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Review Artice

NANO-SUSPENSION TECHNOLOGY: A REVIEW

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ABSTRACT

Solubility is the crucial factor for drug effectiveness, independence of the route of administration. Large proportions of newly discovered drugs are water insoluble, and therefore poorly bioavailable contributing to deserted development effort. These so-called 'Brickellia' candidates can now be delivered by formulating them into nanosuspension. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability. Stability and bioavailability of the drugs can be improved by the Nanosuspension technology. Preparation of nanosuspension is simple and applicable to all drugs which are aqueous insoluble. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspensions can be delivered by oral, parenteral, pulmonary and ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels.

Keywords: Dissolution, Nanosuspension, Solubility enhancement, Saturation solubility, Surfactant.

INTRODUCTION

Various formulation 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 solubility became a hurdle for the formulation of new molecular entities. More than 40% of the new chemical entities being generated through drug discovery programmes are poorly water-soluble or lipophilic compounds[1]. Formulating 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[2]. Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility[3-5]. There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization[6], solubilisation using co-solvents[7], salt form[8], surfactant dispersions[9], precipitation technique[10-11], and oily solution. Other techniques are like liposomes[12], emulsions[13-14], microemulsion[15-16], solid dispersion[17-18] and inclusion complexation using cyclodextrins[19-21] 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. Nanotechnology can be used to solve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanosuspension 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. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs such as naproxen[22], clofazomine[23], bupravaquone[24], nimesulide[25], mitotane[26], amphotericin B[27], omeprazole[28], nifedipine[29] and spironolactone[30] are formulated as nanosuspension.

NANOSUSPENSIONS

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants[31]. 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[32]. 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.

Preparation of nanosuspension

There are two methods for preparation of nanosuspension. They are 'Bottom up technology' and 'Top down technology'[33-34]. 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[35-36].

All-Trans retinoic acid nanosuspensions were prepared with a precipitation method[37]. Use of simple and low cost equipment and also benefit for higher saturation solubility is the advantage for precipitation technique compared to other methods of nanosuspension preparation. Precipitation technique is not applicable to drugs which are poorly soluble in aqueous and non aqueous media. In this technique, the drug needs to be soluble in atleast one solvent which is miscible with nonsolvent. The major challenge is to avoid crystal growth due to Ostwald ripening being caused by different saturation solubilities in the vicinity of differently sized particles. The top down technologies include (a) media milling[38-39] (b) high pressure homogenization[40-41] (c) emulsion diffusion method (d) supercritical fluid method and these are preferred over the precipitation methods.

Media milling (Nanocrystals or Nanosystems)

The method is first developed by liversidge et.al. In this method the nanosusensions are produced using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. The milling medium is framed of glass, zirconium oxide or highly cross-linked polystyrene resin. The milling chamber is charged with the milling media, water, drug and stabilizer, and the milling media or pearls are then rotated at a very high shear rate.

The milling process is performed under controlled temperatures. The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. The unimodal distribution profile and mean diameter of <200, require a time profile of 30-60 min. The media milling procedure can successfully process micronized and non-micronized drug crystals. Once the formulation and the process are optimized, very short batch-to-batch variation is observed in the quality of the dispersion. A nanosuspension of Naproxen with a mean particle size of 300-600 nm was prepared using pearl milling technique[42].

Homogenization

Dissocubes

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The most commonly used homogenizer in the preparation of nanosuspension is the APV micron LAB 40(APV Deutschland GmbH, Lubeck, Germany). However, other piston-gap homogenizers from Avestin (Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid Power Ltd, Stansted, UK) can also be used. The instrument can be operated at pressures varying from 100 to 1500 bars. In some instruments, a maximum pressure of 2000 bars can be reached. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of the drug, the desired mean particle size, and required homogeneity. High-pressure homogenizers are available with different capacities ranging from 40ml (for laboratory purposes) to a few thousand litres (for large-scale production). Before subjecting the drug to the homogenization process, it is essential to form a presuspension of the micronized drug in a surfactant solution using high-speed stirrers.

