Research in Pharmaceutical Sciences, April 2015; 10(2): 95-108
Received: Aug 2014
Accepted: Oct 2014

School of Pharmacy & Pharmaceutical Sciences
IsfahanUniversity of Medical Sciences

Review Article

Nanosizing of drugs: Effect on dissolution rate

S. Maleki Dizaj[1,2], Zh. Vazifehasl[3], S. Salatin[1], Kh. Adibkia[3], and Y. Javadzadeh[3,*]

[1]Department of Pharmaceutical Nanotechnology, Faculty of Pharmacy, Tabriz University of Medical Science, Tabriz, I.R. Iran.
[2]Student Research Committee, Tabriz University of Medical Science, Tabriz, I.R. Iran.
[3]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, I.R. Iran.

Abstract

The solubility, bioavailability and dissolution rate of drugs are important parameters for achieving *in vivo* efficiency. The bioavailability of orally administered drugs depends on their ability to be absorbed via gastrointestinal tract. For drugs belonging to Class II of pharmaceutical classification, the absorption process is limited by drug dissolution rate in gastrointestinal media. Therefore, enhancement of the dissolution rate of these drugs will present improved bioavailability. So far several techniques such as physical and chemical modifications, changing in crystal habits, solid dispersion, complexation, solubilization and liquisolid method have been used to enhance the dissolution rate of poorly water soluble drugs. It seems that improvement of the solubility properties ofpoorly water soluble drugscan translate to an increase in their bioavailability. Nowadays nanotechnology offers various approaches in the area of dissolution enhancement of low aqueous soluble drugs. Nanosizing of drugs in the form of nanoparticles, nanocrystals or nanosuspensions not requiring expensive facilities and equipment or complicated processes may be applied as simple methods to increase the dissolution rate of poorly water soluble drugs. In this article, we attempted to review the effects of nanosizing on improving the dissolution rate of poorly aqueous soluble drugs. According to the reviewed literature, by reduction of drug particle size into nanometer size the total effective surface area is increased and thereby dissolution rate would be enhanced. Additionally, reduction of particle size leads to reduction of the diffusion layer thickness surrounding the drug particles resulting in the increment of the concentration gradient. Each of these process leads to improved bioavailability.

Keywords: Dissolution rate; Nanocrystal; Nanoparticle; Nanosuspension; Nanosizing

CONTENTS

1.INTRODUCTION

The bioavailability of orally administrated drugsdepends on their absorption from the gastrointestinal (GI) tract (1-3). Through this route of administration, poorly water soluble drugs present low bioavailability because of their low solubility in GI media. The rate limiting step in the absorption of these drugs is the dissolution rate in the GI fluids rather than their diffusion through the GI membrane (4).

Absorption is the transition of a drug molecule from the administration site into the blood or lymphatic circulation (4-6). The

*Corresponding authors:Y. Javadzadeh
Tel: 0098 413 3341315, Fax: 0098 413 3344798
Email:javadzadehy@yahoo.com

amount of absorbed drug is affected by physicochemical properties of the active ingredient, pharmaceutical dosage form, and physiological characteristics of the absorption site (7). In the body, passive diffusion is considered as the main mechanism of drug absorption. In this process, drugs must be dissolved before diffusing through the gut wall. Thus, the extent of drug absorption mainly is dependent on its solubility in GI fluids (6). Therefore, one of the determinant parameters for achieving favorable concentration of drug in the systemic circulation (*in vivo* efficiency) is solubility of the drug. The solubility is the maximum quantity of a solute that can be dissolved in a certain quantity of solvent or solution at a specific temperature (4,5). There are some techniques for enhancement of the solubility and therefore the dissolution rate of poorly water soluble drugs. Co-solvency and micro-emulsion (8-11), complexation (12-15), crystal habit alteration (16,17), using more soluble salts (18,19), solid dispersion (7,20-26), liquisolid methods (27-32), and particle size reduction approaches (33-36) are some of the methods have been used so far to enhance drug water solubility. As we know, there are several disadvantages in the use of each technique. For example, salt formation is a complicated process and the dissolution enhancement is not always predictable in this process. This method is not applicable for neutral compounds (37). As another example, solubilization techniques normally show poor stability and insufficient acceptability by patients (3). For selection of a suitable technique for a certain drug, some certain aspects such as physic-chemical properties of drug, nature of excipients and nature of dosage form should be considered (38,39).

Reduction of the particle size often appears to be the first and easiest way to enhance drug dissolution rate.The solubility of drug is often related to the drug particle size. When particle becomes smaller, drug particles have greater interaction with the solvent and then the solubility is increased (4,5). According to the Noyes-Whitney equation (equation 1), when particle size is reduced the total effective surface area of drug particle is increased and thereby dissolution rate is enhanced.

$$dC/dt=DA\ (C_S-C)/h \quad (1)$$

where, dC/dt is the dissolution rate of the drug particles, D is the diffusion coefficient of the drug in the GI media, A is the effective surface area of the drug particles in contact with GI fluids, h is the thickness of the diffusion layer around each drug particle, Cs is the saturation solubility of the drug in solution in the diffusion layer and C the concentration of the drug in the GI fluids. All of these parameters in the equation can be considered as constant, except A and C. A can be increased by reducing the particle size (40).

