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REVIEW ARTICLE

Nanosuspension: A Nano-Heterogeneous Carrier for Drug Delivery System

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ABSTRACT

The basic challenge in pharmaceutical research is to achieve maximum bioavailability for desired therapeutic efficacy but poorly soluble drug always suffers from its erratic absorption as well as bioavailability. Nanosuspension technology can be used resolve the problems of low aqueous solubility and bioavailability. Nanosuspension can be applicable to all less aqueous soluble drugs and it acts tremendously to modify solubility as it belong to a few nanometer size solute particles. The various technologies that have come to prepare nanosuspension are precipitation, milling, high pressure homogenization, emulsion and microemulsion method, dry co-grinding, supercritical fluid method. 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.

Key words: Nanosuspension, solubility, bioavailability, Saturation solubility.

INTRODUCTION

Solubility plays a key role for a drug molecule in order to achieve its maximum activity and effectiveness through its bioavailability because the aqueous solubility becomes a hurdle for the formulation of new drug entities. More than 40% of new drug entities are considered poorly soluble drug or lipophilic compounds [1].Poor soluble drugs often create problem in formulating them into conventional tablet or capsule as they act as dissolution control system. It is a common problem for those drugs belonging to the biopharmaceutical classification system (BCS) classes II and IV but later class of drug has rarely received attention in pharmaceutical research due its low solubility as well as poor permeability [2,3,4].As the performance of the drug molecules solely depends on its intrinsic solubility, so anything that enhance surface area and contact of dissolution medium to the exposed surface by lowering the particle size will influence the dissolution rate too some extent[5]In recent times, the number of techniques have come to resolve the problem of low solubility. Techniques include micronization by lowering the particle size [6], solubilization using co-solvent by lowering interfacial tention [7], salt formation [8], surfactant dispersions [9], precipitation technique[10,11] and oily emulsion. Some other techniques like formation of vesicular structure i.e.liposomes [12], and transferosome[13], emulsions[14,15], microemulsion [16,17], solid dispersion [18,19] and inclusion complexation using cyclodextrins [20,21,22] are useful for drugs having high log P values.

A nanosuspension is a submicron colloidal dispersion of drug particles that are produced by suitable methods and stabilized by surfactants. A pharmaceutical nanosuspension can be defined as the nano-sized drug particle which is finely dispersed in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. In general, the particle size in nanosuspension is always less than 1µm (usually lies between 200nm to 600nm)[23,24]. Nanosuspensions not only increase the surface area but also simultaneously increase the saturation solubility and the solution velocity by increasing the vapour pressure of the particles. Here the dissolution velocity gradually gets increased due to decrease in the diffusional distance on the surface of drug nanoparticles. The saturation solubility gets affected through in situ generation of energies during conversion of drug microcrystals to nanoparticles [25].

The term stability is most important in concern of nanosuspension as differences in particle size in

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nanosuspension always hamper the stability and influences the phenomenon, like Ostwald ripening, that causes further transformation of nanosized particles to microparticle through crystal growth. Thus, uniform particle size is essential for formulation of nanosupension with required stability [26].

Preparation of nanosuspension

Nanosuspension is generally prepared by two methods that are "Bottom up technology" and" Top down technology". "Bottom up technology "follows precipitation method where the drug is dissolved in a solvent, which is then added to a non-solvent which precipitates crystals. Precipitation technique uses simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this technique lies in the fact that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with the nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media [27]. Some nanosuspensions of Carbamazepine [28], Cyclosporine [29], Griseofulvin [30], and Retinoic acid [31] have already been developed by precipitation method.

The "Top down technology" follows the method of disintegration which is preferred over the conventional precipitation technology. Technologies like Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure), combination of Precipitation and High-Pressure Homogenization (Nanoedege) [32,33] and others like Emulsion Solvent diffusion method and Microemulsion as templates [34] are various examples of "Top down technology".

Media milling

This technology was first developed by liversidge *et.al* in 1992. In this method the nanosuspensions 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 composed 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. All the process is performed under controlled temperatures. The main mechanism of the milling media is to generate a high energy and shear forces that need to break the microparticulate drug into nano-sized particles. The media milling procedure are applicable for both micronized and non-micronized drug crystals. This method has some advantages like

- Ease of scale up,
- Little batch to batch variation
- High flexibility in handling large quantities of drugs.

