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Research Article

NANOSUSPENSION: A RECENT APPROACH FOR NANO DRUG DELIVERY SYSTEM

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ABSTRACT

During the last two decades one of the most important problems in drug formulations has been low aqueous solubility of new molecules. However, numerous techniques, such as milling, co-solvent solubilization and solid dispersion have been used conventionally for enhancement of aqueous solubility and solubility rate. Recently, nanoparticle engineering processes have been developed and reported for pharmaceutical applications to increase the dissolution rate of low-soluble drugs which in turn may leads to substantial increases in bioavailability. Rapid strides have been made in the delivery of nanosuspensions by parentral, peroral, ocular and pulmonary routes. Efforts are being made to extend their applications in site-specific drug delivery. In this review we covered various aspects of nanosuspension characterization and various factors involved in formulation procedures, effect of their characteristics and their applicability in delivery of drug molecules at nanoscale. This nano drug delivery system helps in the development of new pharmaceutical technologies and methods for targeted action of various drugs.

Keywords: Nanosuspensions, Solubility, Bioavailability, Nanoscale technology.

INTRODUCTION

Pharmaceutical industries are constantly seeking new approaches in order to obtain an adequate oral bioavailability. Recently, the formulation of drugs as nanoscale systems (which have a size below 1µm) has rapidly evolved as a new and novel drug delivery system[1]. The major characteristic of these systems is the rapid dissolution rate, which enhance bioavailability after oral administration[2]. Nanosuspensions are sub-micron colloidal dispersions of pure drug particles in an outer liquid phase. Nanoparticle engineering enables poorly soluble drugs to be formulated as nanosuspensions alone, or with a combination of pharmaceutical excipients[3]. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parentral and pulmonary administration, with reduced particle size, leading to an increased 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 velocity. Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect[4]. Current techniques used to obtain drug nanoparticles can be divided into two categories:

Bottom up techniques

The techniques in which the nano size is obtained by increasing the the size of particles from molecular range to nano range.

Top down techniques

The techniques in which nano size range of particles is obtained by reduction in size of larger particles.

Although, all marketed products, currently are produced by so-called top-down techniques, in which the nanoparticles are obtained through size reduction into the submicron-range, bottom-up techniques and especially controlled precipitation method, are methods of interest for nanozation of poorly soluble drugs. In this method without any harsh conditions and only with simple equipments one could reduce the particle size to few hundred nanometers range. Therefore, whatever method which is used for the production of nanosuspensions, a careful evaluation of the type and concentration of the stabilizer is a critical stage for the successful production of nanosuspensions. Both polymeric and surfactant stabilizers can be used for this purpose[5].

In past, drug carriers have represented the only group of colloidal drug administration systems. In last years, a fundamentally different group of dispersions i.e. nanosuspensions (drug nanoparticles) are also under development. The key difference from conventional formulations of suspensions is that the particle size distribution of the solid particles in nanosuspensions is usually less than 1 mm, with an average particle size range between 200–600 nm. The increasing frequency of poorly water soluble new chemical entities exhibiting therapeutic activity is of major concern to the development of new formulations in pharmaceutical industry which leads to low turnout in the development of new molecular entities as drug formulations is poor solubility and poor permeability of the lead compounds. Micronization of poorly soluble drugs increases the dissolution rate of the drug due to the increase in surface area, but does not change the saturation solubility. At very low saturation solubility, the achieved increase in dissolution rate does not lead to a sufficiently high bioavailability. The next phase in development process was transformation of a micronized drug powder into drug nanoparticles. In nanosuspensions, the overall bioavailability is improved by an increase in surface area and saturation solubility via particle size reduction[6]. This system cannot be achieved by the conventional milling techniques.

The major advantages of nanosuspension technology are:

- Its general applicability to most drugs and its simplicity.
- Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.
- Rapid dissolution and tissue targeting can be achieved by IV route of administration.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Higher bioavailability and more consistent dosing in case of ocular administration and inhalation delivery.
- Drugs with high log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs[7].
- Improvement in biological performance due to high dissolution rate and saturation solubility of the drug.
- Ease of manufacture.
- Long term physical stability.
- Nanosuspensions can be incorporated in tablets, pellets, hydrogels and suppositories are suitable for various routes of administration.
- Versatility[8].

