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Drug Nanoparticles – An Overview

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1. Introduction

Advances in drug discovery technologies and combinatorial chemistry techniques have led to identification of a number of compounds with good therapeutic potential. However, because of their complex chemistry majority of these compounds have poor aqueous solubility resulting in reduced and variable bioavailability (Lipinski et al., 2002). The variability in systemic exposure observed often makes it difficult for dose delineation, results in fed and fast variability and in slower onset of action. These issues may lead to sub-optimal dosing and concomitantly poor therapeutic response. For compounds with poor aqueous solubility that are ionizable, preparation of salts to improve solubility/dissolution rate is a commonly used approach that had limited success. From a product development standpoint, generally a crystalline salt is preferred due to potential physical and chemical stability issues associated with the amorphous form. Identification of a crystalline salt with adequate aqueous solubility requires screening various counter-ions and solvents/crystallization conditions and at times isolation of a crystalline material is difficult. In some instances the salt formed is extremely hygroscopic posing product development and manufacturing challenges (Elaine et al., 2008).

Currently there are limited formulation approaches for compounds with poor aqueous solubility. The most commonly used approaches are micronisation and solid dispersions of the drug in water-soluble careers for filling into hard or soft gelatin capsules. Micronisation results in particles that are < 5 μm with a very small fraction that is in the sub-micron range. The decrease in particle size results in a modest increase in surface area that may not change the dissolution rate or saturation solubility to significantly impact bioavailability (Jens-Uwe et al., 2008).

Solid dispersion compositions comprise of molecular dispersion of the drug in water soluble and lipid-based surface-active carriers that can emulsify upon contact with the dissolution medium. Formation of molecular dispersions (solid solution) provides a means of reducing the particle size of the compounds to nearly molecular levels (i.e., there are no visible particles). As the carrier dissolves, the compound is exposed to the dissolution media as fine particles that are amorphous, which can dissolve rapidly and concomitantly absorbed. These formulations are filled in soft or hard gelatin capsules. There are several products using this approach in the market, e.g.,

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Sandimmune®/Neoral® (cyclosporin microemulsion), Norvir® (Ritnovir) and Fortovase® (Saquinavir). This approach is generally suitable for highly potent compounds and thus not applicable for moderately potent compounds where the dose requirement may be high (Merisko-Liversidge et al., 2003).

In recent years an area that is gaining popularity with formulation scientists for developing a viable dosage form for poorly soluble compounds that are moderately potent is to develop a formulation incorporating drug nanoparticles, usually less than 1 μm in diameter. For example, when the particle size of the drug is reduced from 8 μm to 200 nm there is 40-fold increase in the surface area to volume ratio. This increase in surface area can provide substantial increase in the dissolution rate if the formulation disperses into discrete particles (Liversidge et al., 1995). The nanoparticle formulation approach is proven to be very useful and invaluable in all stages of the drug product development and has opened opportunities for revitalizing marketed products with suboptimal delivery.

Nanoparticle formulation technologies have provided the pharmaceutical industry with options for addressing solubility and bioavailability issues associated with poorly soluble compounds. In new chemical entities (NCE) development, the technology has been of great value when it is used as a screening tool during preclinical efficacy and / or safety assessment studies in the early development phase. For marketed products requiring life-cycle extension opportunities, nanoparticle formulation strategies provide a means to develop a new drug-delivery platform with improved therapeutic outcome incorporating the existing drug, thus creating new avenues for addressing unmet medical needs.

2. History

Nanotechnology has a long development and application history. However, the most important scientific advancements have only taken place in the last two decades. Heterogeneous catalysts were among the first examples, developed in the early 19th century (Rogers et al., 2001). The earliest example of pharmaceutical application was Danazol that was milled using a bead mill to obtain a median particle size of 169 nm (Robertson, 1983). The Danazol nanosuspension showed enhanced oral bioavailability (82.3 ± 10.1%) as compared to the drug suspension using the "as-is" drug (5.1 ± 1.9%).

The first nanoparticle technology based product approved by FDA was Rapamune® (Sirolimus) - an immunosuppressant developed by Wyeth Pharmaceuticals (now Pfizer). The second product approved by FDA was Tricor® by Abbott Laboratories, an improved formulation of Fenofibrate (for hypercholesterolemia) incorporating drug nanoparticles that reduced the fed-fast variability resulting in no dosing restriction that allowed co-administration with other drugs used for treating lipid disorders. Another product containing Fenofibrate nanoparticles is Triglide®. The product was developed by Skye Pharma using their patented IDD-P® technology and marketed by Sciele Pharma Inc. (Atlanta, USA). Antiemetic drug, Emend® (Aprepitant) was approved by the FDA in March 2003 and launched in the United States by Merck in April 2003. Emend is a capsule containing 80 or 125 mg of Aprepitant formulated as drug nanoparticles using Elan's drug NanoCrystal® technology (Mary et al., 2005). Megace ES® (ES stands for enhanced solubility) is another product containing drug nanoparticles that was developed by Par Pharmaceutical Inc. (USA). It is an aqueous suspension of Megestrol Acetate (a synthetic progestin, anti anorexic) with a dose of

625 mg / 5 mL. The drug nanosuspension reduced the fed and fast variability similar to Tricor®. The product in nanosuspension demonstrated that aqueous nanosuspension can be produced with adequate physical stability with acceptable shelf life using this technology. A list of products developed using nanoparticle technology (Ranjita Shegokar et al., 2010; Rajesh Dubey, 2006) currently available in the market is summarized in Table 1.

Brand	Generic Name	Indication	Drug Delivery Company	Innovator	Status
Rapamune®	Rapamycin, Sirolimus	Immunosuppressant	Elan Nanosystems	Wyeth	Marketed
Emend®	Aprepitant	Anti-emetic	Elan Nanosystems	Merck & Co.	Marketed
Tricor®	Fenofibrate	Hypercholesterolemia	Abbott Laboratories	Abbott Laboratories	Marketed
Megace ES®	Megestrol	Anti-anorexic	Elan Nanosystems	Par Pharmaceuticals	Marketed
Triglide®	Fenofibrate	Hypercholesterolemia	IDD-P Skyepharma	Sciele Pharma Inc.	Marketed
Avinza®	Morphine Sulphate	Phychostimulant	Elan Nanosystems	King Pharmaceuticals	Marketed
Focalin	Dexmethyl-Phenidate HCl	Attention Deficit Hyperactivity Disorder (ADHD).	Elan Nanosystems	Novartis	Marketed
Ritalin	Methyl Phenidate HCl	CNS Stimulant	Elan Nanosystems	Novartis	Marketed
Zanaflex Capusules ™	Tizanidine HCl	Muscle Relaxant	Elan Nanosystems	Acorda	Marketed

Table 1. Overview of nanoparticle technology based products

3. Formulation theory

The basic principle of micronisation and nanonisation is based on increase in surface area leading to enhancement in dissolution rate according to Noyes-Whitney equation (Muller et al., 2000). Poor aqueous solubility correlates with slower dissolution and decreasing particle size increases the surface area with concomitant increase in the dissolution rate.