Nanosizing of drugs has begun since the 90s (41). Nanosizing is the reduction of particle size down to submicron range. Recent advances in milling technology have resulted in reproducible production of particles in 100–500 nm sizes (42,43). Recently, nanotechnology has become a promising approach to increase the dissolution rate of poorly-water soluble drugs. The first example of the application of pharmaceutical nanotechnology was danazol. Danazol is a poorly water soluble compound (10 μg/ml) that classified in BCS as Class II drug (33,41). In 1983 Robertson and coworkers milled it to a median particle size of 169 nm. In their work Danazol nanosuspension showed enhanced oral bioavailability as compared to the drug ordinary suspension (44).

Generally the particle size and shape are important in every stage of a solid dosage form fabrication. Particle size affects mixing, granulation, compression and coating of solid dosage forms (45-48). In the body, dissolution rate of a drug is a function of solubility and particle size. It seems that the simplest way to increase the dissolution rate is particle size modification. By particle size reduction (micronization and nanosizing) of both actives or excipients, dissolution rate can be enhanced (46,49). According to Noyes-Whitney equation when particle size is reduced, the total effective surface area is increased and thereby dissolution rate is enhanced.Additionally, reduction of particle size reduces the diffusion layer thickness surrounding the drug particles and thereby increases concentration gradient (4,50). Additionally, reduction of particle size reduces the diffusion layer thickness surrounding the drug particles and thereby increases concentration gradient (4,50). This process illustrated in Fig. 1.

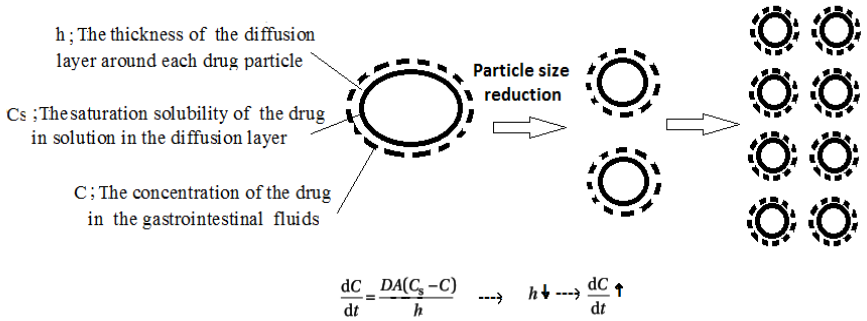

Fig.1. Reduction of particle size reduces the diffusion layer thickness surrounding the drug particles and thereby increases concentration gradient and dissolution rate.

As we know, milling is a common and old pharmaceutical method to reduce particle size and hence raise the dissolution rate of poorly-water soluble drugs (51). Micronization is a technology that coarse drug powder transfer to an ultrafine powder with a mean particle size range of 2-5 μm and usually carried out by jet-milling or top down methods.

Micronization of the poorly soluble drug produces hydrophobic poorly wettable surfaces (52-54). Nighute and Bhise investigated the micronization effect on rifabutin dissolution rate. Improved dissolution rate of drug was obtained in this method (52). Costa and colleagues increased the dissolution rate of efavirenz by micronization method. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1 (HIV-1) belonging to the Class II of the BCS for drugs with very poor water solubility (53).

For many poorly soluble drugs of class II, micronization is not adequate to increase the surface area and consequently the drug dissolution rate. Most often nanosization is necessary to overcome the low dissolution rate and bioavailability problems. By changing the size of the particles from micron size to nano size range, the specific surface area of particles is greatly increased and causes a higher dissolution rate (46,55). For example crystals of aprepitant exhibits a 41.5 fold increase in surface area, when particle size changes from 5 μm to 120 nm (38). By proper formulation of nanoparticles, the dissolution rates and therefore bioavailability will increase. Furthermore the extent of dose will reduce in these formulations (51,55).

2. *Drug dissolution*

The process in which molecules are separated from surface of the solid drug and enter into surrounding solution phase is called dissolution process (5,45). Dissolution is a kinetic, usually diffusion-controlled process (5). Dissolution rate was first described by Noyes and Whitney in 1897 and in 1904; the dissolution rate constant and diffusion coefficient of solutes explored by Nernst and Brunner (46). Both intrinsic (particle size, surface area, crystal habit, and distribution are solid state properties of pure substance) and extrinsic (hydrodynamics and test conditions) factors influence the dissolution rate. Intrinsic dissolution rate is the rate of mass transfer per area of dissolving surface when boundary layer thickness is constant and assuming sink condition (5,45).