Table 1: Potential benefits of nanosuspensions technology over other conventional formulations technologies for poorly soluble drugs[9]

Route of Administration	Advantages Offered
Oral	Rapid onset Reduced fed/fasted ratio Improved bioavailability
Intravenous	Rapid dissolution Tissue targeting Prolonged retention time in systemic circulation
Ocular	High bioavailability More consistent dosing Lesser irritation
Inhalation	High bioavailability More consistent dosing
Subcutaneous/ intramuscular	High bioavailability Rapid onset of action Reduction in tissue irritation

Interesting special features of nanosuspensions are:

- Increase in saturation solubility and consequently an increase in the dissolution rate of the drug.
- Increase in adhesive nature, thus resulting in enhanced bioavailability.
- Increasing the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility.
- Absence of Ostwald ripening, producing physical long term stability as an aqueous suspension.
- Possibility of surface-modification of nanosuspensions for site specific delivery.
- Possibility of large-scale production, the pre-requisite for the introduction of a delivery system to the market.

Techniques to prepare Nanosuspensions

The principle techniques used in recent years for preparing nanosuspensions can be classified into four basic methods:

a) Wet milling
b) Homogenization
c) Emulsification-solvent evaporation
d) Supercritical fluid method

Table 2: Various formulation excipients along with their functions

Excipients	Function	Example
Stabilizers	Wet the drug particles thoroughly, prevent Ostwald's ripening and agglomeration of nanosuspensions, providing steric or ionic barrier	Lecithins, Poloxomers, Polysorbate, Cellulosics, Povidones
Co-surfactants	Influence phase behavior when micro emulsions are used to formulate nanosuspensions	Bile salts, Dipotassium Glycerrhizinate, Transcutol, Glycofurol, Ethanol, Isopropanol,
Organic solvent	Pharmaceutically acceptable less hazardous solvent for preparation of formulation.	Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Ethyl formate, Butyl lactate, Triacetin, Propylene carbonate, Benzyl alcohol.
Other additives	According to the requirement of the route of administration or the properties of the drug moiety	Buffers, Salts, Polyols, Osmogens, Cryoprotectant

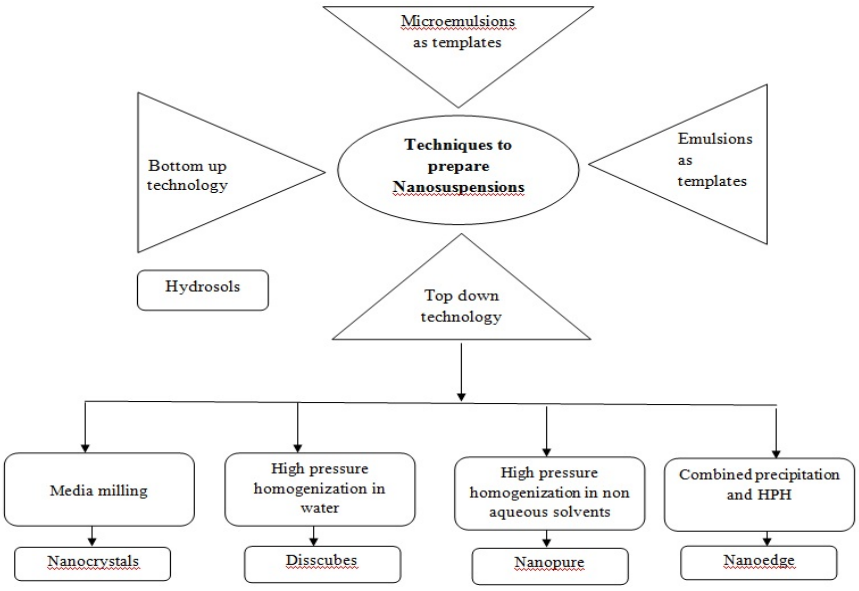

Fig. 1: Various methods for preparation of nanosuspensions

Wet 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. 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 technique. The major drawbacks of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product, degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥5 µm[10].

