NANOSUSPENSION- A NOVEL APPROCH FOR DRUG DELIVERY SYSTEM: AN REVIEW

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ABSTRACT

The poor water solubility of drugs is serious problem for drug formulation. nanoscale systems for the drug delivery have gained much interest as a way to improve the solubility problems. The reduction of drug particles into the sub-micron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. Nanosuspensions are promising candidates that can be used for enhancing the dissolution rate of poorly water soluble drugs. Nanosuspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. Production of drugs as nanosuspensions has been developed for drug delivery systems as an oral formulation and non-oral administration. This review describes the methods of nanosuspension production, formulation, evaluation and applications in pharmaceutical drug delivery as well as the marketed products.

KEYWORDS

Poor water soluble drugs, Nanotechnology, Bioavailability, Drug delivery, Nanosuspension.

INTRODUCTION

More than 40% of the new chemical entities being generated through drug discovery programmes are poorly water-soluble compounds. Formulation of a poorly water soluble drug has always been a challenging problem confronted by the pharmaceutical scientist. The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition into gastrointestinal barrier. Micronization is used for Bcs class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility.[1,2]

Nanotechnology is likely to the revolutionize our lives, in general, and health scenario,in particular. It is emerging descipline that emcompasse an increasingly sophisticated ability to manipulate matter at the nanoscale (0.1 nm to 1000 nm) resulting in new material, product and device that demonstrate new and unusual behaviour. It is one of the most important research and development area in modern science. Apart from this nanomaterial, nanoparticle, and nanocomposite used for the biomedical purpose constitute a burgeoning new field called nanomedicine, which implies the medical application of nanotechnology and related research cause to the designing, testing and optimizing of the pharmaceutical formulations. Nanotechnology is an applicable aspect of a broader area of nano science which is one of the upcoming and highly challenging as well as rewarding key research area in the modern scientific set up. It is the science of small particle having unique properties, which change on altering the size of the particle.[3]

ADVANTAGES OF NANOSUSPENSION

- Decreased particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, area under plasma versus time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects.

- Nanosuspensions can be used for compounds that are water insoluble and which are soluble in oil. However, Nanosuspensions can be used in contrast with lipidic systems, successfully formulate compounds that are insoluble in both water and oils.
- the Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of drug and thereby enhancing its absorption.
- A pronounced advantage of Nanosuspension is that there are many administration routes for Nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.
- Nanosuspension of nanoparticles (NPs) offers various advantages over conventional opthalmic dosage forms, including reduction in the amount of dose, maintenance of drug release over a prolonged period of time, reduction in systemic toxicity of drug, improved drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, suitability for poorly hydrophilic drugs and smaller particles are better tolerated by patients than larger particles, therefore nanoparticles may represent auspicious drug carriers for ophthalmic applications. Nanosuspension has low incidence of side effects by the excipients.
- Nanosuspensions overcome delivery problems for the compounds by removing the need to dissolve them, and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.
- Enhanced resistance to hydrolysis and oxidation, increased physical stability to settling
- Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use. Finally, Nanosuspensions can provide the passive targeting.[4,5]

NEED OF NANOSUSPENSION FOR BIOAVAILABILITY ENHANCEMENT

In nanosuspension technology, the drug is maintained in the required crystalline form with reduced particle size, leading to an enhanced dissolution rate and therefore improved bioavailability. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution speed. Nano sized particles can increase solutions speed and saturation solubility because of the vapor pressure effect. In addition; the diffusional distance on the surface of drug nanoparticles is reduce, thus leading to an increased concentration gradient. enhance in surface area and concentration gradient lead to a much more pronounced increase in the dissolution speed as compared to a micronized product. Another possible explanation for the increased the saturation solubility is the creation of high energy surfaces when disrupting the more or less ideal drug microcrystals to nanoparticles. The stability of the particles obtained in the nanosuspension is attributed to their similar particle size which is created by various manufacturing processes. The absence of particles with large differences in their sizes in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients; similarly, preventing the Oswald ripening effect. Ostwald ripening is responsible for crystal growth as well as subsequently formation of microparticles.[6,7]

PREPARATION METHODS OF NANO- SUSPENSION: For the preparation of nanosuspensions, mostly two methods used namely "Bottom up technology" and "Top down technology" as shown in Figure 1.[17]

