Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (5):384-392
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Nanocrystal technology: A particle engineering formulation strategy for the poorly water soluble drugs

Vishal V. Pande and Vidya N. Abhale*

Department of Pharmaceutics (PG), SRES' Sanjivani College of Pharmaceutical Education and Research, Kopargaon

---

ABSTRACT

Many of the recently developed new chemical entities are poorly water soluble and they create major problems during formulation and development of new dosage form and shows poor bioavailability. The drugs belong to BCS class II has problem of solubility, to overcome the solubility problem nanotechnology is most useful technique. Nanosuspensions are defined as the submicron biphasic colloidal dispersions of pharmaceutical active ingredient particles in a liquid phase, size below 1μm, without any matrix material which are stabilized by surfactants and polymers. Nanosuspensions are nanoparticles being composed of 100% drug without any matrix material. In this review the main focus is given on various techniques conventional as well as patented technology used for preparation of nanocrystals. There are certain characterization paratemeters such as particle size, polydispersibility index, surface morphology, particle surface charge, crystalline state, Surface hydrophilicity, Adhesion properties for the nanocrystals formulation. This is suitable drug delivery system for all commonly used routes of administration such as oral, IV, SC, and IM and topical application. In addition, nanocrystals can be incorporated into the tablets, capsules, fast-melts and lyophilized for sterile product applications.

Keywords: Nanotechnology, Nanosuspension, poorly water soluble.

INTRODUCTION

In last two decade we have observed tremendous increase in new lead compound due to advances in high-throughput screening, combinatorial chemistry, and computer-aided drug design. Out of which nearly 70% of the new chemical entities (NCE) are reported poorly water soluble [1]. Conventional formulations of poorly-water-soluble drugs are frequently facing the problems such as poor and highly variable bioavailability. The dosage form is often times affected by the fed–fasted state of the patient and its onset of action is slower than anticipated. All of these issues lead to sub-optimal dosing and poor performance.[2]From this, there is a necessity for smart technological formulation approaches to make such poorly soluble drugs bioavailable. Making such drugs bioavailable means that they show sufficiently high absorption after oral administration, or they can alternatively be injected intravenously since many years the approaches to increase drug solubility are solubilisation by surfactants, complex formation (e.g. cyclodextrin, macromolecules) self-emulsifying drug delivery systems (SEDDS), microemulsions and especially for oral administration. micronisation of drug powders. Micronization, meaning the transfer of drug powders into the size range between typically 1-10μm.[3] Micronization is a very simple technology (e.g. by jet milling or wet milling). The principle was to increase the dissolution velocity by enlarging the surface area of the drug powder micronisation was or is a technology for case II drugs of the biopharmaceutical classification system (BCS), i.e. drugs having a good permeability but a low oral bioavailability due to their poor solubility and low dissolution velocity. [4] Nowadays, many of the new drugs exhibit such a low solubility that micronisation does not lead to a sufficiently high bioavailability. Consequently, the next step was taken to move from micronisation to nanonisation, that means producing drug nanocrystals. [5,6]

According to definition , drug nanocrystals are nanoparticles being composed of 100% drug without any matrix material, by the definition of nanoparticles the mean particle size is below 1 mm (i.e. in the nanometre range, typically somewhere between 200 and 500nm.[4] Dispersion of drug nanocrystals in liquid media leads to so called "nanosuspensions" (in contrast to "microsuspensions" or "macrosuspensions"). In general the dispersed particles need to be stabilized, such as by surfactants or polymeric stabilizers.[5] Many different techniques exist for the production of nanocrystals, the most commonly used of which are precipitation, pearl milling and high pressure homogenization.So far, four products, namely Rapamune (sirolimus,Wyeth), Emend (aprepitant, Merck), TriCor (fenofibrate, Abbott) and Megace (megestrol acetate, Par Pharmaceutical) have been commercialized.[Invega Sustenna (paliperidone palmitate, Janssen), also based on NanoCrystal technology, has been approved by the US Food and Drug Administration. One commercial product, Triglide (fenofibrate, Skye Pharma), is based on a high-pressure homogenization technique.[6]