Homogenization

Dissocubes

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. Dissocubes was developed by Muller *et al.* in 1999[11]. In this technique, 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. 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. This principle is employed in the APV Gaulin Micron LAB 40 Homogenizer (APV Homogenizer, Lóbeck, Germany) and the NS 1001L-Panda 2K high-pressure homogenizer (Nirosuavi. S.P.A., Parma, Italy). Scholer *et al*. prepared atovaquone nanosuspensions using this technique[12]. An aqueous suspension of atovaquone was dispersed using an Ultra turrax T25, (IKA-Werke GmbH & Co. KG, Staufen, Germany) and was further homogenized in a Gaulin Micron Lab 40 high-pressure homogenizer. After subjecting to pressures of 1.5×10^7 (two cycles), 5×10^7 (two cycles) and 1.5×10^8 (20 cycles) Pa, a nanosuspension of atovaquone with a mean diameter of 279 ± 7 nm and mean polydispersity index of 0.18 ± 0.001 was obtained. To produce a nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling. The major advantage of high-pressure homogenization over media milling is that it can be used for both diluted as well as concentrated suspensions and also allows aseptic production.

Nanopure

Nanopure is suspensions homogenized in water-free media or water mixtures[13]. 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. The results obtained were comparable to Dissocubes and hence can be used effectively for thermolabile substances at milder conditions.

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. 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.

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). The major disadvantage of this technique is the high number of passes through the microfluidizer and that the product obtained contains a relatively larger fraction of microparticles.

Emulsification-Solvent Evaporation Technique

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent 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[14].

Hydrosol method

This is similar to the emulsification-solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

Supercritical fluid method

Supercritical fluid technology can be used to produce 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 loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. In the PCA method, the drug solution is atomized into a chamber containing compressed CO_2. As the solvent is 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 injected 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. The disadvantages of the above methods are use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques, particle nucleation overgrowth due to transient high supersaturation, which may also result in the development of an amorphous form or another undesired polymorph [15].

Characterization of Nanosuspension

A) In vitro evaluation

1. Mean particle size and size distribution

Various parameters of nanosuspensions like saturation solubility, dissolution velocity, physical stability, dissolution velocity physical stability and biological performance depend on the mean particle size and particle size distribution. Mean particle size and particle width (polydispersity index) can be determined by Photon Correlation Spectroscopy (PCS), laser differaction, and coulter

current multisizer. Polydispersity index (PI) should low for the long-term stability of the nanosuspensions. A PI value of 0.1–0.25 indicates a narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. Due to low measuring range (3nm to 3 µm) of PCS, determination of the contamination of the nanosuspension (by drugs having particle size greater than 3 µm) is difficult. So, to detect and quantify the microparticles that might have been generated during the production process) laser diffractometry (LD) analysis should be carried out in addition to PCS analysis. Particles ranging from 0.05–80 µm and in certain instruments particle sizes up to 2000 µm can be measured by using LD. Particle size analysis by the Coulter counter technique is essential (in addition to PCS and LD) for nanosuspensions that are intended for intravenous administration. Coulter counter is a more efficient and appropriate technique than LD analysis as it gives the absolute number of particles per volume unit for the different size classes. It quantifies the contamination of nanosuspensions by microparticulate drugs.

2. Particle charge (Zeta Potential)

Zeta potential determines the stability of the nanosuspension. Both the stabilizer and the drug govern the zeta potential of a nanosuspension. A zeta potential of minimum ±30mV is required for electrostatically stabilized nanosuspension and ±20mV is required in case of electrostatic and steric stabilization.

3. Crystalline state and particle morphology

It is important to know the crystal morphology of the drug in the nanosuspension. Polymorphic or morphological changes in drug that occur during nanosizing can be determined by the knowledge of crystalline state and particle morphology. Amorphous state of the drug formed during preparation of nanosuspension is determined by X-ray diffraction analysis. It gives information about the changes in the physical state of the drug particles as well as the extent of the amorphous fraction. Differential scanning calorimetry can be used additionally. Scanning electron microscopy is also used to get exact information about particle morphology. Effect of high pressure homogenization on the crystalline structure of the drug is estimated by X-ray diffraction analysis in combination with differential scanning calorimetry. Techniques like scanning electron microscopy (SEM), atomic force microscopy (AFM) or transmission electron microscopy (TEM) are preferred for determining the exact size and morphology of nanoparticles in suspension.