Despite advantages it still has some limitation. These are

- generation of residue of milling Media
- Require milling process for hours to days
- Prolonged milling may induce the formation of amorphous lead to instability.

Nanosuspension containing Cilostazol [35] Danazol [36] Naproxen [37,36] was prepared by this method.

High pressure Homogenization

Homogenization techniques enable to pass the suspension through a valve having a narrow aperture under a high pressure. 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 [38].The pressure is a key factor for production nanosized drug particles and the can generally be operated at pressure varying from 100 to 1500 bars but sometimes it can be maximized up to 2000 bars. In homogenization techniques, a presuspension of micronized drug is first prepared adding surfactant in a suitable quantity then presuspension is further subjected into homogenizer. Different capacities of high-pressure homogenizers i.e. 40 ml for laboratory purposes and thousand litres for large-scale production are available.

This method most useful and advantageous over others such as

- General applicability to most drugs,
- Useful for formation of very dilutes as well as highly concentrate nanosuspension
- Simple technique
- Aseptic production possible
- Low risk of product contamination.

It has some limitation like

- High number of homogenization Cycles
- Prerequisite for drug to be in micronized state and suspension formation before homogenization

- Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer [39].

Nanosuspension of some drugs i.e. nimodipine [40],bupravaquone[41,42], carbazepine, cyclosporine, prednisolone and atorvastatin [43]. Albendazole [44], Amphotericin B[45,46], Aphidicolin[47], Atovaquone [48],Azithromycin[49], Budesonide [50], Clofazamine [51], Disodium cromoglycate [52], Fenofibrate [53], Glucocorticoid drugs[54], Ibuprofen[55], Itraconazole[56], Mitotane[57], Nifedipine [58], Oleanolic acid [59], Omeprazole [60], Paclitaxel [61], Spironolactone [62] were prepared by this method.

Nanoedge technology

Nanoedge technology involves on the precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy [63]. This also includes the combination of rapid precipitation and high-pressure homogenization.

In this technique the precipitated suspension is further homogenized to get smaller particle size and avoid crystal growth. It produces nanosized stable dispersion with a short period of time as well it avoids crystal growth. Nanoedge technology is a registered trademark of Baxter International Inc. and its subsidiaries.

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 [38].

Emulsion method

Emulsion method is used as template to form suitable nanosuapension. Here it is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. In this method a organic solvent or solvent mixture containing the drug is dispersed in aqueous phase with measured quantity of surfactant or mixture of susfactants and kept it for some times with vigorous stirring until the emulsion is formed. The obtained emulsion is further homogenized by high pressure homogenization. Emulsion is diluted with water and a conversion droplet into solid particle is occurred. 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. Surfactant composition or amount is kept in a defined limit to ensure high intake of organic phase as well as drug loading in the emulsion due to better solubility of drug in organic phase. Some organic solvents like ethanol, ethyl acetate, chloroform etc are used as oil phase [38].Nanosuspensions of diclofenac [64], acyclovir [65], Breviscapine [66] were prepared by this method.

Microemulsion template

Microemulsions is homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, usually in combination with a cosurfactant and whose diameter is in the range of 10-140 nm [67]. The high drug loading can be achieved in microemulsion due to high solubilization of candidate drug and it is further diluted with water to form nanosized dispersion. Griseofulvin nanosuspension is prepared by microemulsion technique using butyl lactate as oil phase, lecithin and the sodium salt of taurodeoxycholate as surfactant and water [68].

Dry co-grinding

Dry co-grinding process is under the milling techniques where the dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media are perform to produce stable nanosuspension. Various soluble polymer and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. Dry co-grinding process enable to improve surface polarity and transformation from a crystalline to an amorphous form as amorphous form of drug candidate possesses better solubility than crystalline form in aqueous phase [69]. Merits of the dry co-grinding process are

- Easy process.
- No organic solvent required.
- Require short grinding time.

But it has reported that generation of residue of milling media is often found [39].

Some nanosuspension of drugs i.e. Clarithromycin [70], Glibenclamide and Griseofulvin [71], Glisentide [72], Naproxen [73], Phenytoin [74], Nifedipine [75], Indomethacin [76] Pranlukast [69] have been prepared by dry co-grinding method.