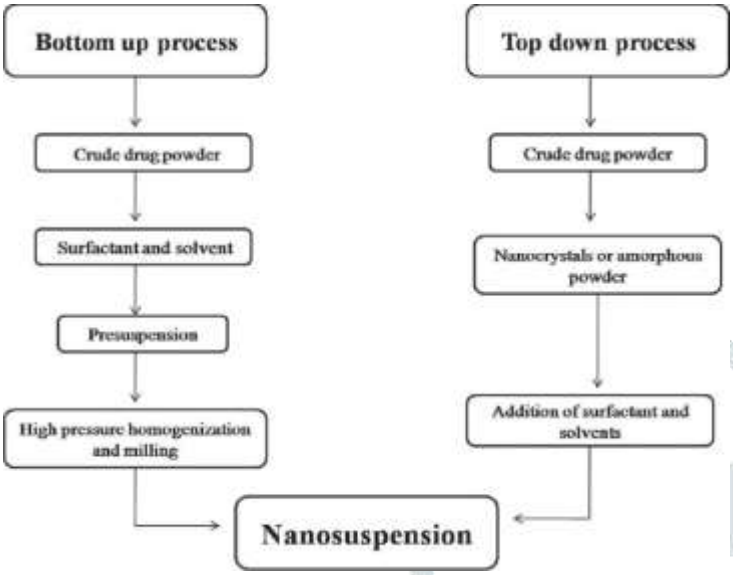

Figure1: Approaches for preparation of nanosuspension

BOTTOM UP TECHNIQUES:

It is the technique in which the Nano size is obtained by increasing the size of particles from molecular range to Nano range[8]. The most used methods of precipitation ('Hydrosol') are called Bottom Up technology. Using a precipitation technique, the drug is soluble in an organic solvent and this solution is mixed with a miscible anti-solvent. In the water-solvent mixtures, the solubility is low and the drug precipitates. Advantage of this method is the use of simple and lowcost equipment's, where limitations are as follows: the drug needs to be soluble in at least one solvent and the solvent needs to be miscible with non-solvent and moreover, it is not applicable such drugs, which are poorly soluble in both aqueous and non-aqueous media.

PRECIPITATION METHOD

Precipitation method is a general method used to prepare submicron particles of poorly soluble drugs.[10,11] In this method, drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size.[12]

TOP DOWN TECHNIQUES

High pressure homogenization (disso cubes): Disso Cubes are engineered using piston- gap-type highpressure homogenizers9. High pressure homogenization has been used to prepare nanosuspension of many poorly water-soluble drugs. Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The instrument can be operated at pressure varying from 100-1500 bars with volume capacity of 40 ml. The concern with this method is the need for small sample particles before loading and the fact that

many cycles of homogenization are required. Before subjecting the drug to the homogenization process, it is essential to form a pre-suspension of the micronized drug in a surfactant solution using high-speed stirrers. During the homogenization process, the drug suspension is pressed through the homogenization gap in order to achieve nano-sizing of the drug.The top down technologies include

a) Media milling

b) High pressure homogenization

MEDIA MILLING

Nanosuspensions are produced by using the thigh-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particles the size reduction. The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. Planetary ball mills (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany) is one example of an equipment that can be used to achieve a grind size below 0.1 µm. A Nanosuspension of Zn-Insulin with a mean particle size of 150 nm was prepared using the wet milling method . The major drawbacks of this technology include the erosion of balls or pearls that can leave residues as contaminants in the final product, degradation of the thermolabile drugs due to heat generated during the process and the presence of relatively high proportions of particles ≥5 µm.[13,14]

HIGH PRESSURE HOMOGENIZATION

High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs15. In high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the substance microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required. Dissocubes technology is an example of this nanotechnology . Müller using a piston-gap-type high pressure homogenizer, which was recently released as a patent owned by SkyePharm16. Other technologies and patents which are based on the homogenization processes.

NANOPURE

Nanopures are suspensions homogenized in water-free media or water mixtures. In the Dissocubes technology, the cavitation is determining factor of the process. But, in contrast to water, oils and oily fatty acids have very low vapour pressure as well as high boiling point. Hence, the drop of static pressure will not be sufficient enough to initiate the cavitation. Patents covering disintegration of polymeric material by the high- pressure homogenization mention that higher temperatures of about 800C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 00C or even below the freezing point and hence are called as"deep-freeze" homogenization. The results obtained were comparable to Dissocubes and hence can be used effectively for thermolabile substances at the milder conditions..[18,19]

NANOEDGE

The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques are results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and longterm stability, can be resolved using the Nanoedge technology. In this technique, the precipitated suspension is further homogenized; leading to reduction in particle size and preventing crystal growth. Precipitation is performed in water using water-soluble solvents such as methanol, ethanol and isopropanol. It is desirable to remove those solvents completely, while 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 high-pressure homogenization.[20]

EMULSION DIFFUSION METHOD

Apart from the use of emulsion as drug delivering vehicle they can also be used as templates to produce Nanosuspension. The use of emulsions as templates is applicable for those drugs that are soluble in volatile organic solvent partially water-miscile solvent. Such solvents can be used as the dispersed phase of the emulsion. An organic solvents or mixtures of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants with stirring to form an emulsion. The obtained emulsion was more homogenized by high pressure homogenization. After homogenization cycles the emulsion was diluted with water, homogenized by homogenizer to diffuse the organic solvent and convert the droplets into solid particles. Since one particle is formed in each emulsion droplet, it is possible to control particle size of the Nanosuspension by controlling the size of the emulsion optimizing the surfactant composition enhance the intake of organic phase and ultimately the drug loading in the emulsion. Originally methanol, ethanol, ethyl acetate chloroform are used as a organic solvents.[19,20]