4. Saturation solubility and dissolution velocity

The dissolution velocity and the saturation solubility are enhanced by formulation of nano suspensions. Reduction in particle size results the increased dissolution pressure and hence the solubility. Change in surface tension occurs as the solubility increases (due to particle size reduction) which lead to increased saturation solubility. Different physiological solutions at different pH and different temperatures are used to carry out the determination of the saturation solubility and dissolution velocity according to the methods reported in the pharmacopoeia. In vivo performance (blood profiles, plasma peaks and bioavailability) of the formulation is assessed by these parameters. Increase in saturation solubility can be explained by Kelvin equation and the Ostwald-Freundlich equations. Determination of the dissolution velocity of nanosuspensions provides the information about the advantages of nanosuspension over conventional formulations, especially in sustained-release dosage forms.

5. Stability

Nanosuspensions Stability depends on the particle size of the suspended particles. Decrease in the particle size to the nano range increases the surface energy of the particles, and the tendency of the particles to agglomerate increases. Therefore the stabilizers are used to decrease the chances of Ostwald ripening and to improve the stability of the suspension by providing a steric or ionic barrier. Stabilizers like cellulosic, poloxamer, polysorbates, lecithin, polyoleate and povidones are generally used in the nanosuspensions. Lecithin is preferred in the development of parentral nanosuspensions[16-21].

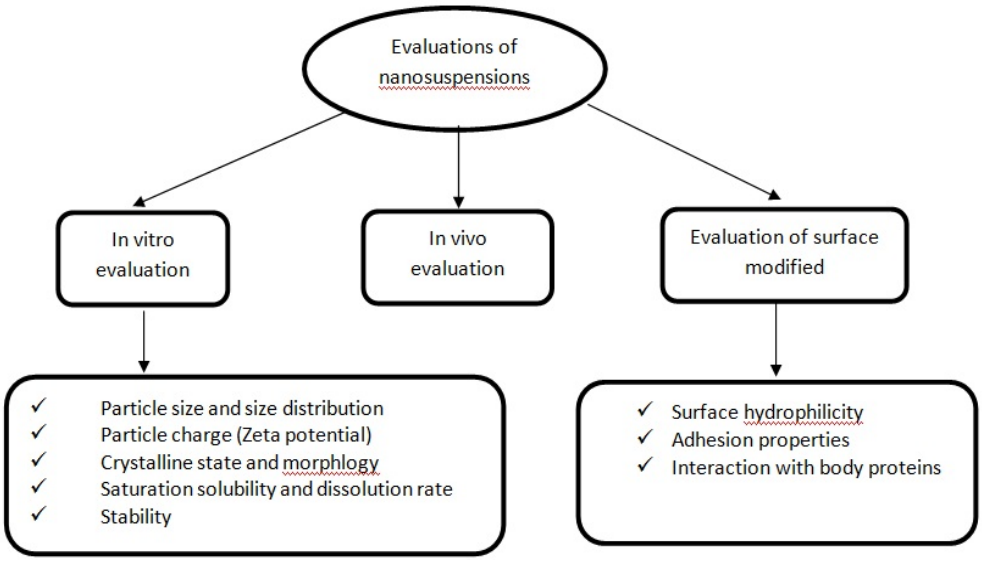

Fig. 2: Flowchart showing various methods for characterization of nanosuspensions

B) In vivo evaluation

Particular drug and route of administration requires the specific in vivo evaluation of the nanosuspensions. Generally the formulations are administered by required route and the plasma drug concentrations are determined by HPLC-UV visible spectrophotometry. Surface hydrophilicity/hydrophobicity (which determines interaction with cells prior to phagocytosis), adhesion properties and the interaction with body proteins are generally evaluated by in vivo parameters. The monitoring of the in-vivo performance of the Nanosuspensions and the establishment of relationship between in-vitro release and in-vivo absorption are required in order to to prepare a successful preparation, irrespective of the route of the administration and the delivery systems.

Rate of dissolution influences the in-vivo biological performance of oral nanosuspensions. Size of nanoparticle and surface properties of the particles determine the organ distribution for intravenously injected nanosuspensions. The in-vivo organ distribution behaviour of the nanosuspension is affected by hydrophilicity/hydrophobicity

and interactions of particles with plasma proteins. Surface hydrophobicity is determined by hydrophobic interaction chromatography and absorption of protein is determined by 2-D PAGE quantitatively and qualitatively after intravenous injection of nanosuspensions of drug in animals[16, 18, 20].

