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Nanosuspension for enhancement of Oral Bioavailability of poorly water soluble Drugs

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ABSTRACT: Modern drug discovery techniques continue to fill drug development pipelines with a high number of poorly soluble New Chemical Entities (NCEs). Most of the poorly water soluble drugs are rejected because they are not converted into a suitable dosage form which is usually a burden for the R&D pharmaceutical companies. Therefore there is tremendous need of research to overcome the challenges in bringing poorly soluble drugs to the market. Nanosuspension systems can be used as an extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. They are defined as the submicron colloidal dispersions of pharmaceutical active ingredient particles in a liquid phase, size below 1µm, without any matrix material which are stabilized by surfactants and polymers. Nanosuspensions are often prepared by commercially available methods such as high pressure homogenization, media milling, emulsification, melt emulsification and supercritical fluid techniques. Solidification and surface modification methods are post-processing techniques used to add particular properties for advanced therapies. Nano-suspensions can be delivered by oral, parenteral, pulmonary routes and also used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels. They not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus, there is growing need to expand the array of nanosuspensions systems to deliver a wide variety of drugs and produce stable formulations which can be easily manufactured, cost-effective, safe and efficacious.

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INTRODUCTIONS:

Many of the newly developed drugs are poorly soluble and they create major problems during formulation and shows poor bioavailability. The problem is even more complex for drugs which belong to BCS Class II category as in such formulations parameters that play a crucial role in the successful formulation of drugs are aqueous solubility, stability at ambient temperature and humidity, photostability, compatibility

with solvent and excipient. Among this aqueous solubilit y became a hurdle for the formulation of new molecular entities [1]. Earlier micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility. There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization, solubilization using co-solvents, salt form, surfactant dispersions, precipitation technique, and oily solution [2]. Other techniques are like liposomes, emulsions, microemulsion, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they lack in universal applicability to all drugs. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents [3].

To overcome these problems nanotechnology is used to improve the solubility as well as bioavailability of poorly soluble drugs. Nanotechnology is the study of extremely small structures. The prefix “nano” is a Greek word which means “dwarf”. The word “nano” means very small or miniature size. Nanotechnology is the treatment of individual atoms, molecules, or compounds into structures to produce materials and devices with special properties. Nanotechnology involve work from top down i.e. reducing the size of large structures to smallest structure e.g. photonics applications in nano electronics and nano engineering, top-down or the bottom up, which involves changing individual atoms and molecules into nanostructures and more closely resembles chemistry biology [4]. Nanotechnology deals with materials in the size of 0.1 to 100 nm; however it is also inherent that these materials should display different properties such as electrical conductance chemical reactivity, magnetism, optical effects and physical strength, from bulk materials as a result of their small size. Nanotechnology offers drugs in the nanometer size range which enhances the performance in a variety of dosage forms [5].

Various advantages of nano-sizing are decreased fed/fasted variability, decreased patient to patient variability, enhanced solubility, increased oral bioavailability, increased rate of dissolution, increased surface area, less amount of dose required and more rapid onset of therapeutic action. Nansuspension is favoured for compounds that are insoluble in water but are soluble in oil, with high log P value, high melting point and high doses rapid onset of therapeutic action. high log P value, high melting point and high doses [6].

Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs such as naproxen clofazomine, bupravaquone, nimesulide, mitotane, amphotericin B, omeprazole and nifedipine are formulated as nanosuspension [7].

NANOSUSPENSIONS:

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility [8]. The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles. Nanosuspension have disclosed the problems associated with the delivery of poorly water soluble and poorly water and lipid soluble drugs and are unequalled because of their simplicity and rewards they confer over other strategies for enhancing solubility [9].

Potential Benefits of Nanosuspension Technology for Poorly Soluble Drugs

- Reduced 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 [10].
- It can be used for compounds that are water insoluble but which are soluble in oil. On the other hand, Nanosuspensions can be used in contrast with lipidic systems, successfully formulate compounds that are insoluble in both water and oils [11].
- Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the 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 ocular 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, enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, suitability for poorly water-soluble drugs and smaller particles are better tolerated by patients than larger particles, therefore nanoparticles may represent auspicious drug carriers for ophthalmic applications [12].