In the homogenization gap, according to Bernoulli's equation, the dynamic pressure of the fluid increases with the simultaneous decrease in static pressure below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature, leading to the formation of gas bubbles, which go off when the suspension leaves the gap (called cavitation) and normal air pressure is reached again. The implosion forces are sufficiently high to break down the drug microparticles into nanoparticles. Additionally, the collision of the particles at high speed helps to achieve the nano-sizing of the drug. The principle is employed in the APV gaulin micron LAB 40 homogenizer (APV homogenizer, Lubeck, Germany) and NS 100 1L-panda 2K high pressure homogenizer (NIROSUAVI. S.P.A., Parma, Italy). Nimodipine nanosuspensions were prepared by using high pressure homogenizer. Nimodipine coarse powder was first disintegrated into microparticles by using fluid jet mill technology. The nimodipine suspension was then subjected to three types of homogenizers, such as microfluidizer processor M-110EH (MFIC, USA), niro-soavi NS1001L (ATS Co.ltd., Italy), and emulsiflex C3 (Avestin Inc., Canada). At first 200 bar with 2 cycles 500 bar with five cycles and then 15-20 cycles at 1500bar were run43. Drugs such as carbazepine, bupravaquone, aphidicolin, cyclosporine, paclitaxel, prednisolone and atorvastatin are also prepared by using high pressure homogenizer[44].

Effect of homogenization pressure

As the pressure increases particle size decreases. The studies carried out on RMKP 22, 4-[N-(2-hydroxy-2-methyl-propyl)-ethanolamino]-2, 7-bis (cis-2, 6-dimethylmorpholin-4-yl)-6-phenyl-pteridine, revealed that an inverse relationship exists between the homogenization pressure and the particle size[45].

Number of homogenization cycles

It is anticipated that as the number of homogenization cycles increases the particle size decreases. It is not possible to achieve the desired particle size in single homogenization cycle.

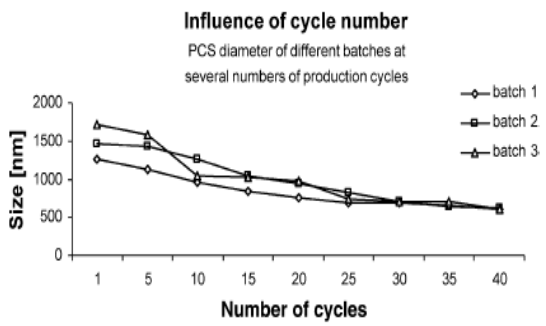

Fig. 1: Influence of applied cycles in regard to PCS diameter.

Typically multiple cycles are required. The number of cycles depends on the hardness of the drug, required homogeneity, and the desired mean particle size required. An omeprazole nanosuspension was prepared by using this technique[28]. The decrease in particle size as a function of three homogenized products was shown in the Fig 1.

Nanoedge

The principle involved in Nanoedge is same that of the precipitation and homogenization techniques. This technique has an advantage of getting smaller particle size and greater stability in short period of time. In this technique the precipitated suspension is further homogenized to get smaller particle size and to avoid crystal growth. Precipitation is performed in water using water miscible solvent, such as methanol, ethanol, and isopropanol. It is desired to remove the solvent completely by including evaporation step to provide a solvent free modified starting material followed by high pressure homogenization.

Nanojet technology

Nanojet technology is also called as opposite stream technology. In this technique a stream of suspension in two or more divided parts were passed with high pressure were made to colloid with each other, due to the high shear forces produced during the process leads to results in the reduction of particle size.

Emulsion solvent 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-miscible 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. Originally methanol, ethanol, ethyl acetate, chloroform are used as organic solvents. However, environmental hazards and human safety concerns about residual solvents have limited their use in routine manufacturing processes. Nanosuspension of ibuprofen[46], diclofenac[47], acyclovir[48] were prepared by this method.

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 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 method46. Formulating ibuprofen nanosuspension by melt emulsification method show greater dissolution rate than formulating by solvent diffusion method.

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 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 CO2), to dissolve the solute to be micronized; at the process condition, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles. Dexamethasone49 phosphate drug nanoparticles (for microencapsulation) and griseofulvin[50] nanoparticles were prepared by using SAS 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[51]. Cyclosporine nanoparticles[52] were prepared by using RESS method. The drug solution is atomized into a chamber containing compressed CO2 in PCA method. The solution gets supersaturated when the solvent is removed and therefore precipitated as fine crystals.