Dissolution kinetics is the primary driving force behind the improved pharmacokinetic properties of nanoparticle formulations of poorly water soluble compounds. Dissolution rate of a drug is a function of its particle size and intrinsic solubility. For drugs with poor aqueous solubility, surface area of the drug particles drives dissolution. As described by the Nernst-Brunner and Levich modification of Noyes-Whitney model the rate of drug dissolution is directly proportional to surface area;

$$dx/dt = (A \times D/\delta) \times (C - X/V) \quad (1)$$

Where X is the amount of drug in solution, t is time, A is the effective surface area, D is the diffusion coefficient of the drug, δ is the effective diffusion boundary layer, C is the saturation solubility of the drug, and V is the volume of dissolution medium.

Saturation solubility usually is a compound specific constant that depends on temperature. This understanding is true for regular particles that are above the micron range however, different for drug nanoparticles. This is because the dissolution pressure is a function of the curvature of the surface that means it is much stronger for a curved surface of nanoparticles. Below a particle size of approximately 2 μm, the dissolution pressure increases distinctly leading to an increase in the saturation solubility. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient. The increase in surface area and concentration gradient lead to much more pronounced increase in dissolution velocity and saturation solubility compared to products containing micronized particles concomitantly resulting in improved bioavailability (Keck et al., 2006).

Increased solubility near the particle surface results in enhanced concentration gradient between the surface and the bulk solution. The high concentration gradient according to Fick's law must lead to an increased mass flux away from the particle surface (Dressman et al., 1998). As the particle diameter decreases, its surface area to volume ratio increases inversely, further leading to an increased dissolution rate. Under sink conditions in which the drug concentration in the surrounding medium approaches zero, rapid dissolution could theoretically occur**.**

4. Production of drug nanoparticles

There are several techniques used to produce drug nanoparticles. The existing technologies can be divided into two categories; 'bottom up' and 'top down'. The bottom-up technologies involves controlled precipitation/crystallization by adding a suitable non-solvent. The top down technologies include milling or homogenization. However, combination techniques that involves pretreatment step followed by size reduction are also being used to produce nanoparticles with the desired size distribution.

4.1 Bottom-up technologies (Precipitation methods)

Precipitation has been applied for many years for preparation of fine particles, particularly in the development of photographic film, and lately for preparation of sub-micron (nano) particles for pharmaceutical applications (Otsuka et al., 1986; Illingworth, 1972). Examples for precipitation techniques are hydrosols developed by Sucker (Sandoz, presently Novartis) and Nanomorph developed by Soliqs/Abbott (Musliner, 1974; Sjostrom et al., 1993; Gassmann et al., 1994; List et al., 1988; Sucker et al., 1994).

In this process, the drug is dissolved in a suitable solvent and the solution is subsequently added to a non-solvent. This results in high super saturation, rapid nucleation and the formation of many small nuclei. Upon solvent removal, the suspension is sterile filtered and lyophilized (Kipp et al. 2003). The mixing processes may vary considerably. Through careful

control of this addition process it is possible to obtain a particle with a narrow size distribution. In the case of Nanomorph, amorphous drug nanocrystals are produced to further enhance dissolution velocity and solubility (Muller et al., 2001a).

Simple precipitation methods, however, have numerous limitations**;** it is very difficult to control nucleation and crystal growth to obtain a narrow size distribution. Often a metastable solid, usually amorphous, is formed which is converted to more stable crystalline forms (Violante et al., 1989; Bruno et al., 1992). Furthermore, non-aqueous solvents utilized in the precipitation process must be reduced to toxicologically acceptable levels in the end product and due to the fact that many poorly soluble drugs are sparingly soluble not only in aqueous but also in organic media. Considering these limitations, the "bottom up" techniques are not widely used for production of drug nanocrystals. Instead, "top down" technologies that include homogenization and milling techniques are more frequently used.

4.2 Top-down technologies

The two top down technology frequently used for producing drug nanoparticles include;

a. High pressure homogenization
b. Milling

a. High pressure homogenization methods

One of the disintegration method used for size reduction is high-pressure homogenization. The two-homogenization principles/homogenizer types used are;

1. Microfluidisation (Microfluidics, Inc.)
2. Piston-gap homogenizers (e.g. APV Gaulin, Avestin, etc.)

b. Microfluidisation for production of drug nanoparticles

Microfluidisation works on a jet stream principle where the suspension is accelerated and passes at a high velocity through specially designed interaction chambers. Frontal collision of fluid streams under high pressures (up to 1700 bar) inside the interaction chamber generates shear forces, particle collision, and cavitation forces necessary for particle size reduction. The Microfluidizer processor keeps a constant feed stream that gets processed by a fixed geometry which produces high shear and impact necessary to break down larger particles. This process yields smaller particles with narrow particle size distribution with repeatability and scalability.

The interaction chamber's exterior and interior is either made of stainless steel, poly-crystalline diamond (PCD) or aluminum oxide. The poly-crystalline diamond chambers typically have a lifetime 3 - 4 times longer than the aluminum oxide ceramic chambers. Single slotted interaction chambers are used for lab-scale manufacturing and multi-slotted chambers for commercial scale. Multi-slotted chambers are comprised of multiple single slots in parallel for processing larger volumes of the products. There are two types of interaction chambers: Y chamber is useful for liquid-liquid emulsions and finds application in preparing liposomes while Z-chamber is typically used for cell disruption and nanodispersion. A schematic representation of mechanism of particle size reduction in high pressure homogenizers is shown in Fig. 1. The selection of correct chamber

depends upon the feed particle size, the application, and the amount of shear and impact required to carryout the operation. The Insoluble Drug Delivery – Particles (IDD-P™) technology developed by SkyePharma Canada Inc. use the Microfluidizer (Jens-Uwe et al., 2008).