Applications of Nanosuspensions

Parentral administration

Parentral route of administration is used when rapid onset of action is required, when drug has extensive first pass metabolism or it is not absorbed by gastrointestinal track. Parentral administration of a drug requires the drug in solubilized form or the drug with particle size less than 5 µm so that blockage of capillaries does not occur. As Nanosuspensions have size of particles in nano range so they are suitable candidates for parentral drug delivery. Various routes of parentral administration like intra-articular, intraperitonal, intravenous injection allow the administration of the drug by means of nanosuspensions suitably. Nanosupensions overcome the problems of solubilization capacity, parentral acceptability, physical instability, high manufacturing cost and difficulties in scale-up as in other parentral formulations. Due to direct nanosizing of the drug particles almost all drugs can be easily processed for parentral administration. They show the increased efficacy of the drug. Nanosuspensions reduce the cost of therapy and improve therapeutic performance of drug by improving the parentrally tolerable dose of drug. Enhancement in the stability of drugs has been noticed in Nanosuspensions. E.g. Clofazimine nanosuspension shows improved stability and efficacy when compared to the liposomal clofazimine in M. avium-infected female mice. Pharmacokinetic profile and biodistribution of the drug in nanosuspension after parentral administration is influenced by a number of factors like physical properties of the drug particles, dose of the drug, the infusion time, the intrinsic solubility of the drug in blood, the interaction of the drug with plasma proteins, pattern of the plasma protein interaction and the phenomenon of natural targeting.

Oral drug delivery

The oral route of the drug delivery is the most common and preferable route due to its long list of advantages. The solubility of the drug and its absorption through the gastrointestinal tract determines the efficiency of the drug administered orally. Therefore a poorly water soluble drug or a drug whose absorption depends on dissolution exhibit low bioavailability and in order to get the therapeutic action high dose of the drug is required. It increases the cost of the therapy. Size reduction of drugs to nano size drastically increases the oral absorption of drug which results in the increased bioavailability.

Bioavailability of the drugs enhance due to the following reasons –

1. Increased surface area (because of reduction in particle size)
2. Increased concentration gradient between the gastrointestinal tract lumen and blood
3. Increased dissolution velocity
4. Increase in the adhesiveness of drug nanoparticles to the mucosa
5. Increased saturation solubility

As the bioavailability increases reduction in the dose of drug occurs subsequently which makes the therapy cost effective. Nanosuspensions can be used in dry dosage form such as tablet or hard gelatin capsule with pellets and directly in a liquid dosage form when aqueous nanosuspensions are formulated.

Pulmonary drug delivery

Drugs that are poor soluble in pulmonary secretions can be administered by the formulation of the nanosuspensions. These drugs are delivered as suspension aerosols or as dry powders by means of dry powder inhalers. Nebulized form of the aqueous nanosuspensions is used for the delivery of drugs to lung. Nebulization is generally done by using mechanical or ultrasonic nebulizers. Nanosuspensions could be used in all available types of nebulizer. Nanosuspensions provide following advantages over the conventional pulmonary formulations:-

1. Rapid diffusion and dissolution of the drug at the site of action (which increases the bioavailability of the drug).
2. Increased adhesiveness of the drug to mucosal surfaces.
3. Prolonged residence time of the drugs at absorption site which prolongs the effect of the drug.
4. Initial quick onset of action and then controlled release of the active moiety (which is required by most pulmonary diseases).
5. Decreased local and systemic side-effects of the drug due to prevention of unwanted deposition of particles in the mouth and pharynx.
6. Even distribution of the drug in the lungs as compared to the microparticulate form of the drug as all droplets of aerosol contains drug nanoparticles (being smaller in size).

Lung infections can be treated by nanosuspensions e.g. bupravaquone nanosuspensions formulated by nebulization. Nanosuspension of Budesonide has also been prepared successfully for pulmonary delivery. It shows a good relationship between the drug concentration in the formulation and the number of micrograms of drug delivered per actuation.

Ocular administration

Nanosuspensions can be explored for the drugs that exhibit poor solubility in lachrymal fluids. Nanosuspensions provide the following benefits for ocular drug delivery:-

1 Prolonged residence time of drug in the cul-de-sac (desired for most ocular diseases for effective treatment).

2 Avoidance of high tonicity created by water soluble drugs.

3 Sustained release of the drug can be obtained by incorporation of nanosuspension in a suitable hydrogel base or mucoadhesive base.