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 autoclavable nanosuspension.

Organic solvent

Organic solvents are used in the formulation of nanosuspension if emulsions or microemulsions are 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.

Other additives

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

CHARACTERIZATION OF NANOSUSPENSION

According to muller's review (2001), the necessity charecterization parameters for nanosuspensions are size and size distribution, particle charge (zeta potential), crystalline status, as well as dissolution velocity and saturation solubility.

Particle size distribution

The most important charecterization parameter for the nanosuspension are the mean particle size and width of particle size distribution (called polydispersity index) which governs the physiocochemical properties like saturation solubility, dissolution velocity, physical stability and even biological performance. It is proved that change in particle size changes saturated solubility and dissolution velocity. Different methods for determining particle size distribution are photon correlation spectroscopy (PCS), laser diffraction (LD), and coulter counter multisizer.

PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1–0.25 indicates a fairly narrow size distribution where as a PI value greater than 0.5 indicates a very broad distribution.PCS determines the particle size in the range of (3nm to 3 µm) it becomes difficult to determine the possibility of contamination of the nanosuspension by microparticulate drugs (having particle size greater than 3µm). Hence, in addition to PCS analysis, laser diffractometry (LD) analysis of nanosuspensions should be carried out in order to detect as well as quantify the drug microparticles that might have been generated during the production process. LD determines the particle size in the range of 0.05-80µm upto 2000µm. The typical LD characterization includes determination of diameter 50% LD (50) and diameter 99% LD (99) values, which indicate that either 50 or 99% of the particles are below the indicated size. For parental use the particle size should be less than 5µm, considering that the smaller size of the capillaries is 5-6µm and hence a higher particle size can lead to capillary blockade and embolism. For nanosuspensions that are intended for intravenous administration, particle size analysis by the Coulter counter technique is essential in addition to PCS and LD analysis. Since the Coulter counter gives the absolute number of particles per volume unit for the different size classes.

Zeta potential (particle charge)

Zeta potential determines the physical stability of nanosuspenson. Zeta potential is an indirect measurement of the thickness of the diffusion layer, i.e. can be used to predict long term stability[53]. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension a minimum zeta potential of ± 30mv is required whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of ± 20mV is desirable.

Crystal morphology

X-ray diffraction analysis in combination with differential scanning calorimetry, scanning electron microscopy is used to determine the polymorphic changes due to impact of high pressure homogenization in the crystalline structure of the drug. Nanosuspension can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressure homogenization. An increased amount of amorphous drug fraction could induce higher saturation solubility.

Saturation solubility and dissolution velocity

Nanosuspension increases the dissolution velocity and saturation solubility. Size reduction leads to 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 surface tension leading to increased saturation solubility.

APPLICATION OF NANOSUSPENSIONS

Bioavailability enhancement

Drug with poor solubility, poor permeability or poor solubility in gastrointestinal tract will leads to poor oral bioavailability. Nanosuspension resolves the problem of poor bioavailability by solving the problem of poor solubility, and poor permeability across the membranes. Dissolution rate was increased in diclofenac when formulated in nanosuspension form. The dissolution rate of diclofenac 1 nanosuspension after 60 min in SGF and H2O is 25% and 10% in SIF compared to relative coarse suspension and the dissolution rate of diclofenac 2 after 60 min in SGF and H2O is 50% and 35% in SIF compared to coarse suspension[47].

Bioavailability of poorly soluble, a COX2 inhibitor, celecoxib was improved using a nanosuspension formulation. The crystalline nano-sized celecoxib alone or in tablet showed a dramatic increase of dissolution rate and extent compared to micronized tablet[54]. Spironolactone and budesonide are poorly soluble drugs. The nanosuspension prepared with different surfactant concentration form shows an increase in flux across the coca-2 cell monolayer compared to saturated solution form Fig 2. The higher flux contributes to the higher bioavailability of nanosuspension formulation[55]. The bioavailability of poorly soluble fenofibrate following oral administration was increased compared to the suspensions of micronized fenofibrate[56].

