta potential Because these parameters mainly affected on safety, efficacy and stability of formulation. [17]

Fig. Methods for characterization of Nanosuspension



In vitro Evaluation

1.Particle size and size distribution

Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility,dissolution velocity, physical stability, etc. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer.(24) The PCS method can measure particles in the size range of 3 nm to 3µm and the LD method has a measuring range of 0.05-80µm. The coulter counter multisizer gives the absolute number of particles, in contrast to the LD method, which gives only a relative size distribution. For IV use, particles should be less than 5µm,considering that the smallest size of the capillaries is 5-6µm and hence a higher particle size can lead to capillary blockade and embolism.(23)

2.Zeta potential

The long term stability study information and Surface charge property information can be know by Zeta potential.

- A minimum zeta potential of ±30 mV is required for a stable suspension stabilized only by electrostatic repulsion,
- whereas, a zeta potential of ±20 mV would be sufficient for combined electrostatic and steric stabilizer(25)

3.crystalline state and 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 calorimetry or differential thermal analysis can be utilized. 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.(27

4.saturation solubility and dissolution rate

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution rate as well as the saturation solubility. These two parameters should be determined in various physiological solutions. The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behavior of the formulation. Bohm et al. reported an increase in the dissolution pressure as well as dissolution rate with a reduction in the particle size to the nanometer range.Size reduction leads to an increase in the dissolution pressure(26)

5.Stability

high surface energy of nanosized particles induces agglomeration of the drug crystals. The main function of the stabilizer is to wet the drug particles thoroughly to prevent Ostwald ripening and agglomeration of the Nanosuspension and form a physically stable formulation by providing a steric or an ionic barrier. Typical examples of stabilizers used in Nanosuspensions are cellulosics,poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral Nanosuspension.(27)

In vivo Evaluation

The establishment of an in-vitro/in-vivo correlation and the monitoring of the in-vivo performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected Nanosuspensions since the in-vivo behavior of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins In fact, the qualitative and quantitative composition of the protein absorption pattern observed after the intravenous injection of nanoparticles is recognized as the essential factor for organ distribution. Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of in vivo behavior. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity, whereas 2-D PAGE can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals.(23,25,27,28)

Evaluation for surface-modified Nanosuspension

- Surface hydrophilicity
- Adhesion properties
- Interaction with body proteins

Application of Nanosuspension

- **Oral administration**

Due to its many well-known benefits, the preferred route of medication administration is orally. Antibiotics taken orally, like atovaquone and buparvaquone", very clearly illustrate this issue. When such medications are nanosized, their oral absorption and subsequently, bioavailability can rise dramatically, Danazole", a gonadotrophin inhibitor, has an absolute bioavailability of 82.3% in nanosuspension, compared to 5.2% in traditional dispersion, after oral administration (30,31).

- **Parentral administration**

Liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 μm to avoid capillary blockage. The current approaches for parenteral delivery include salt formation, solubilization using cosolvents, micellar solutions, complexation with cyclodexInt J Life Sci Pharma Res., Volume11., No 1 (January) 2020, pp P59-66trin and recently liposomes (23)

- **Pulmonary administration**

The drug nanosuspension can be nebulized using commercially available nebulizers. Disposition in the lungs can be controlled via the size distribution of the generated aerosol droplets. drug nanocrystals show an increased mucoadhesiveness, leading to a prolonged residence time at the mucosal surface of the lung 35. Hernandez-Trejo and cowotkers formulate physically stable nanosuspensions were formulated to deliver bupravaquone at the site of lung infection using nebulisation.(29,30).

- **Ocular administration**

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal flui ds. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high to nicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fulids . Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bio availability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflo w and outflow of lachrymal fluids. One example of a Nanosuspension intended for ophathamic controlled delivery was developed as a polymeric nanosuspension of ibuprofen. This nanosuspens ion is successfully prepared using Eudragit RS100 by a quasiemulsion and solvent diffusion met hod. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone e nhance rate, drug absorption and increase the duration of drug action.(16, 17)

- **Target Drug Delivery**

It is also possible to use nanosuspensions as guided drug delivery. Through integrating the drug into the mononuclear phagocytic process, the targeted drug delivery can be planned. Targeted delivery of drugs to macrophages may be used for anti-mycobacterial, fungal drugs if the intracellular pathogen remains. The further action plan for the targeted method of drug delivery is to use different surface coatings for active or passive targeting.Appropriate drug candidates, such as amphotericin B, can easily target pulmonary aspergillosis in the form of pulmonary nanosuspensions rather than stealth liposomes. Scholer demonstrated high concentrations of atovaquone nanosuspension in the brain, lungs, sera, liver and increased therapeutic efficacy against toxoplasma encephalitis in murine mold contaminated with toxoplasma gonidii.(29, 22)

Conclusion

Nanotechnology since to be to be novel , affordable and practical feasible approch . to address drug issues such low bioavailability linked with the delivery of hydrophobic and lipophilic drug .and doses that are poorly soluble in both aqueous and organic solution.Additionally, it modifies the drug's pharmacokinetics, enhancing both its safety and effectiveness. It can be demonstrated as a gift because it is simple to manufacture medications that are not very water soluble into nanosuspensions. Production methods like high-pressure blending and media grinding homogenization has been used well in large-scale manufacturing of nanodispersions. This technology can be used in conjunction with conventional dose forms like pellets, pills, capsules, and parenteral preparations are among their possible uses. Appealing characteristics, like enhanced bioadhesivity, faster dissolving rate, higher saturation solubility, and adaptability applications due to advancements in surface modification and post-production processing ease.

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