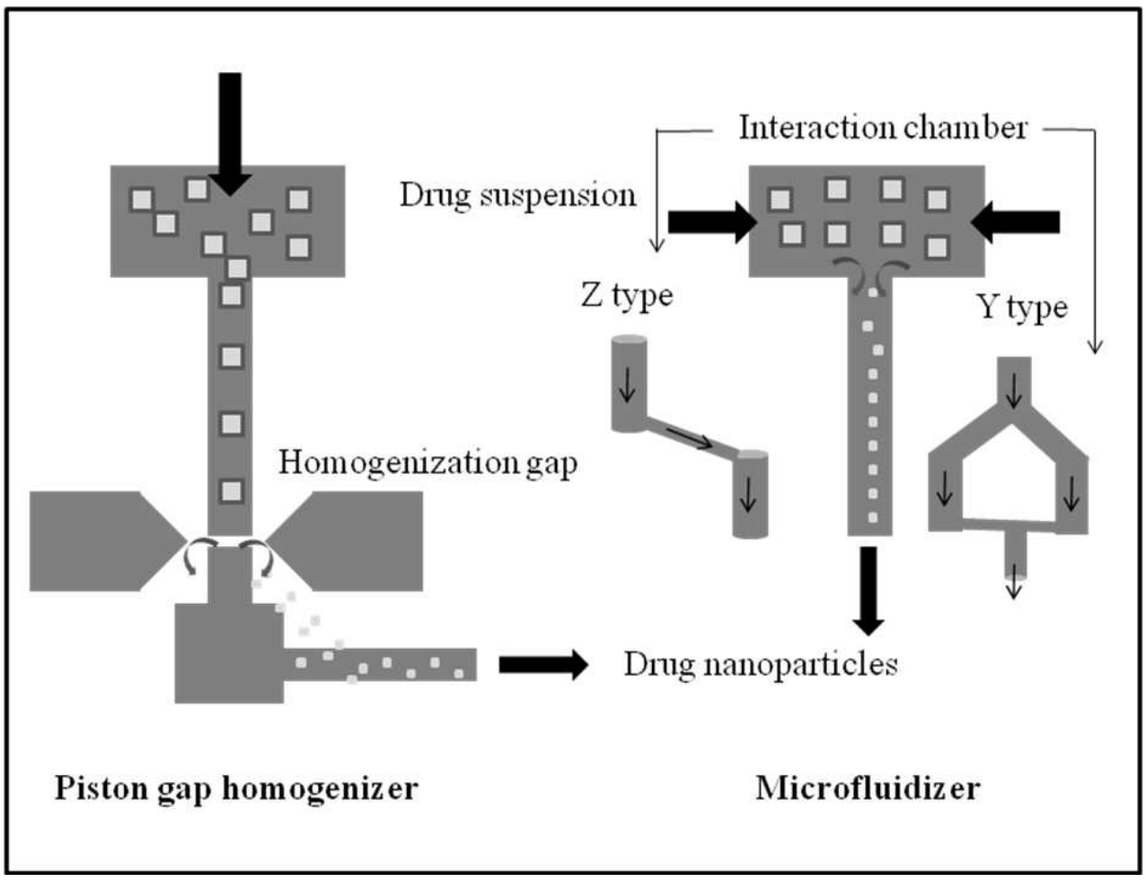


Fig. 1. Schematic representation of mechanism of particle size reduction in high pressure homogenizers

4.2.1 Process parameters affecting particle size

Studies on particle size reduction of a sparingly soluble drug (BCS class II) using the Microfluidizer (Model - Microfluidics M110-P) in our laboratory indicated that particle size reduction depends on various process parameters viz., number of homogenization cycles, homogenization pressure and, stabilizer concentration. At a constant homogenization pressure (30,000 psi) the value of mean particle size d50 decreased with increasing number of cycles from 5 to 60 (Fig. 2). Homogenization pressure has a significant effect on particle size distribution as shown in Fig. 3. At high homogenization pressure (30,000 psi) particle size reduction was significantly higher than at low homogenization pressure (10,000 psi) after 60 homogenization cycles. Surfactant concentration also plays an important role in particle size reduction through particle stabilization by forming a thin layer around the newly formed surface as evident based on the observation that at constant homogenization

pressure and homogenization cycles, particle size reduced with increase in surfactant concentration from 10 mg/mL to 12 mg/mL (Fig. 4).

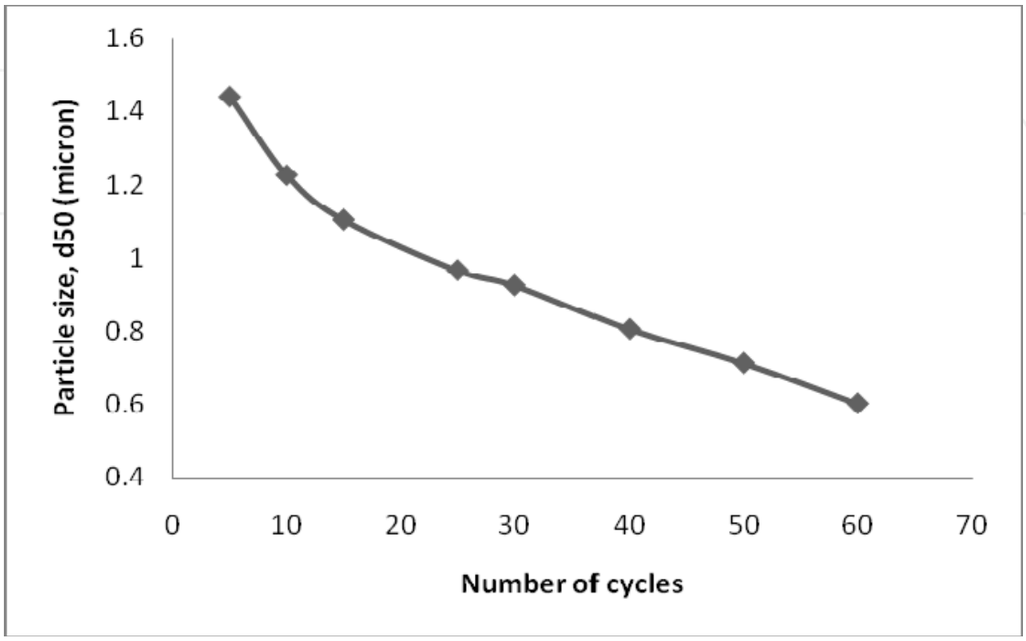


Fig. 2. Effect of number of cycles on mean particle size at constant homogenization pressure