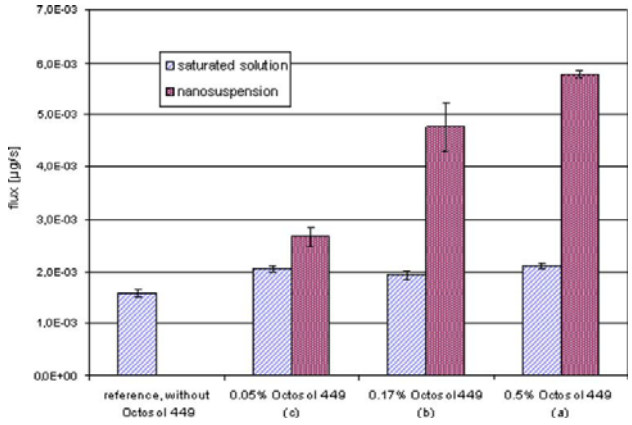

Fig. 2: Fluxes [µg/s] of budesonide nanosuspensions (NS) and saturated solutions (SS) with corresponding surfactant concentrations across Caco-2 cell monolayers, (means±SD; n=3)

Significant difference ($p < 0.05$) was observed between the fluxes from saturated solution vs. nanosuspension at all concentrations of surfactant.

Oral administration of micronized Amphotericin B does not shown any significant effect. However administration in nanosuspension form, showed a significant reduction ($P < 0.5\%$) of the liver parasite load by 28.6%, it indicates that the nanosuspension of amphotericin B has high systemic effect and superior oral uptake in nanosuspension form[27]. The dissolution rate (65% in 10 min) of ibuprofen made as lyophilized nanosuspension power is greater than the micronized drug (<15% in 10min)46. Oral administration of gonadotrophin inhibitor danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2%[57]. The bioavailability of poorly soluble oleanolic acid was enhanced in the nanosuspension formulation. This is due to faster dissolution rate (90%in 10 min) in the lyophilized nanosuspension power form compared to the coarse powder (15% in 10 min)[58]. Antibiotics like atovaquone and bupraquone has poor aqueous solubility. Nanosizing of the drugs leads to increase in oral absorption and subsequent bioavailability[59].

Ocular administration

For delivery of poorly soluble drug in cul-de-sac suspensions and ointments are recommended. Suspensions have advantages of prolonged residual time in cul-de-sac and avoidance of higher tonicity produced by water soluble drugs. The ocular bioavailability of suspensions depends on the dissolution rate of the drug in lachrymal fluid. However the inflow and outflow of lacrimal fluid causes variation in the dissolution rate of the drug. Nanosuspension attains saturation solubility in the lachrymal fluid, representing an ideal approach for the ocular delivery of the hydrophobic drugs. The nanosized drug particles had shown a prolonged residual time in cul-de-sac, giving sustained release of drug. The sustained release of drug for specified time can be achieved by incorporating nanosuspension in hydrogel base, mucoadhesive base, or in ocular inserts. The sustained release in the cul-de-sac can also be achieved by loading the nanosuspension in the polymers. Diclofenac loaded bipolymeric nanosuspension for ophthalmic application showed higher bioavailability in rabbit aqueous humor and improved shelf life[60]. The ocular delivery of hydrocortisone nanosuspension has been shown to enhance drug absorption rate and increase the duration of drug action[61].The ocular anti-inflammatory activity of ibuprofen-eudragit RS100 nanosuspension shows greater activity than ibuprofen lysate[62]. Cumulative percent drug released of acyclovir after 24 hr was between 79.28 to 95% indicating effective Controlled release property of Ophthalmic nanosuspension. Acyclovir loaded nanoparticles have achieved the objectives of increased contact time, prolonged release and decreased frequency of administratio48. Cloricromene hydrochlore showed a higher drug availability in the aqueous humor after drug administration in eudragit nanosuspension, cloricromene loaded eudragit retard nanoparticle suspension appear to offer a promising means of improving the shelf life and bioavailability of this drug after ophthalmic application[63].

Intravenous administration

The parenteral route is an invading route. Despite all these limitations, the parenteral route still retains its value because of its special advantages, such as quick onset of action in case of emergency, reduction in dose of the drug and the ability to target the drug quickly to the desired site of action, especially in the case of severe infections. The parenteral route is often employed as a substitute when the drug is either not absorbed through the gastrointestinal tract or undergoes extensive first-pass metabolism.

