CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

http://doi.org/10.5281/zenodo.4119968

Available online at: http://www.iajps.com ***Review Article***

OVERVIEW OF FORMULATION AND DEVELOPMENT OF NANOSUSPENSION

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Abstract:

Nanosuspensions are important carriers to develop novel drug formulations. the drug research and development field, more or more new drug candidates has been found to be practically insoluble in aqueous solvents and many of them are simultaneously poorly soluble in a organic solvents Since nanosuspension drug delivery system (DDS) was firstly developed in 1994, nanosuspension DDS has attracted more & more attention as a formation solution for a poorly soluble drugs Nanosuspensions can be delivered by oral, parenteral, pulmonary or ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in theOcular inserts and mucoadhesive hydrogels. Currently, efforts are being directed to extending their applications in site-specific drug delivery. Nano refer to particles size range of 1–1000 nm. The reduction of drug particles into the submicron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. This review article describes the preparation methods, characterization, and applications of the nanosuspension.

Keyword: *- Nanosuspension, soluble, bioavailability, drug delivery system, formation*

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QR code

Please cite this article in press Mayuri K. Lonare et al, ***Overview Of Formulation And Development Of Nanosuspension****., Indo Am. J. P. Sci, 2020; 07(10).*

INTRODUCTION:

The pharmaceutical nanosuspension is defined as a very finely dispersed solid drug particles in an aqueous vehicle for either oral , topical use or parenteral , pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 or 600 nm. Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles and lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size (i.e increase in the surface area) leading to an increased dissolution rate and therefore improved bioavailability. Nano sized particles can increase solution velocity and saturation solubility because of the vapor 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. The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size innanosuspensions prevents the existence of different saturation solubilities or concentration gradients, consequently preventing the Ostwald ripening effect. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by the difference in dissolution pressure/saturation solubility between small or large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to a formation of a supersaturated solution around the large particles or consequently to drug crystallization & growth of the large particles[1] Nanosizing techniques are a important tools for improving the bioavailability of water insoluble drugs. Here, the rapid wet milling method was employed to prepare nanosuspensions: 4 types of stabilizers at 4 different concentrations were tested on 2 structurally different drug compounds: indomethacin & itraconazole. Photon correlation spectroscopy (PCS) results showed that the finest nanosuspensions were obtained when 80 wt% (to drug amount) pluronic F68 was the stabilizer for indomethacin and 60 wt% pluronic F127 for itraconazole. Compared to physical mixtures, dissolution rates of a nanosuspensions showed significant increases. The morphology of nanoparticles was observed by transmission electron microscopy (TEM). Crystalline state of drugs before and after milling was confirmed using differential scanning calorimetry (DSC) or X-ray powder diffraction (XRPD). The physical and chemical stabilities of the nanosuspensions after storage for 2 months at room temperature and at 4 °C were investigated using PCS, TEM and HPLC. No obvious changes in particle size and morphology and no chemical degradation of the drug ingredients were seen.[2] Solubility, as well as bioavailability, have found major critical hindrance that affects the fabrication of new pharmaceutical product especially if the drug belongs to BCS class II [3]

ADVANTAGES OF NANOSUSPENSION [4]

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting
- simple production method[5]
- Possibility to a incorporate nanosuspensions in various dosage formats such as a tablets, pellets, & capsules following standard manufacturing techniques. For example, ketoprofen nanosuspension has been a successfully transformed into pellets [6]
- lower fed/fasted variability [7]

Criteria for selection of drug for nanosuspensions [8]

Nanosuspension can be prepared for the API that is having either of the following characteristics:

a) Water insoluble but which are soluble in oil
b) (High logP) or API are insoluble in both water and oils
C) Drugs with a reduced tendency of the crystal to dissolve, regardless of a solvent
d)API with very large dose.