The efficacy of the nanosuspensions depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the release and ocular bioavailability of the nanosuspension is governed by intrinsic dissolution rate of the drug in lachrymal fluids. Suspensions may not give the consistent performance as the intrinsic dissolution rate of the drug varies because of the constant inflow and outflow of lachrymal fluids. Nanosuspension is an ideal approach for ocular delivery of hydrophobic drugs as they improve the saturation solubility of the drug.

Nanosuspensions can be formulated using various types of polymers e.g. polymeric nanosuspension of ibuprofen for ophthalmic controlled delivery which has been prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone show improved shelf-life and the bioavailability after ophthalmic application due to enhanced rate of drug absorption.

Topical formulations

Creams and water-free ointments can be formulated by the incorporation of the drug nanoparticles into the formulations. In the topical dosage form saturation solubility can be enhanced by the use of nanocrystalline form of the drug. It enhances the diffusion of the drug into the skin.

Drug targeting

Nanoparticulate systems have shown great potential in targeting of the drugs, especially to the brain targeting. As the surface properties and in-vivo behaviour of nanosuspensions can be altered easily by changing either the stabilizer or the milieu, so they are good candidates for targeted delivery. Commercially viable

nanosuspensions for targeted delivery are developed due to versatility of the nanosuspension, easy scale-up and commercial production of the nanosuspensions. Targeting of the drug to the brain can be achieved by modifying the surface of nanoparticles by using suitable polymers. E.g. brain targeting of peptide dalargin has been done successfully by the modification of the nanoparticle surface using polyisobutyl cyanoacrylate. Active or passive targeting of the desired site by using various surface coatings (the engineering of stealth nanosuspensions) is the future of targeted drug delivery systems. Various types of targeting has been achieved successfully like targeting of Cryptosporidium parvum (the organism responsible for cryptosporidiosis) by using surface modified mucoadhesive nanosuspensions of bupravaquone, and pulmonary aspergillosis can easily be targeted by amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes. Gastrointestinal bacteria and parasitic infections can be targeted due of enhanced adhesion properties.

Mucoadhesion of the nanoparticles

When nanoparticles are administered orally in the form of a suspension, they diffuse into the liquid media and rapidly encounter the mucosal surface. They adhere to the intestinal surface (bioadhesion) and get immobilized. After adhesion the concentrated suspension acts as a reservoir of particles and enables the rapid adsorption. The first step before particle absorption is the direct contact of the particles with the intestinal cells through a bioadhesive phase. The adhesiveness of the nanosuspensions improves bioavailability as well as the targeting of the parasites persisting in the GIT [18, 20, 21, 22].

Bioavailability enhancement

Poor solubility, poor permeability or poor stability of a drug in the gastrointestinal tract (GIT) renders the poor oral bioavailability of the drug. Nanosuspensions enhance the bioavailability by increasing the solubility and permeability of the drug across the membrane. E.g. bioavailability of oleanolic acid (poorly soluble drug), a hepatoprotective agent, has been improved by formulating a nanosuspension which was proven by the significantly enhanced therapeutic effect. The enhanced bioavailibilty was found due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when it was compared with the dissolution from a coarse powder (15% in 20 min) [23-27].

Future Prospects

Nanosuspension technology is a unique and novel approach to overcome drug problems such as poor bioavailability that are related with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production methods like media milling and high-pressure homogenization have been successfully employed for large scale production of nanosuspensions. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, and can be used for parentral 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. In consideration to data available nanosuspensions can be considered as renaissance in formulation technologies for coming years.