3. *Nano approaches for enhancement of drug dissolution*

Nanometer is one billionth of a meter and nanotechnology is the science of synthesis and manipulation of materials in the nano-scale ranges (56-59). The most important scientific advances of nanotechnology have been in the past two decades. One of the advantages of nano-sized drugs compared to conventional drugs is the particle size of them. For poorly-water soluble drugs, dissolution rate is more affected by particle size and thereby surface area of the drug particles. Nano-sized particles may show increased dissolution rate and saturation solubility because of the vapor pressure effect (45,54,60).

There are two general ways of generating nanosized particles. The first way is to start

with a bulk material and then its breaking into smaller pieces using mechanical, chemical or other form of energy which is referred to as top-down approach. Another approach is to synthesize the material from atomic or molecular species via chemical reactions, allowing for the precursor particles to grow in desired nano size known as bottom-up approach (34). Nanoparticles preparation techniques are summarized in Table 1. Fig. 2 also shows top-down and bottom-up approaches schematically.

Two strategies including solubilization and dissolution rate enhancement are mostly used to enhance the bioavailability of drugs with low water solubility. Self-emulsification and micellization are examples of the first group and particle size reduction asnanosized particles, nanosuspensions and nanocrystalsbelong to latter category (61-63). Here we focused on the recent research works concerning the effect of nanosization on the dissolution rate enhancement of the poorly-water soluble drugs.

3.1. Drug nanoparticles

Generally a nanoparticle is an object with at least one dimension less than 100 nm (64,65). Nanoparticles in drug delivery area, are solid submicron colloidal systems generally made of macromolecular substances and polymers and can be prepared from different materials (66).The drug is entrapped, encapsulated or attached to a nanoparticle matrix (Fig. 3). Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained.

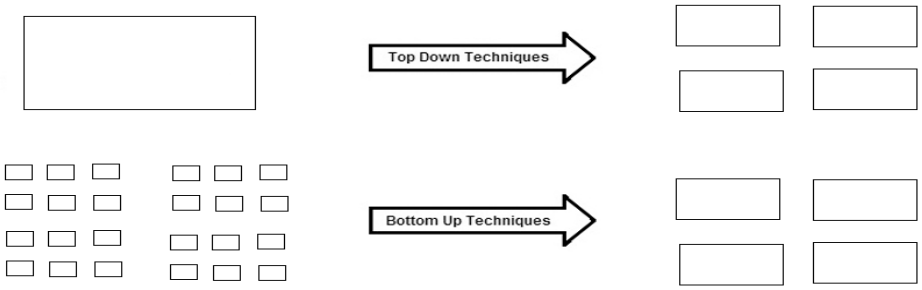

Fig2. Top-down and bottom-up approaches.

Fig. 3. Drug loaded nanoparticle.

Table 1. Preparation techniques of nanoparticles.

Nanoparticle preparation techniques	Examples	Reference
Bottom up	Precipitation, Emulsion as template, Supercritical fluid method	(26,45,61,62)
Top down	Jet milling, High pressure homogenizer, Wet ball milling	(34)
Chemical reaction	Polymerization techniques	(34)
Combination technique	Bottom up + Top down Top down + Top down	(34)

Nanoparticles of drug formulation can be taken orally, parenterally, or by ocular and pulmonary routes. For rapid dissolution in the body or arterial uptake smaller sizes are required, whereas for prolonged dissolution or targeting of mononuclear phagocytic system larger particles are preferred (67). Using of nanoparticles leads to rapid *in vivo* dissolution, fast absorption, and increased bioavailability (68). As mentioned earlier sections, the particles in nanometer range have different physicochemical properties from macroscopic/microscopic scale or atomic scale. Improved pharmacokinetic properties of nanoparticle formulations of poorly water-soluble drugs are affected by dissolution kinetics (41).

Indomethacin is a non-steroidal, anti-inflammatory drug with anti-pyretic effect and is categorized as Class II drug of BCS.Rezaei Mokarram and coworkers compared the dissolution rate of indomethacin nanoparticles with that of physical mixture of micronized drug with polyvinyl pyrrolidine (PVP). They used a controlled pH co-precipitation method to produce indomethacin amorphous nanopartiles in a PVP polymeric matrix. Nano-sized form of the drug showed greater dissolution rate (45% in 30 min) in comparison with micro-sized drug–PVP physical mixture form (10% in 30 min). According to the authors, high dissolution rate of indomethacin nanoparticles compared to either indomethacin or the drug–PVP physical mixture, is attributed to the particle size reduction, the loss of crystalline form, and increased wettability due to the presence of the hydrophilic polymer (69).