- Nanosuspension has low incidence of side effects by the excipients.
- Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them, and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability [13].
- Increased 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 [14].

PREPARATION OF NANOSUSPENSION:

There are two methods for preparation of nanosuspension. They are Bottom up technology and Top down technologies shown in Fig 1. For the production of nanoparticles in Bottom up technology the drug is dissolved in a solvent, which is then added to non-solvent that causes precipitation of the fine drug particles. The Top Down Technologies are the disintegration methods and are preferred over the precipitation methods. The Top Down Technologies include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege) [15].

Bottom-Up Technology:

The term “Bottom-up technology” means that one starts from the molecular level, and goes via molecular association to the formation of a solid particle. That means that we are discussing classical precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a non solvent or changing the temperature or a combination of both. Precipitation is a classical technique in pharmaceutical chemistry and technology [16].

Top-Down Technology:

The top down technologies include a) Media milling b) High pressure homogenization.

Media Milling:

Nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. 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 particle size reduction [17]. 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 [18].

High Pressure Homogenization:

Dissocubes:

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. In this case, the suspension of the drug is made to pass through a small orifice that result in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles [19]. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the center and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean particle size and the required homogeneity [20].

Nanopure:

Nanopure is suspensions homogenized in water-free media or water mixtures. In the Dissocubes technology, the cavitation is the determining factor of the process. But, in contrast to water, oils and oily fatty acids have very low vapour pressure and a high boiling point. Hence, the drop of static pressure will not be sufficient enough to initiate cavitation. Patents covering disintegration of polymeric material by high- pressure

homogenization mention that higher temperatures of about 80 °C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 0 °C or even below the freezing point and hence are called "deep-freeze" homogenization [21].

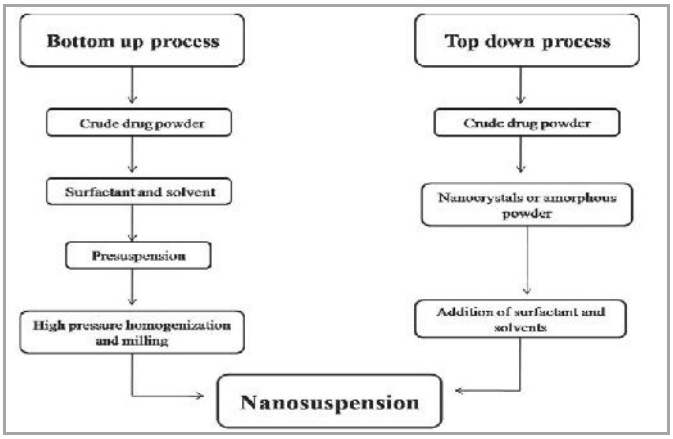

Fig 1. Methods for nanosuspension preparation.

Nanoedge™:

The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a 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, the precipitated suspension is further homogenized; leading to reduction in particle size and avoiding crystal growth [22]. Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and 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 high-pressure homogenization [23].

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 either volatile organic solvent or partially water miscile solvent. Such solvents can be used as the dispersed phase of the emulsion. An organic solvent or mixture 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 further 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 the particle size of the Nanosuspension by controlling the size of the emulsion optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion [24].

Nanojet technology:

This technique, called opposite stream or nanojet technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Equipment using this principle includes the M110L and M110S microfluidizers (Microfluidics). Dearn prepared nanosuspensions of atovaquone using the micro fluidization process. The major disadvantage of this technique is the high number of passes through the micro fluidizer and that the product obtained contains a relatively larger fraction of microparticles [25].

Melt emulsification method:

In this method drug is dispersed in 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 the temperature of emulsion was maintained above the melting point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice-bath. The main advantage of this method (melt emulsification technique) relative to the solvent diffusion method is total avoidance of organic solvents during the production process. Nanosuspension of ibuprofen was prepared by this meth od. Formulating ibuprofen nanosuspension by melt emulsification method show greater dissolution rate than formulating by solvent diffusion method [27].