REFERENCES

1. Shah T, Patel D, Hirani J, Amin AF. Nanosuspensions as drug delivery systems- A comprehensice review. Drug Del Tech. 2007;7: 42-53.
2. Kesisoglou F, Panmai S, Wu Y. Nanosizing-oral formulation development and biopharmaceutical evaluation. Adv Drug Deliver Rev. 2007;59: 631-644.
3. Pandya VM, Patel JK, Patel DJ. Formulation, Optimization and characterization of Simvastatin Nanosuspension prepared by nanoprecipitation technique. Der Pharmacia Lettre. 2011;3(2): 129-140.
4. Muller RH, Jacobs C, Kayer O. Nanosuspensions for the formulation of poorly soluble drugs. In: Nielloud F, Marti-Mestres G, editors. Pharmaceutical emulsion and suspension. New York: Marcel Dekker; 2000. p. 383-407.
5. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov. 2004; 3: 785-796.
6. Kamble VA, Jagdale DM, Kadam VJ. Nanosuspension: A novel drug delivery system. International Journal of Pharma and Bio Sciences. 2010;1(4): 352–360.
7. Nagaraju P, Krishnachaithanya K, Srinivas VDN, Padma SVN. Nanosuspensions: A Promising Drug Delivery Systems. International Journal of Pharmaceutical Sciences and Nanotechnology. 2010;2(4): 679-684.
8. Patravale VB, Date AA, Kulkarni RM. Nanosuspensions. A promising drug delivery strategy. J Pharm Pharmacol. 2004;56: 827–840.
9. Chaubal MV. Application of formulation technologies in lead candidate selection and optimization. Drug Dis.Today. 2004;9(14): 603-609.
10. Chingunpituk J. Nanosuspension Technology for Drug Delivery. Walailak J Sci & Tech. 2007;4(2): 139-153.
11. Moller RH, Grau MJ, Hildebrand GE. Increase of solubility of poorly soluble drugs by transfer to Dissocubes using high pressure homogenization. Proc Int Symp Control Rel Bioact Mater. 1999; 26: 112-3.
12. Scholer N, Krause K, Kayser O, Muller RH, Borner K, Hahn H, Liesenfeld O. Atovaquone nanosuspensions show excellent therapeutic effect in a new murine model of reactivated toxoplasmosis. Antimicrob. Agents Chemother. 2001;45: 1771–1779.
13. Venkatesha T, Reddy AK, Maheswaria JU, Dalithb MD, Kumar CKA. Nanosuspensions: Ideal Approach for the Drug Delivery of Poorly Water Soluble Drugs. Der Pharmacia Lettre, 2011;3(2): 203-213.
14. Prasanna L, Giddam AK. Nanosuspension technology: a review. Int j pharm pharm sci. 2(4): 3540.
15. Jadhav KR, Shaikh IM, Ambade KW, Kadam VJ. Applications of microemulsion based drug delivery system. Cur. Dr. Del. 2006;3(3): 267-273.
16. Banavath H, Sivarama RK, Tahir AM, Sajid AM, Gurudutta P. Nanosuspension:an attempt to enhance bioavailability of poorly soluble drugs**,** International Journal of Pharmaceutical Sciences and Research. 2010;1(9): 1-11.
17. Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: A formulation approach for poorly water-soluble compounds. Eur. J. Pharm. Sci. 2003;18: 113-120.
18. Reddy AK, Venkatesha T, Maheswaria JU, Dalithb MD, Kumar CKA. Nanosuspensions: Ideal Approach for the Drug Delivery of Poorly Water Soluble Drugs. Scholar Research Library. 2011;3(2): 203-213.
19. Dubey R. Impact of nanosuspension technology on drug discovery and development. Drug Deliv Technol. 2006;6: 65–7.
20. Chen Y, Liu J, Yang X, Zhao X, Xu H. Oleanoic acid nanosuspension: preparation, in vitro characterization and enhanced hepato protective effect. J Pharm Pharmacol. 2005;57: 259-64.
21. Kumar AN, Deecaraman M, Rani C. Nanosuspension technology and its applications in drug delivery, Asian J Pharm. 2009;3: 168-73.
22. Trotta M, Gallarete M, Pattarino F, Morel S. Emulsions containing partially water-miscible solvents for the preparation of drug nanosuspensions. J Control Release. 2001;76: 119–128.
23. Bandi R, Ganesh NS, Kotha NS, Lova R, Kavitha K. Nano Particulate Drug-Delivery Systems: An overview. Journal of Pharmacy Research. 2011;4(6): 1688-1690.
24. Rezaei MA, Kebriaee ZA, Keshavarz M, Ahmadi A, Mohtat B. Preparation and in-vitro evaluation of indomethacin nanoparticles. DARU. 2010;18(3): 185 -192.
25. Patel R, Patel KP. Advances in novel parentral drug delivery systems. Asian J Pharm. 2010;4(3): 193-199.
26. Rao GCS, Kumar MS, Mathivanan N, Rao MEB. Nanosuspensions as the most promising approach in nanoparticulate drug delivery systems. Pharmazie. 2004;59: 5–9.
27. Kumar NA, Deecaraman M, Rani C, Mohanraj KP, Venkateskumar K. Formulation, development and in vitro evaluation of nanosuspensions loaded with Atorvastatin calcium. Asian J Pharm. 2010;4: 28-33.