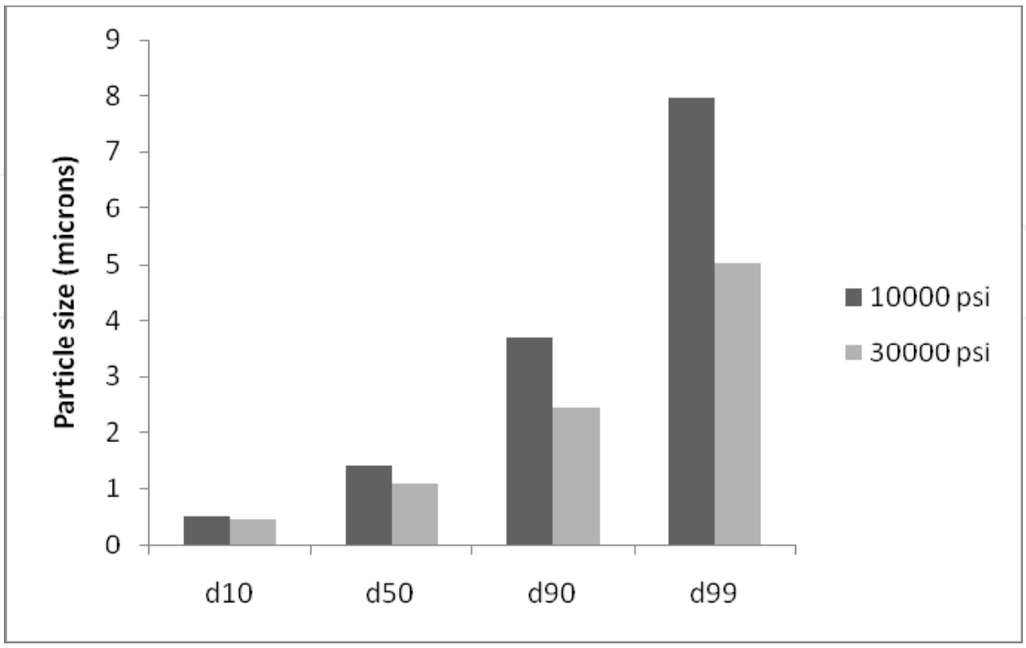


Fig. 3. Effect of homogenization pressure on particle size distribution

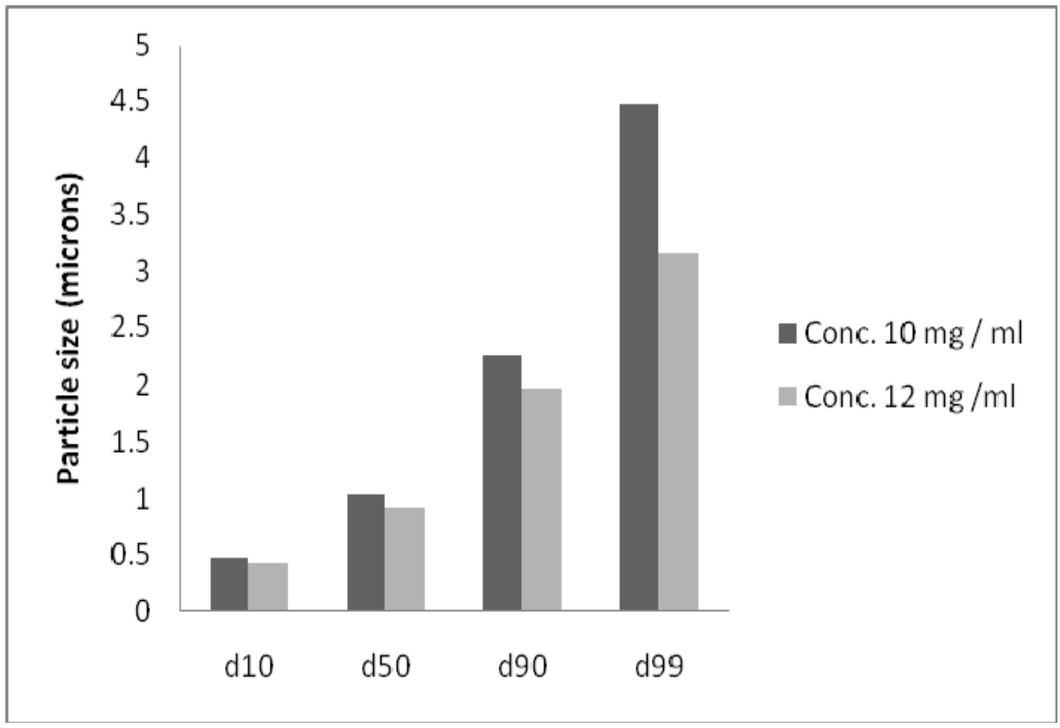


Fig. 4. Effect of surfactant concentration on particle size distribution

4.3 Piston-gap technologies

Using the microfluidisation principle, an alternative technology based on piston-gap homogenizers was developed in the middle of the 1990's for production of drug nanoparticles. Homogenization can be performed in water (DISSOCUBES®) or alternatively in non-aqueous media or water reduced media (NANOPURE®). Dissocubes® technology employs piston-gap homogenizers in which drug powder is dispersed in an aqueous surfactant solution and subsequently forced by a piston through the tiny homogenization gap (5 µm - 20 µm depending upon the viscosity of the suspension and the applied pressure) at a very high pressure (up to 4000 bar). Prior to entering the gap, the suspension is contained in a cylinder with a relatively large diameter compared to the width of the following gap. The resulting high streaming velocity of the suspension causes formation and implosion of the gas bubbles also known as cavitation which results in generation of shockwaves. The drug particle gets reduced by these high shear forces, turbulent flow and powerful shockwaves. Another approach viz., Nanopure® technology (by Pharma-Sol GmbH) is useful for particle size reduction of thermolabile drugs because it use low vapor pressure dispersion media for homogenization that helps in processing at low temperatures due to very little cavitation in the homogenization gap (Muller et al., 1999, 2001b, 2003; Muller RH & Moschwitzer JP, 2005; Jens-Uwe et al., 2008). In addition, there is also a combination process of precipitation followed by a second high-energy homogenization step (NANOEDGE®). The major limitation of this method is that nanoparticulate dispersion of low solid content (usually < 10% w/v) is produced that may be difficult for conversion to solid intermediates required for capsule filling or tableting.

4.4 Milling methods

Conventional milling and precipitation processes generally result in particles much greater than 1 µm. Milling techniques were later refined to enable milling of solid drug particles to sub-micron range. Ball mills are already known from the first half of the 20th century for the production of fine suspensions. In this method, the suspension comprising of drug and stabilizers along with milling media are charged into the grinding chamber. The reduction of particle size occurs because of the shear forces generated due to impaction of milling media. In contrast to high pressure homogenization, this is a low energy technique. Smaller or larger beads can be used as milling or attrition media. The milling media comprise of ceramics (cerium or yttrium stabilized zirconium dioxide), stainless steel or highly cross linked polystyrene resin-coated beads. Potential for erosion of the milling media during the milling process resulting in product contamination is one of the drawbacks of this technology. To overcome this issue, the milling media are often coated (Merisko-Liversidge et al., 2003). Another problem with milling process is the adherence of product to the inner surface of the mill (consisting mainly of the surface of milling media and the inner surface of milling chamber). There are two basic milling principles - either the milling medium is moved by an agitator or the complete container is moved in a complex direction leading to movement of the milling media to generate the shear forces required to fracture the drug crystals. The milling time depends on many factors such as solid content, surfactant concentration, hardness, suspension viscosity, temperature, energy input and, size of the milling media. The milling time may vary from minutes to hours or days depending on the particle size desired (Jens-Uwe et al., 2008).

In the bead milling process used for production of drug nanosuspension, the drug suspension is passed through a milling chamber containing milling media ranging from 0.2 to 3 mm. These media may be composed of glass, zirconium salts, ceramics, plastics (e.g., cross-linked polystyrene) or special polymers such as hard polystyrene derivatives. The drug concentration in the suspension may range from 5 – 40% w/v. Stabilizers such as polymers and/or surfactants are used to aid the dispersion of particles. To be effective the stabilizers must be capable of wetting the drug particles and providing steric and ionic barrier. In the absence of appropriate stabilizers, the high surface energy of the nanometer-sized particles would lead to agglomeration or aggregation of drug crystals. The concentration of polymeric stabilizers can range from 1 – 10% w/v and the concentration of surfactants is generally < 1 % w/v. If required other excipients such as buffers, salts and diluents like sugar can be added to the dispersion to enhance stability and aid further processing (Keck et al., 2006).