Supercritical fluid method:

The organic solvents used in the preparation of conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods are hazardous to

environment and physiological systems. To rectify the problem occurred through the conventional method supercritical fluid technology has been investigated for the preparation of biodegradable micro and nanoparticles, because of the supercritical fluids are environmentally safe. The most common techniques using supercritical fluids are supercritical anti-solvent (SAS), precipitation with compressed anti-solvent process (PCS) and rapid expansion of supercritical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the supercritical fluid (SC CO_2), to dissolve the solute to be micronized; at the process condition, because the solute is insoluble in the supercritical fluid, the extract of the liqui d solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles. Dexamethasone phosphate drug nanoparticles (for microencapsulation) and griseofulvin nanoparticles were prepared by using S AS method. RESS differs from the SAS process in that its solute is dissolved in a supercritical fluid (such as supercritical methanol) and then the solution is rapidly expanded through a small nozzle into a region lower pressure, thus the solvent power of supercritical fluid dramatically decreases and solute eventually precipitates. This method is used for the production of polymeric nanoparticles [28,29].

Dry co-grinding:

Since many years, nanosuspensions are prepared through wet grinding processes by using pearl ball mill. Nowadays, nanosuspensions can be prepared by dry milling methods. Stable nanosuspensions are prepared by using dry grinding of poorly soluble drug with soluble polymers and copolymers after dispersing in liquid medium. Itoh *et al*. have described the colloidal particles formation of many poorly water-soluble drugs like nifedipine, griseofulvin, and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizer [26].

FORMULATION CONSIDERATION:

Stabilizer:

The main function of a stabilizer are to wet the drug particles thoroughly, and to prevent ostwald's ripening and agglomeration of nanosusension in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilize has a pronounced effect on the physical stability and in vivo behaviour of nanosuspesion. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosics, povidones, and lecithins. Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autclaveble nanosuspension [27].

Organic solvent:

These are used in the formulation of nanosuspension if emulsions or microemulsions are used as a template. The pharmaceutically acceptable less hazardou s 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.

Other additives:

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route administration or the properties of the drug moiety [28].

CHARACTERIZATION OF NANOSUSPENSIONS:

Nanosuspensions are characterized in similar ways as those used for conventional suspensions such as appearance, color, odor, assay, related impurities, etc. Apart from the aforementioned parameters, the nanosuspensions should be evaluated for their particle size, zeta potential, crystalline status, dissolution studies and *in vivo* studies.

Color, Odor, Taste:

These characteristics are especially important in orally administered formulation. Variations in taste, especially of active constituents, can offered be attributed to changes in particle size, crystal habit and subsequent particle dissolution. Changes in color, odor and taste can also indicate chemical instability [29].

Mean Particle Size and Particle Size Distribution:

The mean particle size and distribution affects saturation solubility, dissolution rate, physical stability, and *in vivo* performance of nanosuspensions. The particle size distribution and its range named polydispersity index (PI) can be determined by laser diffraction (LD), photon correlation spectroscopy, microscope, and coulter counter PI gives the physical stability of nanosuspensions and should be as lower as possible for

the long-time stability of nanosuspensions. A PI value of 0.1 to 0.25 shows a fairly narrow size distribution and PI value more than 0.5 indicates a very broad distribution. LD can detect and quantify the drug microparticles during the production process. It also gives a volume size distribution and can be used to measure particles ranging from 0.05 up to 2000 µm. The coulter counter gives the absolute number of particles per volume for the different size classes. It is more efficient and suitable than LD to quantify the contamination of nanosuspensions [30].

Zeta potential:

Zeta potential is an indication of the stability of the suspension. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient [30].

Crystalline State and Particle Morphology:

Polymorphic or morphological changes of nanosized particles can be checked by assessing the crystalline state and particle morphology. As nanosuspension requires high-pressure homogenization, change in crystalline structure of formulation occurs which may be converted to either amorphous or other polymorphic forms. Alteration in the solid state of the drug particles and the extent of the amorphous portion is determined by X-ray diffraction analysis and supplemented by differential scanning calorimetry analysis [30].