Advantages

1. It can be given by any route of administration.
2. Reduced tissue irritation in case of subcutaneous/intramuscular administration.
3. Rapid dissolution & tissue targeting can be achieved by IV route of administration.
4. Oral administration of nanosuspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability.
5. The absorption form absorption window can be increased, due to reduction in the particle size.
6. Drug with higher log P value can be formulated as nanaosuspensions to increase the bioavailability of such drugs.
7. Nanosuspensions can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.
8. Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.
9. Possibility of surface-modification of nanosuspension for site specific delivery.
10. Possibility of large-scale production, the prerequisite for the introduction of delivery system to the market.[7]
11. Enhanced solubility and bioavailability of drug.
12. Higher drug loading can be achieved[9]
13. Long term physical and chemical stability (due to absence of Ostwald ripening).

Disadvantages

1. Physical stability, sedimentation & compaction can cause problems.
2. It is bulky sufficient care must be taken during handling & transport.
3. Improper dose.
4. Uniform & accurate dose cannot be achieved.[7-9]

Techniques for Manufacturing of Nanocrystals

1. Bottom up technology
    - 1.1 Anti-solvent precipitation
    - 1.2 Supercritical fluids
    - 1.3 Spray-drying
2. Top down Technology
    - 2.1 Media milling
        - 2.1.1. Bead milling
        - 2.1.2. Dry co-grind
    - 2.2 High pressure homogenizations
        - 2.2.1. Homogenization in Aqueous media (Dissocubes)
        - 2.2.2. Homogenization in Non Aqueous Media (Nanopure)
        - 2.2.3 Nanojet technology
    - 2.3 Emulsion solvent diffusion method
3. Combination technology
    - 3.1 NANOEDGE® Technology
    - 3.2 SmartCrystal® Technology[23]
4. Other methods
    - 4.1. Solvent evaporation
    - 4.2. sonocrystalisation
    - 4.3. melt emulsification
    - 4.4. Bottom-Up NanoCrySP Technology

1. Bottom up technology

Bottom up technology starts with molecule . Principal of this technology is based on precipitation by dissolving the drug in a solvent and adding the solvent to a non-solvent that cause precipitation of the fine drug particle. Example of product which is manufacturing by using this technology is Hydrosols and NanomorphTM, which are developed by Sucker and Soliqs/Abbott respectively. This has the basic advantage of using relatively simple and low-cost equipment. However, this created problems in stirring and mixing when taken up for large-scale production. The major challenge of this technique is to avoid crystal growth that occurs on storage due to Ostwald ripening.

1.1 Precipitation technology:

Within few years ago precipitation technique was used to prepared microsuspension. In this technique the drug is dissolved in an organic solvent in which it is soluble and this solution is mixed with a miscible anti-solvent for precipitation in presence of stabilizer. In the water-solvent mixture the solubility is low and the drug precipitate out . [46] Precipitation has also been combined with high shear processing. This is accomplished by a combination of rapid precipitation and high-pressure homogenization. The baxter healthcare company introduced their patented technology US 6,884,436 known as NANOEDGE. This tecnhnology based on precipitation of friable materials for fragmentation under conditions of high shear and/or thermal energy. sudden super saturation of the mixed solution occurs by rapid addition of drug solution to anti-solvant and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favoured at high super saturation when the solubility of the amorphous state is exceeded.[8-10,33]

1.2 Supercritical fluid methods:

Nanoparticles are produced by various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. Young et al. prepared cyclosporine nanoparticles having diameter of 400 to 700 nm by using this technique. In the PCA method, the drug solution is atomized into the CO2 compressed chamber. As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution becomes supersaturated.[9] The basic disadvantages of the above reported methods are use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques.

