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REVIEW ARTICLE

NANOTECHNOLOGY

A REVIEW ON NANOSUSPENSIONS IN DRUG DELIVERY

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ABSTRACT

Nanotechnology has emerged as an tremendous field in the medicine.Nano refers to particles size range of 1-1000nm.Nanosuspensions are part of nanotechnology.Many of the drug candidates are exhibiting poor aqueous solubility. The use of drug nanosuspension is an universal formulation approach to increase the therapeutic performance of these drugs in any route of administration.A pharmaceutical nanosuspension is defined as very finely colloid,biphasic,dispersed, solid drug particles in an aqeous vehicle , size below 1µm ,without any matrix material , stabilized by surfactants and polymers, prepared by suitable methods for Drug Delivery applications, through various routes of administration like oral ,topical ,parenteral ,ocular and pulmanary routes. This review article describes the preparation methods,characterization and applications of the nanosuspensions.

KEYWORDS

Nanosuspension, Disperse system,milling,homogenization,precipitation,zeta potential,crystalline state,saturation solubility .

INTRODUCTION

A Nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as very finely colloid[1],Biphasic[2],dispersed, solid drug particles in an aqeous vehicle , size below 1µm ,without any matrix material [3], stabilized by surfactants[4] and polymers[5], prepared by suitable methods for Drug Delivery[6] applications, through various routes of administration like oral[7] ,topical ,parenteral[8] ,ocular[9] and pulmanary routes(pulmanory has two references[10,11].A nanosuspension not only solves the problem of poor solubility and bioavailability but also alters the pharmacokinetics of drug and that improves drug safety and efficacy. Nanosuspensions differ from nanoparticles[12], which arepolymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid-lipid nanoparticles[13] (SLN), which are lipidic carriers of drug.In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems nanosuspensions are used as a formulation approach. Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose [14].The use of nanotechnology to formulate poorly water soluble drugs as nanosuspension offers the opportunity to address nature of the deficiency associated with this class of drugs. Nanosuspension has been reported to enhance absorption and bioavailability it may help to reduce the dose of the conventional oral dosage forms. Therefore to maintain the therapeutics, metronidazole may be used as nanosuspension with a nanoparticle size in the nano range typically between 1-1000nm is proposed. The present study is to design metronidazole nanosuspension (MNS) as a novel controlled dosage form that could release the drug in a controlled fashion at the site to have better therapeutic efficiency at a much lower dose[15]. Drug particle size reduction leads to an increase in surface area and consequently in the rate of dissolution as described by the Nernst–Brunner and Levich modification of the Noyes–Whitney equation [16]. In addition, an increase in saturation solubility is postulated by particle size reduction due to an increased dissolution pressure explained by the Ostwald–Freundlich equation [17]. Depending on the production technique applied changes in crystalline structure of drug particles may also occur [18]. An increasing amount of amorphous drug fraction could induce higher saturation solubility. Furthermore, a general adhesiveness to tissues has been described for nanoparticles [19]. A well established model to study intestinal drug absorption is the Caco-2 cell monolayer system [20]. The aims of the present study were to evaluate whether providing the drug in the form of a nanosuspension may improve its epithelial transport. It was hypothesized that nanosuspensions will enhance drug flux resulting from higher transmembraneous concentration gradients[1].Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability [11].Drugs encapsulated within nanosuspensions exist in pharmaceutically acceptable crystalline or

amorphous state. Nanosuspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption. Apart from this, nanosuspensions have some following advantages: firstly, drugs no longer need to be in the soluble form. It is effective for those molecules insoluble in oils ; secondly, the high drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose ; thirdly, nanosuspensions can increase the physical and chemical stability of drugs as they are actually in the solid state ; finally, nanosuspensions can provide the passive targeting.[5]

PREPARATION METHODS OF NANOSUSPENSIONS

The principle techniques used in recent years for preparing nanosuspensions can be classified into four basic methods: (a) Homogenization (b) Wet milling (c) Emulsification-solvent evaporation and (d) Precipitation or microprecipitation method.