Supercritical fluid method

Supercritical fluid method has now received a great attention for production of nanosuspension because conventional method such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods are hazardous to environment and physiological systems. 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).In this method, supercritical anti solvent serves a liquid solvent i.e. methanol, which is completely miscible with the supercritical fluid (SC CO2), that are used to solubilize the solute at process condition as the solute is insoluble in the supercritical fluid but the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles [38]. Dexamethasone [77] phosphate drug nanoparticles (for microencapsulation) and griseofulvin [78] nanoparticles were prepared by using SAS method.

Formulation of nanosuspensions

Nanosuspension formulation requires basically stabilizer or surfactant, proper solvent system and others ingredients for its preparation.

a) Stabilizers: Stabilizer is used to wet the surface of solute or drug particle and retard the Ostwald ripening and agglomeration in order to provide high physical stability which further reflects to its performance. Commonly used stabilizers are polysorbate (Tween/Span series), povidones, cellulosics, poloxomers and lecithin.

b) Organic solvent: Organic solvents are generally used in preparation of nanosuspension if emulsion or microemulsions technologies are used as template for this. These solvent are very hazardous in physiologic and environmental means but still some less hazardous water miscible solvents like methanol, ethanol, chloroform, isopropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol are used over the dichloromethane (reported as a conventional hazardous solvent) [38].

c) Other additives: Uses of other ingredients depends on either the route of administration or physicochemical properties of candidate drug but some additives such as buffers, salts, polyols, osmogent and cryoprotectant are normally used.

Characterization of nanosuspension

In case of nanosuspension, main characterizations are particle size and size distribution as those plays a key role for solubilization and others are particle charge (zeta potential), crystalline status, as well as dissolution velocity and saturation solubility.

Particle size and size distribution

Particle size and size distribution and mean particle size and poly dispersity index are most important for physicochemical properties like saturation solubility, dissolution velocity, physical stability and even biological performance. Particle size and size distribution are generally determined by using different methods like photon correlation spectroscopy (PCS), laser diffraction (LD), coulter counter multisizer and Malvern mastersizer.

Photon correlation spectroscopy is also used for width of particle size distribution or poly dispersity index determination (PI) which further ensures stability of nanosuspension and should be as low as possible for the long-term stability of nanosuspensions. If PI value varies from 0.1-0.25 indicates narrow size distribution whereas a PI value >0.5 indicates
a very broad distribution.

Zeta potential or particle charge

The term Zeta potential is directly related to stability of the nanosuspension and it also predicts the long term stability of nanosuspension. A minimum of zeta potential of ± 30mV is essential to stabilize the nanosuspension elctrostatically and the nanosuspension if stabilized by both electrostatic and steric stabilization should require a minimum zeta potential of ± 20mV.

Crystal morphology study

X-ray diffraction analysis is used to determine physical change of crystalline structure that occurs during high pressure homogenization. A nanosuspension can undergo changes
from the crystalline form to either amorphous form or different polymorphic form because the effect of high pressure homogenization.

Saturation solubility and dissolution velocity

Nanosuspension is able to increase both the dissolution velocity and saturation solubility.
Size reduction indicates the enhancement of effective surface area that turns to increase
dissolution pressure as well as dissolution velocity. As solubility increases that changes the surface tention leading to increase saturation solubility [38].

APPLICATION OF NANOSUSPENSION

Parenteral Administration

Nanosuspension can be delivered either intra-articular or intravenous route. But in case of parenteral administration, solute should be remained in solubilized form or particle or globule size below 5 µm to avoid capillary blockage. Some current approaches have come resolve the drawbacks of poorly soluble drug for parenteral delivery. These are salt formation, solubilization using co-solvent, miceller solution, complexation with cyclodextrin and vesicular system (liposome and transferosome). In recent time, vesicular systems like liposome have been accepted for

parenteral delivery but they have some limitation in terms of physical instability, high manufacturing cost and difficulties in scale-up. However nanosuspension has still been considered as a useful dosage form which employs better efficacy for parenteral administered drugs. More for example, paclitaxel nanosuspension has been found better responses in treating tumour than taxol[61]. O kayser reported that poorly water soluble new antiparasitic compound aphidiocolin revealed better efficacy in EC50 in comparison to DMSO dissolved drug [47].Nanosuspension of poorly soluble antileprotic drug clofazimine showed an enhancement in stability and efficacy over the liposomal clofazimine in *Mycobacterium avium* infected female mice[51]. Rainbow et.al observed that intravenous application of itraconazole, poorly soluble antifungal drug improved antifungal efficacy in comparison to solution of formulation of same drug in rats [56].