1.3 Spray drying

One of the preparation methods of nanocrystals is spray drying. This method is usually used for drying of solutions and suspensions. In a conical or cylindrical cyclone, solution droplets are sprayed from top to bottom, dried in the same direction by hot air and spherical particles are obtained. Spraying is made with an atomizer which rapidly rotates and provides scattering of the solution due to centrifugal effect. The solution, at a certain flow rate, is sent to the inner tube with a peristaltic pump, nitrogen or air at a constant pressure is sent to the outer tube. Spraying is provided by a nozzle. Droplets of solution become very small due to spraying; therefore, surface area of the drying matter increases leading to fast drying. Concentration, viscosity, temperature and spray rate of the solution can be adjusted and particle size, fluidity and drying speed can be optimized. The dissolution rate and bioavailability of several drugs, including hydrocortisone, COX-2 Inhibitor (BMS-347070) were improved utilizing this method.[3,29]

2. Top down technology

The ‘Top Down Technologies’ are the disintegration methods and are preferred over the precipitation methods .This includes

2.1 Media milling (Nanocrystals or Nanosystems)

2.1.1. Bead milling

The method is first developed by liversidge et. al. In this method the nanosusensions are produced using high-shear media mills or pearl mills. [11] The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. The milling medium is made up of glass, zirconium oxide or highly cross-linked polystyrene resin. The milling chamber is fed with the milling media, water, drug and stabilizer and then milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures. The nanosuspension or nanoparticles are form as result of high energy and shear forces generated due to the impaction of the milling media with the drug which 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. A

nanosuspension of Naproxen with a mean particle size of 300-600 nm was prepared using pearl milling technique.[14,44]

2.1.2. Co-grinding

Now a day, nanosuspensions can be also prepared by dry milling techniques. Successful work has been reported in preparing stable nanosuspensions using dry grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media. It is the colloidal particles formation of many poorly water soluble drugs; griseofulvin glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodiumdodecylsulfate (SDS). Various soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. By using this method the Physicochemical properties and dissolution of poorly water soluble drugs were improved because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. Dry co grinding can be carried out easily and economically and can be conducted without need of organic solvents.[15]

2.2 High Pressure Homogenization:

2.2.1. Homogenization in Aqueous media (Dissocubes)

This technology was developed by R.H.Muller in 1999 and first patent was taken by DDS Gmbh and laterward the patent was transferred to Skyp pharmaceuticals. Commonly used homogenizer are the APVMicron Lab 40 (APV Deutschland Gmbh, Lubeck, Germany)and piston-gap homogenizers. In this method, the suspension containing a drug and surfactant is forced under pressure through a Nanosized aperture valve of a high pressure homogenizer. In this method the particle size reduction depend on cavitation principle. The dispersion present in 3cm diameter cylinder is suddenly passed through a very narrow gap of 25µm. According to Bernoulli's law the flow volume of liquid in a closed system per cross section is constant. It leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at diameter from 3cm to 25µm.Then water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The particles cavitation forces are sufficiently high to convert the drug micro particles into nanoparticles. In this the final particle size of drug nanocrystal is based on power density of homogenizer, number of homogenization cycles, temperature and homogenization pressure. [19]

2.2.2. Homogenization in Non Aqueous Media (Nanopure)

Nanopure is one the technology in which suspension is homogenized in water-free media or water mixtures. In the Dissocubes technology the cavitation is the principle determining factor of the process. oils and oily fatty acids have very low vapour pressure and a high boiling point as compare to water. 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 thermo labile 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 thermo labile substances at milder conditions.[17]

2.2.3. Nanojet technology

This technology called opposite stream or nanojet technology. This method consist of microfluidizer which 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 due particle collision and high pressure results in particle size reduction. Equipment using this principle includes the M110L and M110S micro fluidizers. Dearn prepared nanosuspensions of atovaquone using the micro fluidization process. [21]The major disadvantage of this technique is the high number of passes through the micro fluidizer and that the product obtained contains a relatively larger fraction of microparticles.[18]