Preparation of nanosuspensions were reported to be a more cost effective and technically more simple alternative, particularly for poorly soluble drugs and yield a physically more stable product than liposomes; conventional colloidal drug carriers . Nanosuspension engineeringprocesses currently used are preparation by precipitation, high pressure homogenization, emulsion and milling techniques [21].

For the nanosuspensions manufacture, there are two converse methods -'bottom-up' and the 'top-down' technologies [22]. The bottom-up technology is an assembling method from molecules to nano-sized particles, including microprecipitation, microemulsion, melt emulsification method and so on. The top-down technology is a disintegration approach from large particles, microparticles to nanoparticles, such as high-pressure homogenization and media milling method.

1. HOMOGENIZATION

The process can be summarized into three steps: firstly, drug powders are dispersed in a stabilizer solution to form pre-suspension; then pre-suspension was homogenized by the high-pressure homogenizer at a low pressure for several times as a kind of premilling, and finally was homogenized at a high pressure for 10-25 cycles until the nanosuspensions with the desired size were prepared [5.]

2. MILLING

Recently, nanosuspensions can be obtained by dry milling techniques [21].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 [2].

Media milling is a further technique used to prepare nanosuspensions [23,24]. Nanocrystal is a patent protected technology developed by Liversidge et al [25].In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling.High energy and shear forces generated as a result of impaction of the milling media with

the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. The major concern with this method is the residues of milling media remaining in the finished product could be problematic for administration .

3. *PRECIPITATION*

Precipitation has been applied for years to prepare submicron particles within the last decade [26,27] , especially for the poorly soluble drugs. Typically, the drug is firstly dissolved in a solvent. Then this solution is mixed with a miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually water) leads to sudden supersaturation of drug in the mixed solution, and generation of ultrafine crystalline or amorphous drug solids. This process involves two phases: nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate but low growth rate is necessary. Both rates are dependent on temperature: the optimum temperature for nucleation might lie below that for crystal growth, which permits temperature optimization [28].

4. *LIPID EMULSION/MICROEMULSION TEMPLATE.*

Another way to produce nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion [29]. Moreover, microemulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension . An example of this technique is the griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate [30]. The advantages of lipid emulsions as templates for nanosuspension formation are that they easy to produce by controlling the emulsion droplet and easy for scale-up. However, the use of organic solvents affects the environment and large amounts of surfactant or stabilizer are required.

STABILIZERS USED IN NANOSUSPENSIONS

Stabilizer plays an important role in the formulation of nanosuspensions. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening (Rawlins 1982; Mu¨ ller & Bo¨ hm 1998) and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions [31].

Typical examples of stabilizers used in nanosuspensions are cellulosics, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral nanosuspensions [32].

CHARACTERIZATION TECHNIQUES

Nanosuspensions are characterized for appearance, color, odor, assay, related impurities, particle size, zeta potential, crystalline status, dissolution studies and in

vivo studies.Among this, the most important characterization techniques were discussed .

1. MEAN PARTICLE SIZE AND PARTICLE SIZE DISTRIBUTION

The mean particle size and the span of particle size distribution (polydispersity index, PI) are two important characteristic parameters because they affect the saturation solubility, dissolution rate, physical stability, even in-vivo behavior of nanosuspensions [5].It has been indicated by Mu¨ ller & Peters (1998) that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug [31].Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer [2].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 whereas a PI value greater than 0.5 indicates a very broad distribution [31].The coulter-counter gives the absolute number of particles per volume unit for the different size classes, and it is a more efficient and appropriate technique than LD for quantifying the contamination of nanosuspensions by microparticulate drugs [5].

2. SURFACE CHARGE (ZETA POTENTIAL)

Zeta potential gives certain information about the surface charge properties and further the long-term physical stability of the nanosuspensions.The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself [31].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 [2].