PREPARATION OF NANOSUSPENSION:

For the preparation of nanosuspensions, mostly two methods namely “Bottom up technology” and “Top down technology” are used, as shown in Figure 1.[9]

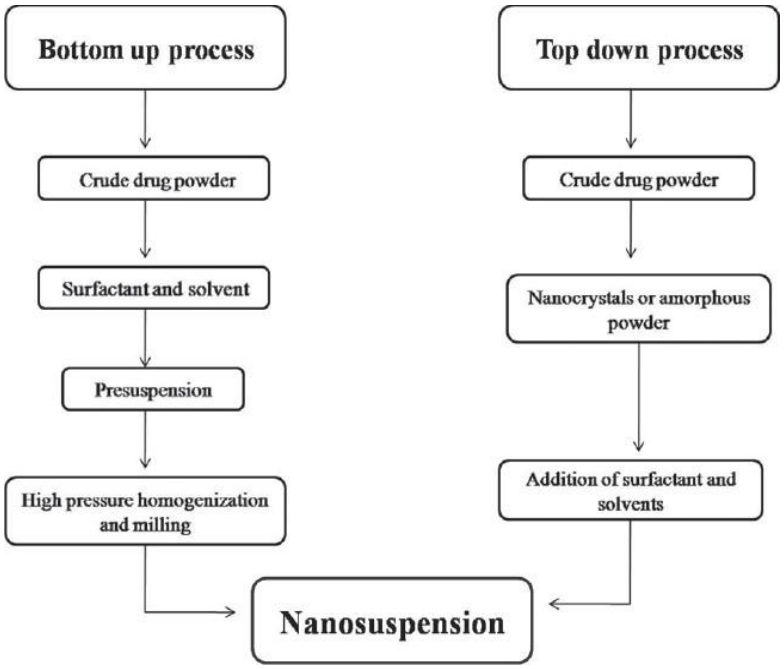

Figure 1:-

The top -down process follows disintegration approach from large particles, microparticles to a Nanosized particles [10].

Examples are:-

- High pressure homogenization
- Nanoedge
- Nanopure
- Media milling (Nanocrystals).

Bottom-up process is an assembly method forms nanoparticles from molecules [11].

Examples are:-

- Solvent-Antisolvent method / precipitation
- Super critical fluid process
- Emulsification Solvent evaporation technique
- Lipid emulsion/Micro-emulsion template. The principle techniques used in recent years for preparing nanosuspensions are

High pressure homogenization: -

It is most widely used method for preparing nanosuspensions of many poorly aqueous soluble drugs[12] This technique involve the following three steps: First, drug powders are dispersed in a stabilizer solution to form presuspension; after that, presuspension is the homogenized by high pressure homogenizer at the low pressure sometimes for premilling; and finally homogenized at a high pressure for 10 to 25 cycles until the nanosuspensions are formed with desired size.[4]

Homogenization in Aqueous Media (Dissocubes)

Dissocubes technology was developed by Muller in 1999. The instrument can be operated at pressure varying from 100 to 1 500 bars (2 800 – 21 300 psi) ,up to 2 000 bars with volume capacity of 40 ml (for laboratory scale). For preparation of the nanosuspension, it is essential to prepare a presuspension of the micronized drug in a surfactant solution using high-speed stirrer. According to a Bernoulli's Law, the flow volume of liquid in the closed system per cross section is constant. The reduction in diameter from 3 cm to 25 µm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this, water starts boiling at room temperature or forms gas bubbles, which implode when a suspension leaves the gap (called cavitation) or normal air pressure is reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogenizer, homogenization pressure. Preprocessing like micronization of drug and high-cost instruments increases the overall cost of dosage form. Various drugs like Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine Or Dexamethasone were prepared as nanosuspensions using this method.[13]

Homogenization in Nonaqueous Media (Nanopure)

Nanopure is suspension homogenized in water-free medium. It is “deep-freeze” homogenization where the drug suspensions in nonaqueous medium are homogenized at 0°C or sometimes below the freezing point. Because of a very high boiling point & low vapor pressure of the water, oils, & fatty acids, the

drop of static pressure is not enough to begin cavitation in a nanopure technology.[14]

Nanoedge

The basic principles of Nanoedge are same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size or better stability in the shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology. In this technique, a precipitated suspension is further homogenized, leading to a reduction in particle size and avoiding crystal growth. Precipitation is performed in a water using water-miscible solvents such as methanol, ethanol Or isopropanol. It is desirable to remove those solvents completely, although they can be tolerated to a certain extent in the formulation. For an effective production of nanosuspensions using the Nanoedge technology, an evaporation step can be included to provide a solvent-free modified starting material followed by highpressure homogenization.[15]

Nonojet :

It is also called as opposite stream technology, uses 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 during the process particle size is reduced. [16]

Media milling: Nanocrystal is a patent protected technology developed by Liversidge et al. In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. A major concern with this method is a residue of milling media remaining in the finished product could be problematic for administration. [17, 18,19]

Advantages

Simple technology

Low-cost process regarding the milling itself

Large-scale production possible to some extent (batch process).