2.3. Emulsion solvent diffusion method

Apart from the use of emulsion as drug delivering vehicle they can also be used as 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, diclofenac, acyclovir were prepared by this method.[14]

3. Patented Technologies of Nanosuspension

3.1 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.[12,18-20]

3.2 SmartCrystal® technology

Recently SmartCrystal® technology was first developed by PharmaSol GmbH and was later acquired by Abbott. It is a tool-box of different combination processes in which process variations can be chosen depending upon the physical characteristics of the drug (such as hardness). The process H42 involves a combination of spray-drying and HPH. Within few homogenization cycles the nanocrystals is prepared. Process H69 (Precipitation and HPH) and H96 (lyophilization and HPH) yield nanocrystals of amphotericin B within a size range of about 50 nm[41]. S. Kobierski et al. (2008) produced nanocrystals in a two-step process i.e. pre- milling followed by high pressure homogenization (HPH). Nanosuspensions of cosmetic active hesperidin were produced by ball-milling process and with combination process. Both the prepared nanosuspensions were kept for storage. Nanosuspension prepared using SmartCrystal® technology was found to be of a smaller size indicating better physical stability. Also combination technique is faster and more economical as compared to HPH alone . Möschwitzer and Müller43 (2005) prepared spray dried hydrocortisone acetate powder from nanosuspension produced by HPH with a micron LAB 40 and planetary monomill “pulverisette”. The number of cycles required could be distinctly reduced. Additionally, a smaller particle size and better particle size distribution could be obtained. Another finding of the study was that the application of different homogenization pressures (e.g. 300 and 500 bar) was equally efficient. Therefore, during large scale production, low homogenization pressures (300 bars) may be preferred to reduce wearing of the machin.[23]

4. Other technologies

4.1 Solvent Evaporation:

In the solvent evaporation method, the solutions of polymer are prepared in volatile solvents and emulsions. But from the past years dichloromethane and chloroform were used which was now replaced by ethyl acetate which has a better profile of toxicology. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. These methods require high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. By ultracentrifugation the solidified nanoparticles are collected which was washed with distilled water to remove the additives like surfactants, and then it was lyophilized. The particle size was influenced by the concentration of polymer, stabilizer and the speed of homogenizer.[19]

4.2 Sonocrystallization

Recrystallization of poorly soluble material using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is sonocrystallization. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. It not only enhances the nucleation rate but also an effective means of size reduction & controlling size distribution of the active pharmaceutical ingredient (API). Most applications used ultrasound in the range 20 khz -5mhz. Sonocrystallization technique or technology has also been studied to modify the undesirables of NSAID’S i.e. poor solubility and dissolution rate and consequently the poor bioavailiability. Flubiprofen was poured in deionized water at 25°C and sonicated for 4 minutes at an amplituted of 60% and cycle is 40 sec on and 10 sec off. The particle size of treated flubiprofen was significantly reduced and the increased solubility of treated flurbiprofen was about 35%. The intrinsic dissolution rate of treated flubiprofen increased by 2-fold. The dissolution studies obtained that 90% of the drug was released within 20 minutes for treated flubiprofen as compared to untreated flubiprofen obtained 60% release of the drug.[3]

4.3. Melt emulsification method

Solid lipid nanoparticles are mainly prepared by melt emulsification method. Kipp and co workers firstly prepare nanosuspensions of ibuprofen by using melt emulsification method. It is a four-step procedure. Drug is first added to aqueous solution having stabilizer. The solution is heated at temperature higher than the melting point of the drug and then homogenized by high-speed homogenizer for the formation of emulsion. The temperature is maintained above the melting point of the drug during overall process. Finally, the emulsion is cooled to precipitate the particles. The particle size of nanosuspension mainly depends on parameters like drug concentration, concentration and type of stabilizers used, cooling temperature, and homogenization process.[22]