In the other study Liu and colleagues combined crystal habit modification and particle size reduction to synthesize celecoxib (CXB) nanoparticles. CXB is weakly acidic and has a low solubility in water. In their work CXB nanoparticles showed markedly enhanced dissolution rate and oral bioavailability due to particle size reduction and crystal habit modification. They combined the anti-solvent precipitation under sonication and high pressure homogenization methods. This combination has been shown a promising method for producing small, uniform and stable CXB nanoparticles. They used acetone and water as solvent and anti-solvent respectively. Then drug solvent system was injected into aqueous solution containing hydroxypropyl methycellulose (HPMC) and sodium dodecyl sulfate and maintained under sonication. Finally the CXB suspensions were further homogenized by high pressure homogenization. Spray-drying method was used for solidification of CXB nanosuspensions, because it requires less time and energy compare to lyophilisation. According to their results, CXB nanoparticles increased the saturation solubility of CXB four-fold and consequently the drug was completely dissolved in the phosphate buffer dissolution medium within 5 min, while only 30% of raw CXB was dissolved at same time interval. Respectively, the C_{max} and $AUC_{(0\text{-}24\ h)}$ of CXB nanoparticles were approximately three-fold and two-fold greater than those of the CXB capsules (70).

Kakran and coworkers enhanced dissolution rate of quercetin, a poorly water-soluble antioxidant, by fabricating of nanoparticles. In their work, three methods were applied to enhance quercetin dissolution rate: solid dispersion with PVP and pluronic F127, complex formation with β-cyclodextrin and fabrication of nanoparticles. Their results showed that complex form and solid dispersion state of quercetin improved drug dissolution rate significantly, but the dissolution rate of quercetin nanoparticles was much higher than the untreated drug. They used evaporative precipitation of nanosuspension to produce nanoparticles and studied the influence of various anti-solvents on the shape and size of the nanoparticles. Smallest particles (220 nm) were obtained with hexane as anti-solvent. The particles were big, irregular and flake when water used as anti-solvent, while in the presence of benzene or hexane as anti-solvent, the particles were smaller with needle shape (23).

Ibuprofen is an NSAID with low oral bioavailability due to slow dissolution behavior. Mansouri and colleagues reduced the particle size of ibuprofen using solvent/anti-solvent precipitation technique and produced nanoparticles with diameter of approximately

300-400 nm. They used the isopropyl alcohol as solvent, water as anti-solvent and sodium dodecyl sulfate, PVP, sodium lauryl sulfate, and Tween 80 as stabilizer. The precipitated nanoparticles in solvent/anti-solvent system were oven-dried and nanoparticles of ibuprofen were produced. In comparison with free drug, the prepared nanoparticles showed improved dissolution rate (2.3 times greater dissolution in purified water in first 30 min). In their study anti-solvent precipitation was used as a simple and effective approach to produce nanoparticles of poorly water-soluble drug ibuprofen (62).

Meloxicam, an anti-inflammatory drug, is very insoluble in water and has low bioavailability. Raval and patel prepared meloxicam nanoparticles that showed remarkable improvement in dissolution rate because of particle size reduction and changing to amorphous form. These nanoparticles were prepared by anti-solvent precipitation in the presence of HPMC and sodium dodecyl sulfate (SDS) at high pressure homogenization. Due to this combination, stable nanoparticles of meloxicam with remarkable improvement in dissolution rate were produced. The drug dissolution rate showed a significant increase from 7% for free drug to 82% for meloxicam nanoparticles. They used spray-drying method for solidification of meloxicam nanoparticles (8).

Badawi and coworkers prepared itraconazole (ITZ) crystalline nanoparticles (the mean particle size ranged from 0.23 to 0.34 μm) using sono-precipitation technique (relatively simple and low-cost method). They formulated twelve ITZ nanocrystals formulations using methylene chloride (solvent phase) and ethyl alcohol (anti-solvent phase). Tween 80 or one of stabilizers amongst pluronic F127, HPC, HPMC, or inutec SP1 was used as stabilizer for antisolvent or solvent phase stabilizer, respectively. The final solution was cooled down and prepared nanocrystals were oven dried. Compared to pure ITZ, prepared nanocrystals showed 3.8-8.6 times improvement in dissolution rate in 10 min (71).

Albendazole is a class II drug with low bioavailability characteristics. Koradia and colleagues tried to enhance the solubility and dissolution rate of this drug by preparing crystalline nanoparticle formulations (638.7 nm-814.8 nm). Anti-solvent precipitation technique in the presence of sodium lauryl sulfate as stabilizer was used. Four formulations with different concentration of PVP K30 (0.05, 0.1, 0.2 and 0.4%) were prepared. All formulations were in the nano-size range and showed marked improvement in drug dissolution and solubility compared to pure drug of micron size. PVP K30 in 0.4% concentration showed highest dissolution rate (70% in 60 h). Un-milled drug (in micron size) showed only 10% in this period of time (72).