The milling chamber has a rotor fitted with disks that can be accelerated at the desired speed (500 – 5000 RPM). The rotation of the disk accelerates the milling media radially. The product flows axially through the milling chamber where the shear forces generated and/or forces generated during impaction of the milling media with the drug provides the energy input to fracture the drug crystals into nanometer-sized particles. The temperature inside the milling chamber is controlled by circulating coolant through the outer jacket. The process can be performed either in a batch mode or in a recirculation mode. The milled product is subsequently separated from the milling media using a separation system. A schematic of the bead milling process is shown in Fig. 5.

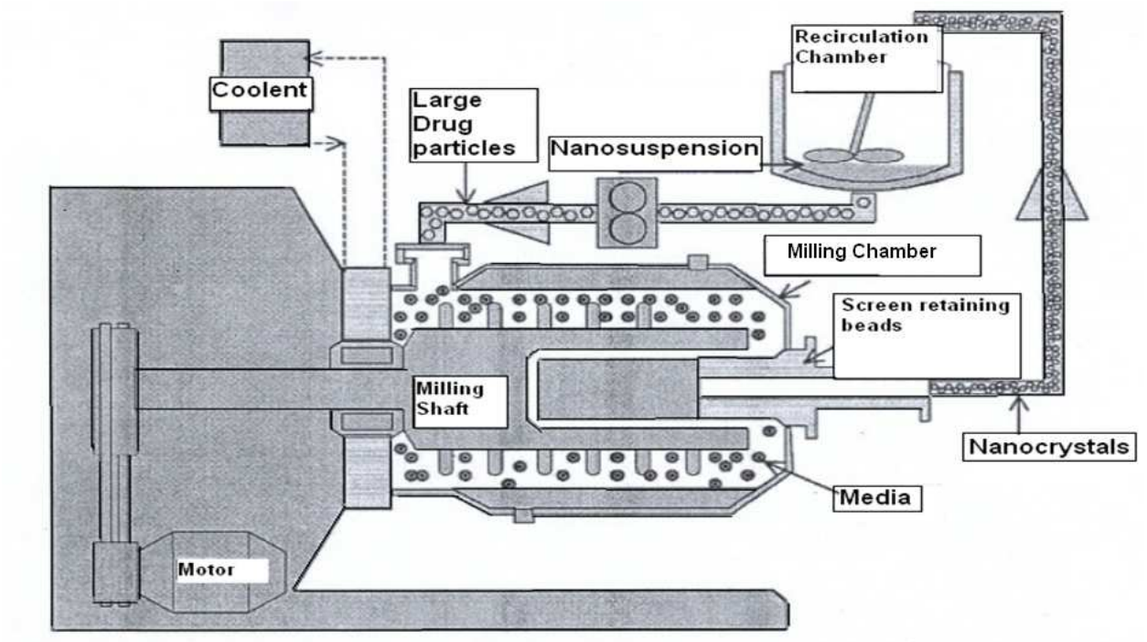


Fig. 5. Schematic of wet bead milling process used for production of drug nanoparticles

Scaling up the bead milling process is relatively easy and convenient because the process variables are scale independent. The batch size can be increased above the void volume (volume in between the hexagonal packaging of the beads) using the mill in a recirculation mode. The suspension is contained in the product container and is continuously pumped through the mill in a circular motion. This increases the batch size with concomitant increase in the milling time because the required exposure time of the drug particles per unit mass to the milling material remains unchanged.

Surfactants or stabilizers have to be added to ensure physical stability of the nanosuspensions. In the manufacturing process the drug substance is dispersed by high speed stirring or homogenizer in a surfactant/ stabilizer solution to yield a macro suspension. The choice of surfactants and stabilizers depends not only on the physical principles (electrostatic versus steric stabilization) and the route of administration. In general, steric stabilization is recommended because it is less susceptible to electrolytes in the gut or blood. Electrolytes if added can reduce the zeta potential and subsequently impair the physical stability, especially of ionic surfactants. In many cases an optimal approach is the combination of a steric stabilizer with an ionic surfactant, i.e, a combination of steric and electrostatic stabilization. There is a wide variety of bead mills available in the market, ranging from laboratory-scale to industrial-scale volumes. The ability for large-scale production is an essential prerequisite for introduction of product into market. In general, bead milling offers a convenient process for production of drug nanoparticle at high concentrations necessary for solid dosage form processing with ease of scale-up for commercial manufacturing.

5. Process optimization for the production of drug nanoparticles

Experimental design has been applied widely to formulation development, and is useful in process optimization and process validation (Fisher RA, 1926). A manufacturing process optimized using design of experiments (DOE) should result in a robust process amenable for seamless scale-up and validation (Dhananjay et al, 2010; Nekkanti et al, 2009a). The process variables in media milling can be optimized using design of experiments (DOE) to understand the effect on particle size, milling time and percentage yield (Nekkanti, et al., 2010). Though a number of statistical designs are reported, a face centered centre composite design (CCD) is often used because it provides information on direct effects, pair wise interaction effects and curvilinear variable effect (Billon et al., 2000; Vaithiyalingam & Khan, 2002; Tagne et al., 2006). For example, a design matrix prepared based on 3 variable factors at three levels (-1, 0, +1) to compute the design using statistical software program Design Expert (version No. 7.3.1) is summarized in Table 2.

S. No	Process Parameters	Level		
		Low (-1)	Center (0)	High (+1)
1	Disk Speed (RPM)	2000	2350	2750
2	Pump Speed (RPM)	40	50	60
3	Bead Volume in Milling Chamber (%)	60	70	80

Table 2. Process variables (factors) and levels

A stepwise regression can be used to generate quadratic equations for each response variable. Analysis of variance (ANOVA) and regression is used to evaluate the significant effects and model building for each response variable. Each response is then fitted to a second-order polynomial model and, the regression coefficients for each term in the model can be estimated along with R^2 and adjusted R^2 of regression model to understand how these parameters effect the critical product attributes either through non-linear, quadratic or interaction effects.

The interaction effect of pump and disc speed on milling time is shown in Fig. 6. The plot indicates that at lower disk speed the milling time (to achieve the desired particle size) increases. This may be attributed to the fact that at low disk speed the shear forces generated by accelerating beads may not be sufficient to fracture the drug crystals into smaller particles. The milling efficiency was high when the disk and pump were run at moderate speeds.

The interaction effect of pump speed and bead volume on particle size is shown in Fig. 7. The plot indicates that increase in pump speed and bead volume resulted in larger particles where as, their interaction resulted in a decrease in particle size. Both pump speed and bead volume have an effect on particle size with bead volume having a significant impact in controlling the drug particle size due to increased probability of impaction.

The interaction effect of disk speed and bead volume on yield is shown in Fig. 8. The plot indicates that the process yields obtained was significantly affected by disk speed and bead volume. At lower disk speed and higher bead volume there was a decrease in yield; this may be attributed to loss in the milling chamber due to sticking.