4.4. Bottom-Up NanoCrySP Technology

G. Shete, Y. Pawar et al, National Institute of Pharmaceutical Education and Research (NIPER) introduced a newer method to generate nanocrystalline solid dispersion (NSD) of hesperetin using NanoCrySP technology: a novel bottom-up process based on spray drying to generate solid particles containing drug nanocrystals dispersed in the matrix of small molecule excipients (WO2013132457 A2). The purpose of their study to improved oral bioavailability and pharmacodynamic activity of hesperetin nanocrystals generated using a novel bottom-up NanoCrySP Technology. Hesperetin and mannitol were used in 1:1 ratio and NSD was generated using spray drying. The process of NSD formation is based on classical nucleation theory wherein mannitol contributed to crystallization of hesperetin by acting as plasticizer, crystallization inducer and by providing heterogeneous nucleation sites. Hesperetin was found to exist as nanocrystals dispersed in the matrix of mannitol with average crystallite size of 137 nm in the NSD.

Evaluation of Nanocrystals:

1. In-Vitro Evaluations
    1. Mean Particle size and size distribution
    2. Particle charge (Zeta Potential)
    3. Crystalline state and morphology
    4. Saturation solubility and dissolution velocity
2. In-Vivo Evaluation
3. Evaluation for surface-modified Nanosuspensions
    1. Surface hydrophilicity
    2. Adhesion propertiesss
    3. Interaction with body proteins[18,22,24]

1. Mean particle size and size distribution

Photon Correlation Spectroscopy30 (PCS) is used to determined the mean particle size and the width of particle size distribution (called Polydispersity Index). The saturation solubility; dissolution velocity and biological performance depends on particle size and polydispersity index (PI). PCS measures the particle size in the range of 3nm- 3 µm only. PCS is a versatile technique but has low measuring range. Laser Diffractometry (LD) is also used to determined particle size distribution. LD measures volume size distribution and measures particles ranging from 0.05- 80µm. Atomic Force Microscopy is used for visualization of particle shape.[24]

2. Zeta potential (particle charge distribution)

Zeta potential determines the physical stability of nanosuspenson. Zeta potential gives an idea about thickness of the diffusion layer, i.e. can be used to predict long term stability. In order to obtain a Nanosuspensions exhibiting good stability, for an electrostatically stabilized Nanosuspensions 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.[24,25]

3. Crystal structure/ morphology

X-ray diffraction analysis in supplemented 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. 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. The techniques such as scanning electron microscopy (SEM), atomic force microscopy (AFM) or transmission electron microscopy (TEM) are preferred in order to get an actual understanding of particle morphology.[26]

4. Saturation solubility and Dissolution velocity

The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be determined using methods reported in the various literatures. The investigation of the dissolution velocity of nanosuspensions reflect the advantages that can be achieved over conventional formulations, especially when

designing the sustained release dosage forms based on nanoparticulate drugs. The evaluation of saturation solubility and dissolution velocity helps in determining the invitro behavior of the formulation.[27]

5. In Vivo Biological Performance

Irrespective of the route and the delivery system employed the establishment of an in vitro/in vivo correlation and the monitoring of the in vivo performance of the drug are an essential part of the study. IVIVC is more important in the case of intravenously injected nanosuspensions since the in vivo behaviour of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins.[42] After the intravenous injection of nanoparticles the qualitative and quantitative composition of the protein absorption pattern observed and is recognized as the essential factor for organ distribution . Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of in-vivo behavior. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity, whereas 2D PAGE can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals.[25]