Disadvantages

Potential erosion from a milling material leading to product contamination.

Duration of the process not being very production friendly.

Potential growth of germs in a 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. [20, 21,22,23]

Solvent and anti-solvent:

Precipitation method has been used for long years for the preparation of submicron particles. It is mainly used for the poorly soluble drugs. The first drug is dissolved in a suitable solvent. This solution is then mixed with the miscible antisolvent system in a presence of surfactants. Rapid addition of drug solution into the antisolvent leads to the sudden supersaturation of drug in the mixed solution forms ultrafine drug solids. Precipitation method involves two phases-nuclei formations or crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but the low growth rate is necessary. Both rates are depending on temperature. In this technique, the drug needs to be soluble in at least one solvent which is miscible with a nonsolvent.[24].

SUPERCRITICAL FLUID PROCESS

The particle size reduction was achieved more by the solubilization and nanosizing technologies through the super critical fluid process. Super critical fluids (SCF) are noncondensable dense fluids whose temperature, pressure are greater than its critical temperature (Tc) and critical pressure (Tp). This process allows the micronization of drug particles to submicron level. Recent advances in SCF process are to create nanoparticulate suspension of particle size of 5 to 2000nm in diameter [25] The low solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry

Emulsification-solvent evaporation technique:

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a nonsolvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer [26]

Lipid emulsion/microemulsion template:

Lipid emulsions as templates are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspension which is stabilized by surfactants. Another way to produce nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion. Moreover, microemulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable & isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of a surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension [17]. An example of this technique is a griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin & the sodium salt of taurodeoxycholate [27]

Formulation Consideration: -

Stabilizer

A main function of the stabilizer is to wet the drug particles thoroughly, and to prevent ostwald's ripening and agglomeration of Nanosuspensions in order to yield the physically stable formulation by providing steric or ionic barrier. The type or amount of stabilize has a pronounced effect on a physical stability & in vivo behavior of Nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosics, povidones, and lecithins.

Lecithin is a stabilizer of choice if one intends to develop the parentally acceptable and autoclavable nan suspension.[28]

Organic Solvent: -

Organic solvents are used in the formulation of Nanosuspension if emulsions or micro emulsions used as a template. The pharmaceutically acceptable less hazardous water miscible solvent, such as methanol, ethanol, chloroform, ispropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol, are preferent in the formulation over the conventional hazardous solvents, such as dichloromethane. [28, 29]

Co-Surfactants

The choice of co-surfactant is a critical when using micro emulsions to formulate Nanosuspensions. Since co-surfactants can greatly influence phase behaviour, a effect of co-surfactant on uptake of a internal phase for selected micro emulsion composition & on drug loading should be investigated. Although the literature described the use of bile salts or dipotassium glycyrrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be a safely used as co-surfactants in the formulation of microemulsions.[30]

Other additives

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant.

Post-Production Processing

Post-production processing of Nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when a best possible stabilizer is not able to a stabilize the Nanosuspension for a longer period of time & there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as a lyophilization and spray drying may be employed to produce a dry powder of nano-sized drug particles. Rational selection has to be made in these unit operations considering a drug properties and economic aspects. Generally, spray drying is more economical & convenient than lyophilization. The effect of post-production processing on the particle size of the nanosuspension and moisture content of dried nanosized drug should be given due consideration. [29 30]

- **Evaluation of nanosuspensions**

A) In-Vitro Evaluations 1. Particle size and size distribution

2. Particle charge (Zeta Potential)

3. Crystalline state and morphology

4. Saturation solubility and dissolution velocity B) In-Vivo Evaluation C) Evaluation for surface-modified Nanosuspensions