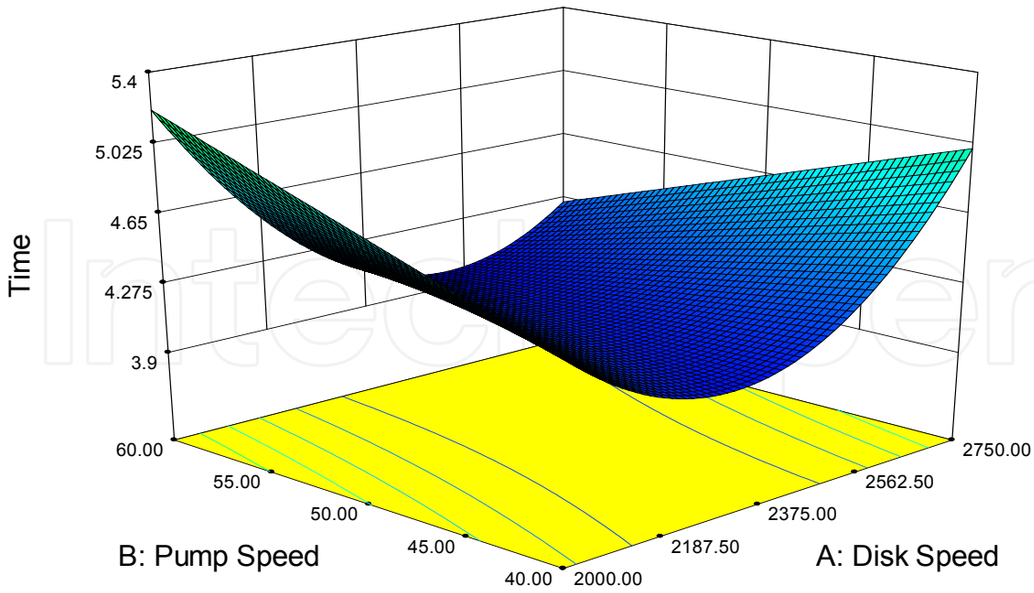


Fig. 6. Effect of disk and pump speeds on milling time

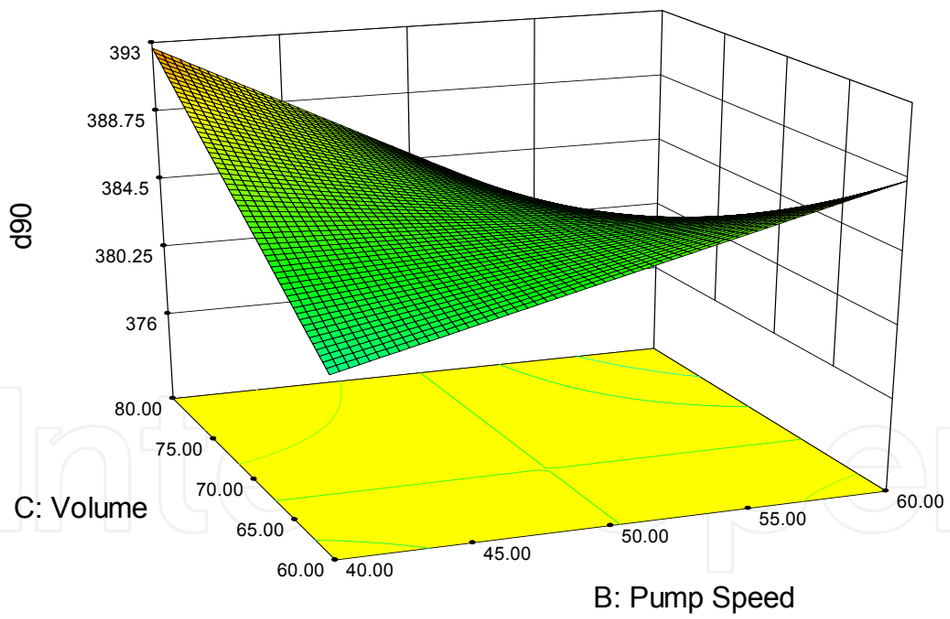


Fig. 7. Effect of pump speed and bead volume on particle size

The robustness of the model used can be validated based on confirmatory trials to ascertain difference between predicted and experimental values. The use of DOE for process optimization will result in a robust scalable manufacturing process with design space established for critical process parameters that can balance milling time, particles size and yield.

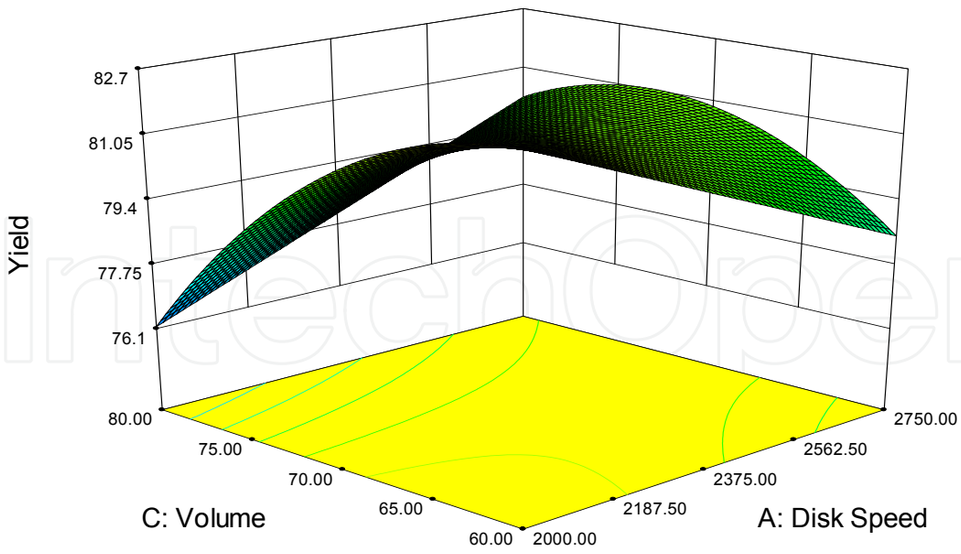


Fig. 8. Effect of disk speed and bead volume on yield

6. Conversion of nanosuspension into solid intermediate

For production of solid intermediate, the water has to be removed from the drug nanosuspension to obtain a dry powder required for tabletting or capsule filling. The objective of solid nanoparticle system is to release the drug nanoparticles in the gastrointestinal (GI) fluids as fine non-aggregated suspension and ensure physical stability upon long term storage. The solvent from nanosuspension can be removed using drying processes such as fluid bed coating / granulation, spray drying and freeze drying. Freeze drying is considered as a complex and cost-intensive process leading to a highly sensitive product. The main challenge is to preserve the re-dispersibility of the nanoparticles upon reconstitution in aqueous media and gastrointestinal fluids. The re-dispersants must be incorporated in the nanosuspensions prior or during the drying step. Commonly used re-dispersants include sugars such as lactose, sucrose and mannitol (Chu, 2000). Generally, re-dispersibility depends on the choice of re-dispersants, surfactants and polymeric stabilizers. The loading capacity of solid intermediate with drug nanoparticles can be adjusted by varying excipient concentrations.