APPLICATIONS

1. Oral Drug Delivery

Drugs Administered orally suffers with major problems like poor solubility, incomplete dissolution and insufficient efficacy. [46] Nanosuspensions are specially used to enhance the absorption rate and bioavailability because of their smaller particle size and larger surface to volume ratio.[31] In comparison to 20% of micronized drugs in case of azithromycin nanosuspension, more than 65% drug was found to be dissolved in 5 hours. Nanosuspension enjoys the benefits like improved oral absorption, low intersubject variability and dose proportionality. Nanosuspensions containing drug can be incorporated in various dosage forms like tablets, capsules and also fast melts by using standard manufacturing techniques. [22, 28, 34]

2. Parenteral administration

The conventional parenteral preparations (particularly for intravenous administration) of poorly soluble drugs are contains harsh solvent or co-solvants which is often associated with toxic effects and large injection volumes. Aqueous nanosuspensions are an ideal formulation to overcome these problems e.g. Paclitaxel nanosuspensions cause less toxicity as compared to Taxol with Chremophor EL.[46]. In comparison to conventional paclitaxol solution dosage form its nanosuspension was reported to enhance the anti fungal effect in rats. As compared to solutions the nanosuspensions having higher drug loading capacity and hence the injectable dose can be distinctly reduced. The various techniques are used for sterilization of nanosuspension such as autoclaving, using gamma radiations or by sterile filtration using 0.22 mm filter.[23,41]

3. Pulmonary drug delivery

Nanosuspension in case of Pulmonary drug delivery is used for those drugs which are poorly soluble in pulmonary secretion. 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. The advantage is that Increased adhesiveness of the drug to mucosal surfaces, Prolonged residence time of the drugs at absorption site which prolongs the effect of the drug, and hence we get Initial quick onset of action. [30,39]. 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.[21,40]

4. Bioavailability Enhancement

Many of newly developed molecules having the problem of poor water solubility and also poor permeability . Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane.[34,44] As compared to conventional naproxen the oral administration of naproxen nanoparticles lead to an area under the curve (AUC) (0-24 h) of 97.5 mg-h/l which is just 44.7 mg-h/l for naprosyn suspensions and 32.7 mg-h/l for anaprox tablets. The Oral administration of the gonadotrophin inhibitor in conventional dispersion (Danocrine) only shows 5.2% absolute bioavailability but in the form of nanosuspension Danazol its about 82.3%. Kayser et al. developed the nanaosuspension Amphotericin B showed a significant improvement in its oral absorption in comparison with the conventional commercial formulation.[18,30,34-41]

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. [42]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. Kayser et al formulated a nanosuspension of Aphidicolin to improve drug targeting against leishmania infected macrophages. He stated that nanosuspension formulation had an enhanced activity with an EC (50) of 0.003 mcg/ml which is about 0.16mcg/ml in the conventional form. 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.[18,43]

6. Topical formulations

Nanosuspension also incorporated into topical dosage form .Drug nanoparticles can be incorporated into creams and water-free ointments.[45] The nanocrystals form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug across the skin.[39,47,48] Nanosuspensions in case of ocular drug delivery systems offer advantages includes Nanoparticle modified surface by appropriate bioerodible polymer results in prolonged residual time in cul-de-sac desired for effective treatment. Commonly reported polymers in ocular nanosuspensions are poly(alkyl cyanoacrylates), polycaprolactone, and poly(lactic acid)/poly(lactic-co-glycolic acid) . Employing polymers in ocular drug delivery significantly prolongs drug ocular residence time and improves bioavailability.[32]

CONCLUSION

The ease of their manufacturing makes Nanocrystals the choicest nanoparticles. The drug Nanocrystals being unique in nanoformulation options with significant merits, the researches comprising scalable formulations for the production of drug Nanocrystals open a new channel and unleashed a new platform for the design of these nanoformulations. It was understood that a successful scale up demands necessary product characterization, proper choice of equipment, development of an optimized formula and satisfactory stability study results. Solubility enhancement alone is not the only important factor; rather it becomes even more important when a drug has a narrow therapeutic window where it can be absorbed. In these cases the increased solubility and dissolution velocity lead to an acceptable bioavailability. In addition, the nanocrystal technology enables formulations to be developed without the need of problematic surfactants (eg, Cremophor EL) which may cause tremendous side effects or untoward reactions.