1.Surface hydrophilicity

2. Adhesion properties

3. Interaction with body proteins

A) In vitro Evaluation:

1.Mean particle size and size distribution:

The mean particle size and the width of particle size distribution called Polydispersity Index. Particle size and polydispersity index (PI) governs the saturation solubility, dissolution velocity and biological performance. Polydispersity Index & the particle size distribution can be determined by a photon correlation spectroscopy (PCS). A PI value of 0.1-0.25 indicates a fairly narrow size distribution, if PI value greater than 0.5 indicates a very broad distribution. The particle size distribution can also be determined by laser diffraction (LD) or Coulter counter multisizer. The coulter-counter gives the absolute no. of particle per volume unit for the different size classes and it is more efficient and appropriate technique than LD for quantifying the contamination of nanosuspensions by micro particulate drugs. Laser Diffractometry (LD) measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force microscope is used for visualization of particle shape [31]

2. Particle Charge (Zeta Potential)

The determination of a zeta potential of the nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension. The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension, a minimum zeta potential of 30 mV is required, whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of 20 mV is desirable [32]

3. Crystalline State and Particle Morphology

The assessment of a crystalline state and particle morphology together helps in understanding polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Additionally, when nanosuspensions are prepared drug particles in an amorphous state are likely to be a generated. Hence, it is essential to investigate the extent of amorphous drug nanoparticles generated during the production of nanosuspensions. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis [33, 34] and can be supplemented by differential scanning calorimetry [35]. In order to get an actual idea of particle morphology, scanning electron microscopy is preferred [33].

4. Saturation solubility and dissolution velocity:

The nan suspension increases 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 [36]

In vivo evaluation: -

The establishment of an in vitro/in vivo correlation and the monitoring of the in vivo performance of the drug are 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 a drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity or 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 [37-41]. Hence, suitable techniques have to be used in order to evaluate a 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 [42], whereas 2D PAGE [37] can be employed for the quantitative, qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals [43]

1. Surface hydrophilicy:

Surface hydrophilicy is considered as one of a important parameters affecting the in vivo organ distribution after i.v. injection. Adsorption of plasma proteins which is the akey factor for organ distribution and the interaction with cells before phagocytosis can be determined by a surface hydrophobicity. Surface hydrophobicity must be determined in the aqueous dispersion medium. The best technique used earlier was hydrophobic interaction chromatography (HIC), to determine the hydrophobicity of bacteria, & then shifted to the characterization of nanoparticulate drug carrier [44].

2. Adhesion properties:

Bio adhesive studies are conducted in Male Wistar rats. Generally, each rat receives single dose of 10 mg of nanoparticles which are combined with drug (approx.45 mg particles/kg body weight). Abdominal cavity of the animal cut opened, the stomach, small intestine and cecum is removed and rinsed with phosphate saline buffer. The stomach, small intestine or cecum is cut into 2cm length and digested in alkali for 24hr. Then added 2ml of a methanol & centrifuged. 1 ml sample of supernatant is assayed by spectroflurimetry to estimate a number of

nanoparticles of drug adhered to mucosa. If necessary standard curves can be prepared for calculation [44]

3. Interaction with body prote

In-vitro interaction between body protein -mucin and the nanoparticles can be studied by incubating nanoparticles and mucin (4:1 weight ratio) either in neutral or acidic medium. The incubation is processed at 370C temperature with stirring. The dispersion is then centrifuged, intest plate 150µl of each supernatant taken and added with 150µl BCA Protein Assay Reagent Kit. The plate is then incubated for 2 h at 37º C. By following this procedure absorbance of mucin is measured at λmax of the drug. Total amount of mucin absorbed to nanoparticles is determined by taking the difference between its initial concentration and the concentration in dispersion after incubation and centrifugation [44]

Pharmaceutical application of nanosuspension: -

Oral Drug Delivery

Poor solubility, incomplete dissolution, Or insufficient efficacy are the major problem of oral drug administration. Due to smaller particle size and much larger surface to volume ratio, oral nanosuspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs.[45] In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugs.[46] The nanosuspension have advantages like improved oral absorption, dose proportionality, and low intersubjective variability. By using standard manufacturing techniques, drug nanosuspensions can be simply incorporated into various dosage forms like tablets, capsules, and fast melts. A nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over a period of 24 hours.[47]