In spray drying process the nanosuspension is atomized using a rotary or air-jet atomizer. In this process fast drying of the liquid feed happens due to the large surface area created by the atomization of the liquid feed into fine droplets and high heat transfer coefficients generated. The short drying time and consequently fast stabilisation of feed material at moderate temperatures make spray drying suitable for producing nanoparticles of drugs that are thermolabile. The spray drying process in general comprise of the following steps;

- **Atomization:** The liquid feed in the form of drug suspension is atomized into droplets by means of a nozzle or rotary atomizer. Nozzles use pressure or compressed gas to atomize the liquid feed while rotary atomizers employ an atomizer wheel rotating at high speed.

- **Drying:** Hot process gas (air or nitrogen) is brought into contact with the atomized feed using a gas disperser for drying. The balance between temperatures, feed flow rate and droplet size controls the drying process.
- **Particle formation:** As the liquid evaporates from the droplet surface the solid nanoparticle that is formed falls into the bottom of the drying chamber.
- **Recovery:** The dried nanoparticles are separated from the exhaust gas using a cyclone separator.

Depending on the spray conditions and nature of formulation, the resulting powder may be filled into hard gelatin capsules or blended with extra granular excipients and compressed in to tablets. In the case of drugs which are acid liable, the capsule or tablet can be coated with enteric polymers to protect acid labile drug from gastric fluids.

An alternative way to convert nanosuspension into solid intermediate is suspension layering onto water soluble carriers. The binders that are necessary for layering must be added before the milling process. The suspension is layered at a predetermined rate on to the water-soluble carriers using a top spray fluid bed process. Top-spraying is the most well known process for drug layering. A top-spray fluid bed processor (FBP) has three components;

- An air-handling system, which can be equipped with humidification or de-humidification and dew-point control
- A product container and expansion chamber
- An exhaust system

The nanosuspension is sprayed into the fluid bed from the top against the air flow (counter current). The granules are dried as they move upward in the fluid bed, small droplets and low viscosity of the spray medium ensures that distribution is uniform resulting in granules with a narrow size distribution (Nekkanti et al., 2008; Basa et al., 2008). The critical process variables of the top-spray layering method include the suspension spray rate, inlet air temperature, fluidization air volume, process air humidity, and the atomization air pressure (Gu et al., 2004).

7. Characterization of drug nanoparticles

There are various techniques used for characterization of drug nanoparticles. There is no single method that can be selected as the "best" for analysis. Most often the method is chosen to balance the restriction on sample size, information required, time constraints and the cost of analysis. Following methods are used commonly for characterization of drug nanoparticles.

7.1 Particle size and size distribution

The characterization of particle size of nanosuspensions is done to obtain information about its average size, size distribution and change upon storage (e.g. crystal growth and/or agglomeration). Particle size distribution of drug nanoparticles can be measured using the following techniques;

7.1.1 Spectroscopy

As nanosuspensions usually comprise of submicron particles, the appropriate method used to evaluate particle size distribution is photon correlation spectroscopy (PCS). In PCS or dynamic light scattering analyses scattered laser light from particles diffusing in a low viscosity dispersion medium (e.g. water). PCS analyze the fluctuation in velocity of the scattered light rather than the total intensity of the scattered light. The detected intensity signals (photons) are used to measure the correlation function. The diffusion coefficient D of the particles is obtained from the decay of this correlation function. Applying Stokes-Einstein equation, the mean particle size (called z-average) can be calculated. In addition, a polydispersity index (PI) is obtained as a measure for the width of the distribution. The PI value is 0 in case particles are monodisperse. Incase of narrow distribution, the PI values vary between 0.10 – 0.20, values of 0.5 and higher indicate a very broad distribution (polydispersity). From the values of z-average and PI, even small increases in size of drug nanoparticles can be evaluated. The extent of increase in particle size upon storage is a measure of instability. Therefore, PCS is considered as a sensitive instrument to detect instabilities during long-term storage (Kerker, 1969).

7.1.2 Laser Diffraction

Laser Diffractometry (LD) developed around 1980 is a very fast and used routinely in many laboratories. The instrument is also used for quantifying the amount of microparticles present, which is not possible using PCS. LD analyses the Fraunhofer diffraction patterns generated by particles in a laser beam. The first instruments were based on the Fraunhofer theory which is applicable for particle sizes 10 times larger than the wavelength of the light used for generating the diffraction pattern. For particle less than 6.3 µm (in case of using a helium neon laser, wavelength 632.8 nm) in size, the Mie theory is used to obtain the correct particle size distribution. The Mie theory requires knowledge of the actual refractive index of particles and their imaginary refractive index (absorbance of the light by the particles). Unfortunately, for most of pharmaceutical solids the refractive index is unknown. However, laser diffractometry is frequently used as a preferred characterization method for nanosuspensions because of its "simplicity" (Zhang et al., 1992; Calvo et al., 1996).

7.2 Microscopy

Microscopy based techniques can be used to study a wide range of materials with a broad distribution of particle sizes, ranging from nanometer to millimeter scale. Instruments used for microscopy based techniques include optical light microscopes, scanning electron microscopes (SEM) transmission electron microscopes (TEM) and atomic force microscopes (AFM). The choice of instrument for evaluation is determined by the size range of the particles being studied, magnification, and resolution. However, the cost of analysis is also observed to increase as the size of the particles decreases due to requirements for higher magnification, improved resolution, greater reliability and, reproducibility. The cost of size analysis also depends upon the system being studied, as it dictates the technique used for specimen preparation and image analysis. Optical microscopes tend to be more affordable and comparatively easier to operate and maintain than electron microscopes but have limited magnification and resolution (Molpeceres et al., 2000; Cavalli et al., 1997).

The surface morphology of 'as-is' drug and spray dried nanoparticles for a sparingly soluble drug, Candesartan cilexetil, examined using scanning electron microscope (Hitachi S-520 SEM, Tokyo, Japan) is shown in Fig. 9. The scanning electron micrographs of "as-is" drug and drug nanoparticles as shown in these Figures illustrate the recrystallization of water-soluble carrier around the drug creating a highly hydrophilic environment preventing particle interaction and aggregation.