REFERENCES

[1] E. Che, X. Zheng, C. Sun, D. Chang, T. Jiang, S. Wang, *AJPS*, **2012**, 7,2, 85-95.
[2] E.M. Liversidge, G. G. Liversidge, E. R. Cooper, *Eur. J. Pharm. Sci.*, **2003,** 18, 113–120.
[3] S. V. Sawant, V.J. Kadam, K. R. Jadhav, S. V. Sankpal, *International Journal Of Science Innovations And Discoveries*, **2011,** 1,3,1-15.
[4] C. M. Kecka, R. H. Muller, *Eur. J. Pharm. Biopharm*,**2006,** 62, 3–16.
[5] J. Junghanns, R. H. Müller, *Int. J. Nanomedicine*, **2008,** 3,3, 295–309.
[6] L. Peltonen, J. Hirvonen, *JPP*,**2010** 62, 1569–1579.
[7] A. N. Mane, S. S. Gilda, A. A. Ghadge, N. R. Bhosekar, R. R. Bhosale, *Sch. Acad. J. Pharm*, **2014**, 3,1, 82-88.
[8] M. Soumya, S. Gupta, R. Jain, R. Mazumder, *Int. j. res. dev. pharm. l. Sci.*, 2013, 2, 642-649.
[9] T. Sravani, S. Rajashekhar, V. U. Maheshwara Rao, K. S. Sriyanka, B. C. Shilpai, M. Ashok, T. Sravani , *SPJPBS*, **2014**, 2,2, 174-183.
[10] R. Dhanapal, J. Vijaya Ratna, *IJPRR*, **2012**, 2 (1), 46-52.
[11] K. Bala Krishna, ch. Prabhakar, *International Journal of Pharma and Bio Sciences*,**2011**, 2,1, 549-558.
[12] R. L. Shid, S. N. Dhole, N. Kulkarni, S. L. Shi, *Int. J. Pharm. Sci. Rev. Res*, **2013**, 22,1, 20, 98-106.
[13] G. P. Kumar, K. G. Krishna, *International Journal Of Drug Delivery*, **2011**, 3, 546-557.
[14] P. Lakshmi, G. A. Kumar, *Int. J. Pharm. Sci*, **2010**, 2, 4, 35-40.
[15] P. Mittal, P. Singh, A. Verma, M. P. Khinchi, D. Agarwal , *AJPRD*, **2013**,1 , 6, 2-12.
[16] M. Patel, A. Shah, N. M. Patel, M. R. Patel, K. R. Patel, *JPSBR*, **2011**, 1,1, 1-10.
[17] J.S. Paun , H.M. Tank, *Asian J. Pharm. Tech*., **2012**, 2,4,157-168.
[18] G. Geetha, U. Poojitha, K. Khan, *IJPRR*, **2014** 3,9,30-37.
[19] P. Nagarju, K. Krishnachaithanya, V.D.N. Shrinivas, S.V.N. Padma, *Int. J. Pharm. sci. nanotechnology*, **2010**,2, 4,679-684.
[20] G.V. Yadav, S.R. Singh, *Pharmacophore*, **2012,** 3 , 5, 217-243.
[21] I. Nikhitha, C. H. Vijaya vani, A. Swarna rekha, *International Journal of Trends in Pharmacy and Life Sciences*, **2015** ,1,2, 269-278.
[22] S. Bansal, M. Bansal, R. Kumria, *International Journal Of Research In Pharmaceutical And Biomedical Sciences*, **2012,** 3,1,406-419.