MICRO EMULSION TEMPLATE

This technique attend 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 method makes use of partially water-soluble solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phases instead of hazardous solvents.[20,22]

SUPERCRITICAL FLUID METHOD

Supercritical fluid technology can be used to produce the nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and precipitation with compressed anti-solvent process (PCA).The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to the loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. Young et al. prepared cyclosporine nanoparticles in the size range 400-700 nm using this process. In the PCA method, the drug solution is atomized into the chamber containing compressed CO . As the solvent was removed, the solution gets supersaturated and thus precipitates as fine crystals. The supercritical anti- solvent process uses a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is introduced into the supercritical fluid and the solvent gets extracted by the supercritical fluid and the drug solution gets supersaturated. The drug is then precipitated as fine crystals. Nanoparticles of griseofulvin, a drug with poor solubility, were prepared by Chattopadhyay et al. using this method.[18,22]

MELT EMULSIFICATION METHOD

In this method drug is dispersed into the aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and temperature of emulsion was maintained above the melting point of the drug. The emulsion was then cooled down slowly to room temperature or on an icebath.[21,22]

DRY CO-GRINDING

Recently, Nanosuspensions can be obtained by dry milling technique.it is use in preparing stable Nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used.[22,23]

FORMULATION OF NANOSUSPENSION [24,25]

Stabilizer: The main function of a stabilizer is to wet the drug particles , and to prevent ostwald's ripening and agglomeration of Nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilizer has a pronounced effect on the physical stability as well as in vivo behavior of nanosuspension. Stabilizers that have been used for poloxomers, polysorbate, cellulosics, povidones, and lecithins. Lecithin is the stabilizer of choice if one intends to develop parentally acceptable and autoclavable nanosuspens**.**

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

Co-Surfactants: The choice of co-surfactant is critical when using micro emulsions to formulate Nanosuspensions. Since co-surfactants can greatly modify phase behavior, the effect of co-surfactant on uptake of the internal phase for selected micro emulsion composition as well as on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as cosurfactants, various solubilizers, like Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of nanosuspensions.

Other additives: According to the requirement of the route of administration and the properties of the drug moiety, nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant.

PHARMACEUTICAL APPLICATION OF NANOSUSPENSION

By using postproduction processing, nanosuspensions are prepared into various dosage forms. Nanosuspension enhances es dissolution rate and absorption of drug due to smaller particle size and larger surface area.

Oral Drug Delivery

Poor solubility, incomplete dissolution, and insufficient efficacy are the major issues 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.[27]In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugs.[27] The nanosuspension have advantages like improved oral absorption, dose proportionality, and low intersubject variability. By using standard manufacturing techniques, drug nanosuspensions can be simply incorporated into the various dosage forms like tablets, capsules. The nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over the period of 24 hours.[28]

Parental Drug Delivery

The present approaches for parental delivery involved micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have the limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc. To solve above problems, the nanosuspension technology is used. Nanosuspensions are administered through various parental routes like intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions enhance the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden.[29] Clofazimine nanosuspension showed an improvement in stability and efficacy above the liposomal clofazimine in Mycobacterium avium-infected female mice.[30] Rainbow et al. showed that intravenous nanosuspension of itraconazole increased efficacy of antifungal activity in rats relative to the solution formulation.[31]

Pulmonary Drug Delivery

For pulmonary delivery, nanosuspensions can be nebulized through mechanical or the ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid has been successfully prepared in the form of nanosuspension for pulmonary delivery.[32]Aqueous suspensions of the drug can be easily nebulized and given by pulmonary route as the particle size is very small. Different types of nebulizers are available for the administration of liquid dosage forms. Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc.[33]

Ocular Drug Delivery

Nanosuspensions are used in ocular delivery of the drugs for sustained release of drug. Experiment showed high bioavailability of drug in aqueous humor of rabbit eye. Thus, nanosuspension formulation offers a promising way of improving the shelf-life and bioavailability of drug after ophthalmic application.[34]

Targeted Drug Delivery

Nanosuspensions are suitable for targeting particular organ because of their surface properties. Along with this, it is easy to alter in vivo behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system and which allows region-specific delivery. This can be used for targeting the antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens go on intracellularly. Kayser formulated an aphidicolin nanosuspension that improved drug targeting to macrophages which Leishmania infected. He stated that the drug in the form of nanosuspension.[35]

CONCLUSION

Drugs with poor solubility and low bioavailability are called 'brick dust' candidates once abandoned from formulation development work can be rescued with nanosuspensions technology. A nanosuspension not only solve the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. Nanosuspension technology can be combined with traditional dosage forms such as tablets, capsules, pellets, and can be used for parenteral products. To take advantage of nanosuspension drug delivery, simple formation technologies and variety applications, nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future.

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