3.2. Drug in the form of nanocrystals

Drug nanocrystals are nanoscopic crystals of the drug with a mean diameter below 1000 nm (54). The most applied methods for preparing of nanocrystals include nano-precipitation, high pressure homogenization, wet milling and spray drying (57,73). In the topical dosage form, the nanocrystals increase saturation solubility of the drug enhancing the diffusion of the drug into the skin (66,72,74). Drug nanocrystals are different from nanoparticles consisting of a matrix and an incorporated drug. In other words these are composed of 100% drug in crystalline form and nono-size range (66).

During recent years, the drug nanocrystals have rapidly evolved into a promising drug delivery strategy. Nanocrystals of sirolimus, aprepitant, fenofibrate, megestrol acetate, paliperidone palmitate have been fabricated and their products are currently in the market. Sirolimus nanocrystals (Rapamune®) were the first marketed product introduced in 2000. It is available in two formulations, as oral suspensions and as a tablet (50). Rapamune tablets show a 21-27% increased bioavailability compare to rapamune solution. The oral single dose of rapamune is 1 or 2 mg and the total tablet weight is approximately 365 mg for 1 mg drug containing formulation. This implies that tablets contain a very low percentage of its total weight as nanocrystals (66,75). Aprepitant nanocrystals (Emend®) is a capsule containing pellets of nanocrystalline aprepitant and was the second nanocrystalline

drug product introducedand market in 2001. This medication is used for the treatment of emesis in a single dose of either 80 or 125 mg (66,75). TriCor® tablet which contains fenofibrate nanocrystals and Megace ES® containing megestrol acetate for the treatment of HIV-associated anorexia and cachexia were the third and fourth nanocrystalline drug product marketed thereafter (66).

Nifedipine (NIF) is a poor water soluble drug with solubility of 20 µg/ml of water. Because of low aqueous solubility, it has low dissolution rate and poor oral bioavailability. NIF nanocrystals that prepared by Hecq and coworkers showed greater dissolution rate compared to the un-milled commercial NIF. They used high pressure homogenization for particle size reduction. According to the authors, this method is considered as a simple and acceptable way for particle size reduction and could be generalized depending on the hardness of drug and the type of stabilizer utilized. In nano-size drug crystals 95% of the drug is dissolved following 60 min compared to 5% for the un-milled drug (76).

As another example, nanocrystal of cilostazol (a synthetic antiplatelet agent with vasodialating effect) was prepared by Jinno and colleagues. They found that the nanocrystal technology is an efficient method to improve the oral bioavailability of cilostazol. They showed that nanocrystals of cilostazol has greater dissolution rate than common form. They prepared three types of suspensions with different particle size distributions (the hammer-milled, the jet-milled cilostazol crystals and the nanocrystal spray-dried powder of cilostazol). The median particle diameters of cilostazol in the hammer milled, the jet-milled and the nanocrystal were 1300, 2400 and 220 nm, respectively. The dissolution rate for these formulations was 45%, 80% and 95% in 60 min, respectively (77).

Nitrendipine is an antihypertensive drug which is almost insoluble (about 1.9–2.1 µg/ml) in water. Quan and coworkers prepared nitrendipine nanocrystals with the mean particle size of 175 ± 13 nm using a precipitation homogenization process. They employed spray drying to solidify the nanocrystals. The *in vitro* dissolution rate of the nanocrystals showed significant improvement compared to a commercial tablet and the C_{max} of the nanocrystals was approximately 15-fold greater than commercial tablet (78).

In other study, Lai and colleagues prepared piroxicam (PRX) in different nanocrystalline formulations using a high pressure homogenization technique using poloxamer 188 as a stabilizer. PRX is a lipophilic and poorly water-soluble drug. Dissolution study of PRX nanosuspensions showed a higher dissolution rate compared with the coarse PRX. Authors concluded that the improvement in PRX dissolution rate is mainly caused by the increased surface-to-volume ratio due to the nanosization of drug particles (79). In the other study, Sun and coworkers investigated the effect of particle size reduction on the dissolution rate of coenzyme Q_{10}. They prepared the nanocrystals of coenzyme Q_{10} in 80-700 nm range using the solvent/non-solvent method and without any surfactant or polymer. The bioavailability of coenzyme Q_{10} after oral administration in beagle dogs was increased significantly compared to coarse suspensions. With the particle size of 80 nm, the maximum bioavailability was enhanced 7.3 times compared to coarse suspension (73).