[23] D. Bhowmik, G. Harish, S. Duraivel, B. Pragathi Kumar, V. Raghuvanshi, K. P. Sampath Kumar, *The Pharma Innovation – Journal*, **2012,**1(12),50.
[24] K. B. Sutradhar, S. Khatun, I. P. Luna, *Journal of Nanotechnology* ,**2013** , 1- 12 .
[25] B. K. Nanjwade, G. K. Derkar, H. M. Bechra, V. K. Nanjwade, F.V. Manvi, *J. Nanomed Nanotechnol* , **2011,** 2, 2, 1-7.
[26] S. R. Shah, R. H. Parikh, J. R. Chavda, N. R. Sheth, *J.Pharm. Innov* , **2014.**
[27] V. B. Junyaprasert, B. Morakul, *AJPS*, **2015,** I3-23.
[28] B. P. Sahu, M.K. Das, *Int. J. Pharmtech. Res*, **2013,** 5,2, 553-561.
[29] A. J. Raval, M. M. Patel, *Int. R. J. of Pharmaceuticals*, **2011,** 1,2, 42-49.
[30] A. Papdiwal, V. Pande, K, Sagar, *Der Pharma Chemica*, **2014,** 6,3, 161-168.
[31] G. S. El-Fekya, G. Zayedb, A. R. H. Farrag, *Int. J Pharm Pharm Sci*, **2013,** 5,1, 213-219.
[32] V. M. Pandya , J. K. Patel, D. J. Patel , Der Pharmacia Lettre, **2011,** 3,2, 129-140.
[33] P. P. Ige, R. K. Bariaa, S. G. Gattani, *Colloids Surf B Biointerfaces* ,**2013,** 108, 366– 373.
[34] P.F Steffi, M. Srinivasan, *Int. J. Pharmtech Res.*, **2014** ,6,2,842-849.
[35] J. Hecq, M. Deleers, D. Fanara, H. Vranckx, K. Amighi, *Int J Pharm* **2005,** 299, 167–177.
[36] D. Liu, H. Xu, B. Tian, K. Yuan, H. Pan, S. Ma, X. Yang, W. Pan, *AAPS ,Pharm. Sci.Tech*, **2012,** 13, 1, 295-304.
[37] A R.Bhargavi, *IJPT*, **2011,** 3,3, 1503-1511.
[38] B. P. Sahu, M. K. Das. *Appl Nanosci*, **2014,** 4, 189–197.
[39] S. Katteboinaa, V. S. R. Chandrasekhar P, *Int. J. Pharmtech. Res*, **2009** ,1,3, 682-694.
[40] P. Amsa, S. Tamizharasi, M. Jagadeeswaran, T. Sivakumar, *Int.J. of Pharm. Sci*, **2014,** 6,1,265-269.
[41] Y. Lu, Z. Wang, Tonglei Li, H. McNally, K. Park, M. Sturek, *Journal of Controlled Release*, **2014,** 176, 76–85.
[42] V. R. Patel, Y. K. Agrawal , *Jour .Adv. Pharm. Technol. Res*, **2011,** 2 ,2, 81-87.
[43] M. Kakran, R. Shegokar, N. G. Sahoo, L. A. Shaal, L. Li, R. H. Müller, *Euro. J. Pharm. Biopharm*, **2012,** 80, 113–121.
[44] R. K. Kotecha, S. Bhadra, Rajesh Ks (**2013**) Formulation & Process Development Of Azithromycin Ophthalmic Nanosuspension. Int J Pharm Pharma Sci : 5(4) .
[45] L. Chen, Y. Wang, J. Zhang, L. Hao , H. Guo , H. Lou, D. Zhang, *Euro. J. of Pharm. Biopharm.* **2014,** 87,160–169.
[46] A. Memon, P. U. Patel, H. M. Sheth, D. J.Patel , *IJPFR*, **2013** 3,1, 42-53.
[47] S. Pattnaik, K. Swain, J. V. Rao, *IJPBS*, **2013,** 3, 4,324-327.
[48] G. Shete, S. Y. Pawar, K. Thanki, S. Jain, A. K. Bansal, National Institute of Pharmaceutical Education and Research (NIPER).