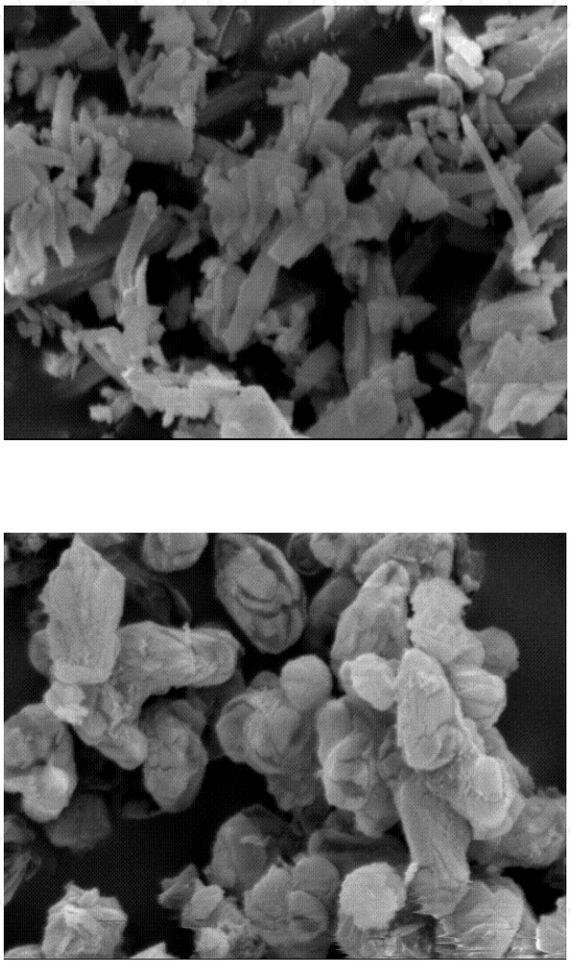


Fig. 9. SEM micrographs of "as-is" drug (left); spray-dried drug nanoparticles (right).

7.3 Solid-state properties

7.3.1 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is used to determine the crystallinity of drug nanoparticles by measuring its glass transition temperature, melting point and their associated enthalpies. This method along with X-ray powder diffraction (XRPD) described

below is used to determine the extent to which multiple phases exist in the interior and their interaction following the milling process.

7.3.2 X-ray powder diffraction (XRPD)

X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays generated by a cathode ray tube are filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. The interference obtained is evaluated using Bragg's Law to determine various characteristics of the crystal or polycrystalline material (Hunter et al., 1981).

7.4 Saturation solubility

Saturation solubility evaluations to ascertain drug nanoparticles are usually carried out in buffer media at different pH conditions using a shake flask method. In this method excess amount (100 mg/mL) of drug ("as-is" and dried suspension containing microparticles or nanoparticles) is added to 25 mL of buffer medium maintained at 37°C and shaken for a period up to 24 hours. The samples are filtered using 0.10 μm pore size Millex-VV PDVF filters (Millipore Corporation, USA) prior to analysis and concentrations determined using an HPLC method. The results from saturation solubility for "as-is", micronized and spray dried nanoparticles of Candesartan cilexetil used as a model drug is summarized in Table 3 to demonstrate the impact of particle size on saturation solubility.

Solvents	Solubility (mg/mL)		
	"as-is" drug*	Micronized drug*	Spray dried drug nanoparticles
0.1 N HCl	0.011	0.016	0.134
Acetate buffer pH 4.5	0.001	0.014	0.106
Phosphate buffer pH 6.8	0.001	0.012	0.105
Water	0.000	0.001	0.073

*Solubility was tested in respective solvents containing surfactant and Stabilizer.

Table 3. Saturation solubility of "as-is", micronized and nanoparticles of Candesartan cilexetil

The saturation solubility of Candesartan cilexetil nanoparticles is significantly higher than jet-milled particles and "as-is" drug at all pH conditions. These results clearly demonstrate that reduction in particle size to sub-micron or nanometer range affects saturation solubility resulting in enhancement of dissolution rate.

The effect of particle size of Candesartan cilexetil following oral administration in male Wistar is shown in Fig. 10. As seen there is a significant enhancement in the rate and extent of drug absorption for nanosuspension. The rate and extent of drug absorption

showed a 2.5-fold increase in the area under the plasma concentration - time curve (AUC_{0-t}) and a 1.7-fold increase in the maximum plasma concentration (C_{max}) and, significant reduction in the time required (1.81 hours as compared to 1.06 hours) to reach maximum plasma concentration (T_{max}) when compared to the micronized suspension (Nekkanti et al., 2009b).

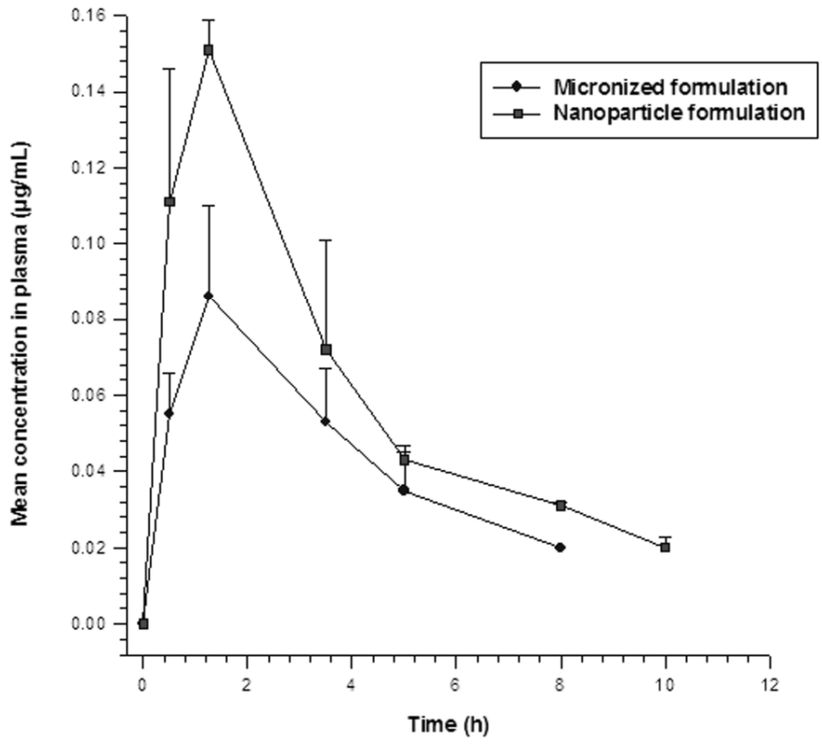


Fig. 10. Plasma concentration–time profiles following oral administration of micronized suspension and drug nanosuspension to male Wister rats

8. Conclusion

Enhancing solubility and dissolution rate of poorly soluble compounds correlates with improved pharmacokinetic (PK) profile. The approach herein can be extended to other BCS class II compounds where absorption is either solubility and/or dissolution limited. The manufacturing process used is relatively simple and scalable indicating general applicability of the approach to develop oral dosage forms of poorly soluble drugs. The enhanced

bioavailability should translate into reduced dose, mitigate food effects, offer better dose delineation and result in faster onset of action that may translate into improved therapeutic outcome.

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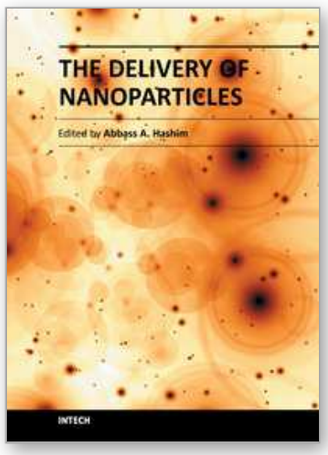
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