3.3. Drug nanosuspension

Nanosuspensions contain colloidal dispersion of drug nanocrystals in a liquid dispersion medium such as water, aqueous solutions, or nonaqueous media which stabilized by surfactants and/or polymeric stabilizers (3,37,80). Nanosuspension method is one of the promising methods in improving the dissolution rate of poorly-water soluble drugs. A nanosuspension not only can overcome the poor solubility and bioavailability of low water soluble drugs, but also could modify the pharmacokinetic profiles of drugs and thus improve their safety and efficacy (81,82). Nanosuspensions are prepared by precipitation, high pressure homogenization, emulsion and milling techniques (83,84). The particles in nanosuspensions are stabilized with mixture of surfactants or polymers (38,85). Also by

addition of a suitable tonicity modifier agent, the formulation may be used for intravenous injection. The formulations could also be further processed into standard dosage forms such as capsules and tablets for oral administration (40). Fig. 4 shows the preparation steps for a drug nanosuspension.

Atovaquone is an antibiotic for treating opportunistic pneumocystis carinii infections in HIV patients, non-complicated plasmodium *falciparum malaria* and *leishmania* infections. The form of nanosuspension of atovaquone was also prepared by Schöler and colleagues in 2001 (75). The nanosuspension formulation showed excellent therapeutic effect in a new murine model of reactivated toxoplasmosis.

Itraconazole is a poorly water-soluble drug with low bioavailability. Nakarani and coworkers formulated itraconazole in a nanosuspension with a mean particle size of 294 nm by pearl milling technique using zirconium oxide beads as a milling media. They used poloxamer 407 as a stabilizer and glycerol as a wetting agent. The *in vitro* dissolution profile of drug from nanosuspension formulation showed 90% drug release in 10 min compared to 10 and 17% for pure drug and marketed formulation (Canditral capsule) respectively (86).

Jain and coworkers designed mucoadhesive nanosuspension of ciprofloxacin in average particle size ranging between 503 to 1844 nm. They prepared four different formulations using different polymers including soya lecithin, pluronic F68, polyvinyl alcohol, and PVP. The formulation with soya lecithin exhibited fast dissolution rate as compared to the others. These nanosuspensions showed 45-56% drug release in 10 h which is much greater than that of the conventional ciprofloxacin formulations (87).

Sigfridsson and colleagues investigated the effect of particle size reduction on dissolution rate enhancement of poorly water-soluble acidic or basic compounds. They showed that there is a correlation between particle size and *in vivo* exposure of an acidic compound. Nanosuspention of an acidic compound provided higher *in vivo* exposure due to the improved dissolution rate and oral bioavailability. Their results also revealed that for a basic compound, with the same doses, due to high solubility at gastric pH and the basic p*Ka*, microsuspension is sufficient and more particle size reduction does not require(40).

Olmesartan medoxomil is one of anti-hypertensive agents. Its orally administration is limited due to the poor aqueous solubility (<7.75 μg/ml) and low absolute bioavailability (only 26%).

Using media milling technique, Thakkar and colleagues prepared its nanosuspensions to enhance the oral bioavailability of olmesartan medoxomil by improving its solubility and dissolution rate. Drug in from of nanosuspension showed significantly higher dissolution rate than the conventional drug suspension as well as from the marketed tablet formulation. More than 70% of the drug (for lyophilized nanosuspension formulation) was dissolved within 5 min and about 100% was dissolved within 15 min, while the conventional drug showed only 12% dissolution at the end of 5 min and 92% after 60 min (88).

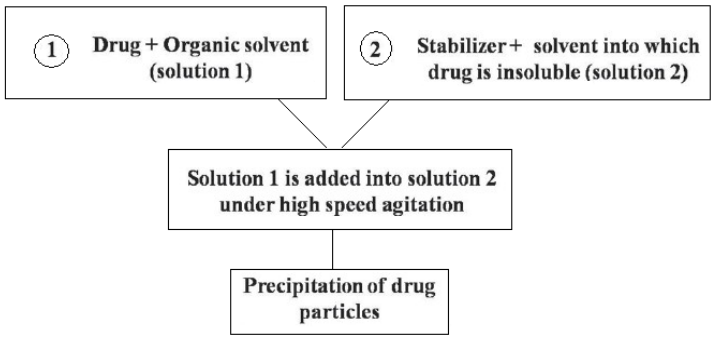

Fig. 4. The preparation steps for a drug nanosuspension.

Hou and coworkers prepared azithromycin nanosuspensions with mean particle size of about 200 nm by the combination of reactive precipitation and freeze-drying in the presence of biocompatible stabilizer. Solid nanoparticles were then obtained by lyophilization of the nanosuspensions. *In vitro* studies showed that the dissolution rate increased obviously in comparison of raw azithromycin (89).

Pranlukast is one of the potential drugs in the treatment of asthma. Due to its poor water solubility, it has limited clinical applications. Wang and coworkers prepared nanosuspensions of pranlukast (318.2 ± 7.3 nm) through high-pressure homogenization method. They used poloxamer 407 as stabilizer and PEG 200 as surfactant. *In vitro* study of dissolution behavior of nanosuspensions showed remarkable fast dissolution rate resulting in complete drug release in 30 min.