In vivo studies in mouse model of sarcoma-180 solid tumour demonstrated significantly greater inhibition of tumour growth following a treatment with oridonin nanosuspension than ordonin solution at the same dosage. The mice injected with oridonin nanosuspension showed a highest reduction in tumour volume and tumour weight at the dose of 20mg/kg compared to the oridonin solution, with the tumour inhibition rate increased from 42.49% for oridonin solution to 60.23% for oridonin nanosuspension. Atovaquone when taken orally shows poor therapeutic activity against TE because of its poor absorption[64]. The bioavailability of nimodipine is low when given orally due to first pass metabolism in liver. But the nanosuspension of nimodipine given through i.v., the saturation solubility is increased[43]. The concentration of clofazimine nanosuspension after i.v concentration in livers, lungs and spleens reached comparably high, well in excess of the minimum inhibitory concentration for most mycobacterium avium strains. Further study indicates that the nanocrystalline clofazimine was as effective as liposomal clofazimine in reducing bacterial loads in the liver, spleen and lungs[23]. IV administration of omeprazole nanosuspension is suitable in order to protect it from chemical degradation of orally administered omeprazole28. The bioavailability of poorly soluble drug tarazepide is increased in the nanosuspension form than the conventional solubilization techniques such as surfactants, cyclodextrins etc[65].

Pulmonary administration

Aqueous nanosuspension can be nebulized using mechanical or ultrasonic nebulizer for lung delivery. The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. At the same time, the increased adhesiveness of the drug to mucosal surfaces offers a prolonged residence time for the drug at the absorption site. This ability of nanosuspensions to offer quick onset of action initially and then controlled release of the active moiety is highly beneficial and is required by most pulmonary diseases. Moreover, as nanosuspensions generally contain a very low fraction of microparticulate drug, they prevent unwanted deposition of particles in the mouth and pharynx, leading to decreased local and systemic side-effects of the drug. The pharmacokinetic studies of fluticasone after the intratracheal administration of nanosuspensions showed deep lung deposition and fast lung absorption, with solubility playing an important role in lung retention and duration of action[66]. Using an ultrasonic nebulizer, Budenoside drug nanoparticles were nebulized and the pharmacokinetics showed comparable AUC, higher Cmax and lower Tmax as that of the pulmicort respules[67].

Targeted drug deliver

Nanosuspensions can also be used as targeted drug delivery. The targeted drug delivery can be designed by incorporating the drug into the mononuclear phagocytic system. Targeted drug delivery can be used for the anti-mycobacterial, fungal or leishmanial drugs to macrophages if the infectious pathogen is persisting intracellular. The further plan of action for targeted drug delivery system is by using various surface coatings for active or passive targeting. Peter formulated a nanosuspension of clofazimine, permitting passive targeting to the reticuloendothelial system. Nanocrystalline drug concentration of clofazimine in liver, spleen, and lungs reached comparably high concentrations than liposomal formulation for most mycobacterium avium strains[23]. Similarly, conditions such as

pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes[27]. Scholer shown, atovaquone nanosuspension concentration in brain, lungs, sera, liver is high and has improved therapeutic efficacy against toxoplasma encephalitis in murine mold infected with toxoplasma gonidii[59].

Mucoadhesion of the nanoparticles

A nanoparticle has an ability to adhere to the mucosa surface due to small particles. The adhesion of the particles is the first step before particle absorption. To further increase the adhesive time nanosuspensions are formulated with hydrogels made from mucoadhesive polymers, e.g. different types of carbopol and chitosan. The adhesiveness of the nanosuspension not only helps to improve the bioavailability but also improves targeting of the parasites persisting in the GIT, eg *cryptosporidium parvum*. Bupravaquone mucoadhesive nanosuspensions have been reported to demonstrate an advantage in TRC alpha-deficient mice infected with cryptosporidium parvum oocytes[68].

Topical formulations

Drug nanoparticles can also be incorporated into water free ointments and creams, which have an increased saturation solubility and enhanced diffusion of drug into the skin[69-71].

CONCLUSION

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Productions techniques such as media milling and high pressure homogenizer are used for large scale production of nanosuspensions. Nanosuspensions can be administerd through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension form.

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