Parenteral Administration

In emergency cases such as cardiac arrest and anaphylactic shock parenteral administration is the first choice [48]. Parenteral administration includes administration of dosage forms by subcutaneous, i.v., intramuscular, and intra-arterial methods [49]. Advantages of this type of administration include avoidance of first-pass metabolism, reliable doses, and higher bioavailability. Control over the dose or rate allows more predictable pharmacodynamic and pharmacokinetic profiles after i.v. administration compared to oral administration [50]. Administered drug particles are required to be smaller than 5 µm to prevent blockage of capillaries [51]. The study on mice investigated tumour growth inhibition rate and showed that oridonin in the form of nanosuspension decreased considerably a volume and weight of the tumour. Oridonin in the form of nanosuspension raised the rate of tumour inhibition to 60.23% compared to 42.49% for the conventional form [52]. Nanosuspensions improve therapeutic efficiency and reduce the cost of therapy through improved dosing efficiency and smaller injection volumes.

Pulmonary drug delivery

Potentially, nanosuspensions can minimize many problems associated with the conventional dry powder inhalers or suspension type inhalation aerosols. Conventional aerosols have many limitations such as limited diffusion and dissolution in the alveolar fluids, rapid clearance and short residence time due to ciliary movement, deposition in pharynx and upper respiratory tract due to agglomeration and aggregation of the particles [53]. Nanoparticulate nature of a drug can offer quick onset of action due to rapid diffusion & dissolution in the alveolar fluids. Furthermore, it can sustain the release of drug because of its increased affinity to the mucosal surfaces. Antioxidant coenzyme Q10 nanosuspension stabilized with PEG32 stearate demonstrated maximum respirable fraction (70.6%) having smallest mass median aerodynamic diameter (3.02 µm) in comparison to nanosuspension stabilized with lecithin and Vitamin E TPGS. In vitro cellular toxicity carried out utilizing A549 human lung cells showed no noticeable cytotoxicity for the nanosuspension [54]. Due to the unique physicochemical characteristics, uniform and narrow size distribution of the nanoparticles, it is unlikely to cause uneven drug distribution and drug delivery in lung, when compared to microparticulate inhalation aerosols. The lung distribution rate of hydrophobic budenoside nanosuspension was found to be very high (872.9 ng/g) and exceptionally different ($p < 0.05$), when compared to coarse drug particles ($p < 0.01$) and micronized drug particles [55].

Conversion of nanosuspensions to solid oral and inhalable dosage forms lessens the physical instability associated with their liquid state and enables targeted drug delivery. Most frequently used solidification methods include spray and freeze-drying techniques. Redispersibility of solid nanocrystalline formulations is essential for potential oral and pulmonary clinical application [56]

Ocular Drug Delivery

Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids [57]. The protective barriers of the eye make drug delivery difficult without tissue damage. Poor drug absorption and penetration of drugs to intraocular tissues limit

the delivery of drugs. Use of nanoparticles and nanosuspensions for drug delivery to the intraocular tissues is being developed. One example is cross-linked polymer nanosuspensions of dexamethasone, which show enhanced anti-inflammatory activity in a model of rabbit eye irritation [58].

Target Drug Delivery:

Nanosuspensions can be used for targeted delivery as their surface properties andin vivo behavior can easily be altered by changing the stabilizer. Their versatility and ease of scale up enable the development of commercially viable nanosuspensions for targeted delivery especially in the brain targeting. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems [59].

CONCUSSION:

The Nanosuspension is solved poor bioavailability problem of hydrophobic drugs or drugs which are poorly soluble in aqueous and organic solution. Nanosuspension is not only solves the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy.Nanosuspension drug delivery has obtained great success in the preparation of insoluble drugs. The nanosuspension technology can confer a series of special characteristics to the drugs, such as the enhanced dissolution rate and saturation solubility. The Nonosuspension also increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing makes the nanosuspensions technology, a unique and commercially feasible method.

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