In vivo bioavailability of these nanosuspension formulations showed 4.38 fold improvement compared to raw crystals of the drug (80).

Cerdeira and colleagues prepared nanosuspensions of miconazole and itraconazole (antifungal drugs) by media milling method with mean particle size of approximately 210 nm. These drugs have low water solubility, which limits their bioavailability and antifungal effects. They used sodium dodecyl sulfate in combinations with either cellulose ethers (HPC or HPMC) or poloxamers as stabilizer.

Compared tothe coarse drug suspension, dissolution of the miconazole nanosuspension (spray-or freeze-dried) was enhanced twice in 10 and 20 min. Freeze-dried itraconazole nanosuspensions did not show faster dissolution than freeze-dried coarse suspension but itraconazole nanosuspension in spray-drying form showed fast dissolution to the extent that 60% of the drug was dissolved in less than 10 min as compared to 30-45 min with the coarse suspension (84).

Simvastatin, a hypolipidemic drug, has an oral bioavailability of less than 5%. Athul prepared nanosuspension of simvastatin with particle sizes in the range of 240-244 nm by high pressure homogenization method using PVP K30 as stabilizer. The homogenized nanosuspension was then freeze dried. These formulations showed maximum drug release of 98.73% in 1 h compared with raw drug that showed a maximum release of only 45.90% (83,90).

Felodipine is a poorly water-soluble antihypertensive drug (91). Sahu and Das prepared nanosuspension of felodipine (60–330 nm) by nanoprecipitation alone and in combination with ultra-sonication method using ethanol as solvent and water as antisolvent. According to their results the nanosuspension of felodipine can increase the dissolution rate of drug and improve its oral bioavailability.

Their results showed that the dissolution profiles of nanosuspension formulation showed up to 79.67 % release in 4 h. The authors also stated that the nanoprecipitation with ultra-sonication is potential approach to formulate homogenous nanosuspensions with uniform-sized stable nanoparticles of felodipine (3). Some of research works in which the dissolution rate of drugs have shown improvement via nanosizatin aresummarized in Table 2.

4. Nanotechnology issues

Applying of nanoparticles has various benefits such as an increases in dissolution rate, bioavailability and rate of absorption of poorly water-soluble drugs , delivery systems with high payloads, extended circulation times and active targeting capabilities, protecting from opsonization and clearance in the bloodstream (45,57). For decades pharmaceutical scientists have been using nanoparticles to reduce toxicity and side effects of drugs. Inspite of above mentioned advancements, there are some disadvantages and safety concerns about nanoparticles. Recently it is realized that these carrier systems themselves may impose risks to the patient.

The particle size reduction is a good method to increase the dissolution rate of poorly water-soluble BCS-class II and IV drugs but there are possibility of disorder induction and solid state modification.

Table 2. Some of research works in which the dissolution rate of drugs has shown improvement via nanosization.

Drug name	Preparation method	Type of nanoparticles	Reference
Indomethacin	Controlled pH co-precipitation method.	Amorphous nanopartiles	(32,69)
Celecoxib	Anti-solvent precipitation under sonication and high pressure homogenization methods.	Amorphous nanopartiles	(70)
Quercetin	Evaporative precipitation of nanosuspension.	The particles were big, irregular and flake type when water used as anti-solvent, but in the presence of benzene or hexane as anti-solvent, the particles were smaller and needle shaped.	(23)
Ibuprofen	Solvent/anti-solvent precipitation.	Amorphous nanopartiles	(62)
Meloxicam	Anti-solvent precipitation.	Amorphous nanopartiles	(8)
Itraconazole (ITZ)	Sonoprecipitation technique.	Crystalline nanoparticles	(71)
Albendazole	Anti-solvent precipitation technique.	Crystalline nanoparticles	(72)
Nifedipine (NIF)	High pressure homogenization.	Nanocrystal	(76)
Cilostazol	The hammer milled and the jet-milled.	Nanocrystal	(77)
Nitrendipine	Precipitation homogenization process.	Nanocrystal	(78)
piroxicam (PRX)	High pressure homogenization technique.	Nanocrystal	(79)
coenzyme Q_{10}	Solvent/non-solvent method and without any surfactant or polymer.	Nanocrystal	(73)
Itraconazole	Media milling.	Nanocrystal	(84)
Atovaquone	High-pressure homogenization.	Nanocrystal	(75)
Ciprofloxacin	High-pressure homogenizationcombination with ultra-sonnication method.	Nanocrystal	(87)
Olmesartan medoxomil	Media milling method.	Nanocrystal	(88)
Azithromycin	Reactive precipitation and freeze-drying.	Nanocrystal	(89)
Pranlukast	High pressure homogenization method.	Nanocrystal	(80)
Miconazole	Media milling method.	Nanocrystal	(84)
Simvastatin	High pressure homogenization method.	Nanocrystal	(83)
Felodipine	Nanoprecipitation alone and in combination with ultra-sonnication method.	Nanocrystal	(37)

The particle size reduction also deteriorates flow properties and wettability of particles and develops electrostatic forces, leading to problematic formulations (3). Also neurological and respiratory damage, circulatory problems and toxicity of nanoparticles are concerns associated with the use of nanoparticles (92-94). Therefore monitoring of the particle size reduction and development of methods for the safe utilization of nanoparticles are necessary.