3. CRYSTALLINE STATE AND PARTICLE MORPHOLOGY

The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing [5].Nanosuspensions 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 [2].The changes in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis [33] and supplemented by differential scanning calorimetry [34].In order to get an actual idea of particle morphology, scanning electron microscopy is preferred (Mu¨ ller & Bo¨ hm 1998)

4. SATURATION SOLUBILITY AND DISSOLUTION VELOCITY.

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs [31].The assessment of saturation solubility and dissolution velocity

helps in determining the in vitro behavior of the formulation [2].

APPLICATIONS

Applications of nanosuspensions had land marking history and the applications given are few.

1. ***ORAL DRUG DELIVERY***

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. .Orally administered antibiotics such as atovaquone and bupravaquone reflect this problemvery well.Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability [31].

The oral administration of naproxen nanoparticles lead to an area under the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with just 44.7 mg-h/l for naprosyn suspensions and 32.7 mg-h/l for anaprox tablets [35]. Oral administration of the gonadotrophin inhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2% [36]. A nanosuspension of Amphotericin B developed by Kayser et al.showed a significant improvement in its oral absorption in comparison with the conventional commercial formulation. [37]

2. ***PARENTERAL DRUG DELIVERY***

One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages [2].Peters et al. prepared clofazimine nanosuspensions for IV use and showed that the drug concentrations in the liver, spleen and lungs reached a comparably higher level, well in excess of the minimum inhibitory concentration for most Mycobacterium avium strains.[38] Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using conventional solubilization techniques, such as use of surfactants, cyclodextrins, etc., to improve bioavailability.[39]

3. ***PULMONARY DRUG DELIVERY***

Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in lungs.[2]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 (Ponchel et al 1997) 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 activemoiety is highly beneficial and is required by most pulmonary diseases.[31]Budenoside drug nanoparticles were successfully nebulized using an ultrasonic nebulizer.[40]

4. ***OCULAR DRUG DELIVERY***

Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. Nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal

approach for ocular delivery of hydrophobic drugs and Nanoparticulate nature of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug.[31]Pignatello et al. prepared Eudragit retard nanosuspensions of cloricromene for ocular delivery.[41] They observed that the drug showed a higher availability in rabbit aqueous humor. The polymeric nanosuspensions of flurbiprofen and ibuprofen have been successfully formulated using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 (Bucolo et al 2002; Pignatello et al 2002b,c). The ocular anti-inflammatory activity of Ibuprofen-Eudragit RS100 nanosuspensions was greatly improved when compared with an aqueous solution of Ibuprofen lysinate. Further, the aqueous humor drug concentration was significantly higher in groups treated with Ibuprofen-Eudragit RS when compared with the Ibuprofen- treated group.[2]

5. *TARGETED DRUG DELIVERY*

Nanosuspensions can be used for targeted delivery as their surface properties and in-vivo behavior can easily be altered by changing either the stabilizer or the milieu. The engineering of stealth nanosuspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems.[31]Kayser formulated a nanosuspension of Aphidicolin to improve drug targeting against leishmania-infected macrophages. He stated that the drug in the conventional form had an effective concentration (EC 50) of 0.16 mcg/ml whereas the nanosuspension formulation had an enhanced activity with an EC (50) of 0.003 mcg/ml.[42] Scholer et al. showed an improved drug targeting to the brain in the treatment of toxoplasmic encephalitis in a new murine model infected with Toxoplasma gondii using a nanosuspension formulation of Atovaquone.[43]

6. *MUCOADHESION OF THE NANOPARTICLES*

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface.The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption.[44] The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT, e.g.,Cryptosporidium parvum.[2]Mucoadhesive bupravaquone nanosuspensions, because of their prolonged residence at the infection site, revealed a 10-fold reduction in the infectivity score of Cryptosporidium parvum as compared to the bupravaquone nanosuspensions without mucoadhesive polymers.[31]

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