Peroral administration

Oral route is considered as most satisfactory route for drug delivery system due to its ease of application. JP Remon prepared the ketoprofen nanosuspension and then incorporated into pellets to get drug release in sustained manner over a period of 24h [79].Nanosuspensions of atovaquone were used for treatment of *Pneumocytis carinii* infection for HIV patients, non complicated Plasmodium falciparum and leishmanial infection [48].Another study was conducted with atovaquone as a form of suspension and found increase in oral bioavailability relative to the micronized commercial product Wellvone [80]. Amphotericin B, a well known poorly soluble antifungal drug as nanosuspension was found better oral bioavailability when compared with commercially available products like Fungizone, AmBisome and micronized amphotericin B [45].

Bupravaquone nanosuspensions have been used for the *Cryptosporidium parvum* infection, the main pathogen causing severe diarrhea in immunosuppressant HIV patients [80]. Nanosuspension fenofibrate showed better bioavailability in comparison to conventional suspensions of micronized drugs when administered orally [53].

Ophthalmic drug delivery

In ophthalmic drug delivery, prolong drug residence time in cul-de-sac always favors better treatment of most ocular disease and activity of drug in nanosuspension depends on the intrinsic solubility in lachrymal fluids as well as in ocular bioavailability. R Pignatello *et.al* developed ibuprofen nanosuspensions using Eudragit RS 100 as polymer by a quasi-emulsion and solvent diffusion method [81]. Other nanosuspension for ocular delivery with some steroidal drugs such as glucocorticoids, hydrocortisone, Prednisolone and dexamethasone were used [54].

Pulmonary drug delivery

Nanosuspension is the optimum product for lung drug delivery system as it utilizes nebulizer which through the drug particle to the large surface area of the lungs by mechanical or ultrasonic means.MA Kasem et.al developed the nanosuspension of budesonide, a poor water soluble corticoids for pulmonary delivery [50]. Bupravaquone nanosuspensions were prepared for treatment lungs infection by using nebulizer [82].

Target drug delivery

Nanosuspension is approximate product for targeted drug delivery system as it possesses nanosized solute or drug dispersion and its modified structure is extensively set at the specific site for absorption. Now a day the engineered stealth nanosuspension is prepared by using various surface coating for active or passive targeting of desired site. The surface modified mucoadhesive bupravaquone nanosuspension has been developed for targeting of *Cryptosporidium parvum* which is a causative organism for cryptosporidiosis [41].In another case, amphotericinB in nanosuspension has been targeted to treat pulmonary aspergillosis and achieved fruitful results at the end [83].

Topical administration

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin [84-86].

Table1: Some recent works on nanosuspension to be marketed [87]

Drug	Used for	Route	Status
Paclitaxel	Anticancer	Intravenous	Phase IV
Budesonide	Antiasthamatic	Pulmonary	Phase I
Busulfan	Anticancer	Intrathecal	Phase I
Fenofibrate	Hypolidemic	Oral	Phase I
Thymectacin	Anticancer	Intravenous	Phase I/II
Insulin	Antidiabetic	Oral	Phase I
Calcium Phosphate	Mucosal vaccine adjuvant for Herpes	Oral	----------
Silver	Eczema, atopic dermatitis	Topical	Phase I

Cytokine Inhibitor	Crohn's disease	Oral	Phase II

Table 2: Current marketed nanosuspension products [39]

Produ ct name	Drug compound	Uses	Company	Nanoparticle technology
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Elan Drug Delivery Nanocrystals®
EMEND®	Aprepitant	Antiemetic	Merck	Elan Drug Delivery Nanocrystals®
TriCor®	Fenofibrate	Treatment of hypercholesterolemia	Abbott	Elan Drug Delivery Nanocrystals®
MEGACE® ES	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical	Elan Drug Delivery Nanocrystals®
Triglide™	Fenofibrate	Treatment of hypercholesterolemia	First Horizon Pharmaceutical	SkyePharma IDD®-P technology

Moreover nanosuspension technology can be combined with conventional dosage form like tablets, capsules, pellets and it will become a topic of interest with especial reference to peroral administration in future.

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