Density:

Specific gravity or density of the formulation is an important parameter. A decrease in density often indicates the presence of entrapped air within the structure of the formulation. Density measurements at a given temperature should be made using well mixed, uniform formulation; precision hydrometer facilitate such measurements [30].

Droplet Size:

The droplet size distribution of micro emulsion vesicles can be determined by either light scattering technique or electron microscopy. Dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm [30].

Viscosity Measurement:

The viscosity of lipid based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37 °C by a thermo bath and the samples, for the measurement are to be immersed in it [31].

Dissolution velocity and saturation solubility:

Nanosuspensions have an important advantage, that it can increase the dissolution velocity 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. It has been reported an increase in the dissolution pressure as well as dissolution velocity with a reduction in the particle size to the nanometer range. Size reduction leads to an increase in the dissolution pressure. An increase in solubility that occurs with relatively low particle size reduction may be mainly due to a change in the surface tension leading to increased saturation solubility. Muller explained that the energy introduced during the particle size reduction process leads to an increase in the surface tension and an associated increase in the dissolution pressure [32].

***In-Vivo* Biological Performance:**

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 i.e. surface hydrophobicity and interactions with plasma proteins. 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 to evaluate the surface properties and protein interactions. 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 [33].

APPLICATION OF NANOSUSPENSION:

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

Oral drug delivery:

Oral drug delivery is the most widely preferred route of administration of drugs. But, some drugs possess the problem of limited bioavailability due to poor solubility and absorption which ultimately reduces its efficacy. In such cases, Nanosuspension can solve the problem as it helps in improving the dissolution rate and absorption due to increased surface area and enhanced adhesiveness.

Nanosuspension can lead to increased mucoadhesion which can increase gastrointestinal transit time and lead to increased bioavailability. The enhancement in oral bioavailability can be attributed to increased surface area, saturation solubility and the adhesiveness of the drug Nanosuspension. Taste masking of particulate system is also easily possible [34].

Parental Drug Delivery:

The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc.

To solve the above problems, the nanosuspension technology is used. Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden. Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal clofazimine in *Mycobacterium avium* infected female mice. Rainbow *et al*. showed that intravenous nanosuspension of itraconazole enhanced efficacy of antifungal activity in rats relative to the solution formulation [35].

Ocular delivery:

Nanosuspension can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. Nanosuspensions represent an ideal approach for ocular delivery of hydrophobic drugs due to their inherent ability to improve saturation solubility of drugs [34].

Pulmonary:

Nanosuspensions can be advantageous for delivering drugs that exhibit poor solubility in pulmonary secretion. Currently available approaches for pulmonary delivery such as aerosols or dry powder inhalers possess certain disadvantages such as limited diffusion at required site, less residence time etc, which can be overcome by Nanosuspensions. Fluticasone and budesonide have been successfully formulated as Nanosuspension for pulmonary Delivery [35].

Dermal:

The nanocrystalline form possesses increased saturation solubility resulting in enhanced diffusion of the drug into the skin. Nanocrystals also exhibit various properties such as increased penetration into a membrane, enhanced permeation and bioadhesiveness which could be very useful for dermal application [35].

Targeted Drug Delivery:

Nanosuspensions are suitable for targeting particular organs 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 which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly. Kayser formulated an aphidicolin nanosuspension that improved the drug targeting to macrophages which were Leishmania infected. He stated that the drug in the form of nanosuspension had EC_{50} of 0.003 µg/ml, whereas the conventional form had 0.16 µg/ml [36].

CONCLUSION:

Developing a customized formulation for poorly soluble drugs requires achieving the best balance of dose, polymer, and API loading to allow the final drug product to have the required stability, manufacturability and performance. The ultimate goal is to achieve a robust manufacturing process that takes into account disintegration and dissolution of the oral dosage form, hardness, content uniformity, waste, and productivity thus nanosuspensions was found to be a distinctive and commercially feasible approach to solve the problems of hydrophobic drug such as poor solubility and poor bioavailability. For large-scale production of nanosuspensions, media milling and high-pressure homogenization technology have been successfully used. Striking characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of postproduction processing,

have widened the applications of nanosuspensions for various routes of administration.

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