5. CONCLUSION

Since, designing and development of new drug entities is complex and time consuming which requires high cost. Therefore, improving the solubility properties ofconventional drugs may be an appropriate idea to increase bioavailability of poorly water-soluble drugs. Nanosizing of drugs in form of nanoparticles, nanocrystals or nanosuspensions, without complicated synthesis processes can be used as a simple method to increase dissolution rate of drugs and consequently their bioavailability. Using of these systems has resulted in the improved dissolution rate and therefore bioavailability after oral administration. Amongthese systems, preparation of drug nanocrystals is a simple, effective and promising method in delivery of poorly water-soluble drugs by oral route, because these are only composed of drug in crystalline form and nonosized range. Spray drying method has been employed most commonly to solidify the nanostructurs. Its low cost makes this method very popular in industries. In addition to greater bioavailability, nanoparticles provide smaller drug doses, and hence reduce the toxicity and dosage variability. Due to some disadvantages of nanoparticles, monitoring the fabrication process of nanostructures is necessary.

REFERENCES

1. Bhadoriya SS, Mangal A, Madoriya N, Dixit P. Bioavailability and bioactivity enhancement of herbal drugs by Nanotechnology: a review. J Curr Pharm Res. 2011;8:1-7.
2. Chowdary K, Enturi V. Enhancement of dissolution rate and formulation development of Efavirenz tablets employing starch phosphate a new modified starch. Int J Pharm Sci Drug Res. 2011;3:80-83.
3. Sahu BO, Das MK. Nanosuspension for enhancement of oral bioavailability of felodipine. Appl Nanosci. 2014;4:189–197.
4. Chaudhary A, Nagaich U, Gulati N, Sharma V, Khosa R. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: a recent review. J Adv Pharm Educ Res. 2012;2:32-67.
5. Jung JY, Yoo SD, Lee SH, Kim KH, Yoon DS, Lee KH. Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. Int J Pharm. 1999;187:209-218.
6. Carsten E, Kwang Jin K. Drug absorption studies: *in situ*, *in vitro* and in silico models. New York: Springer; 2008. p. 182–215.
7. Kawakami K. Modification of physicochemical characteristics of active pharmaceutical ingredients and application of supersaturatable dosage forms for improving bioavailability of poorly absorbed drugs. Adv Drug Deliv Rev. 2012;64:480-495.
8. Raval AJ, Patel MM. Preparation and characterization of nanoparticles for solubility and dissolution rate enhancement of meloxicam. Intl R J of Pharmaceuticals. 2011;1:43-49.
9. Pandya P, Gattani S, Jain P, Khirwal L, Surana S. Co-solvent evaporation method for enhancement of solubility and dissolution rate of poorly aqueous soluble drug simvastatin: *in vitro–in vivo* evaluation. AAPS Pharm Sci Tech. 2008;9:1247-1252.
10. Maleki Dizaj S. Preparation and study of vitamin A palmitate microemulsion drug delivery system and investigation of co-surfactant effect. J Nanostruct Chem. 2013;3:59.
11. Nokhodchi A, Aliakbar R, Desai S, Javadzadeh Y. Liquisolid compacts: the effect of cosolvent and HPMC on theophylline release. Colloids Surf B Biointerfaces. 2010;79:262-269.
12. Jagdale SC, Jadhav VN, Chabukswar AR, Kuchekar BS. Solubility enhancement, physicochemical characterization and formulation of fast-dissolving tablet of nifedipine-betacyclodextrin complexes. Braz J Pharm Sci. 2012;48:131-145.
13. Dhanaraju MD, Kumaran KS, Baskaran T, Moorthy MS. Enhancement of bioavailability of griseofulvin by its complexation with beta-cyclodextrin. Drug Dev Ind Pharm. 1998;24:583-587.
14. Shulman M, Cohen M, Soto-Gutierrez A, Yagi H, Wang H, Goldwasser J, *et al*. Enhancement of naringenin bioavailability by complexation with hydroxypropoyl-β-cyclodextrin. PloS one. 2011;6:e18033.
15. Sabzevari A, Adibkia K, Hashemi H, De Geest B, Mohsenzadeh N, Atyabi F, *et al*. Improved anti-inflammatory effects in rabbit eye model using biodegradable poly beta-amino ester nanoparticles of triamcinolone acetonide. Invest Ophthalmol Vis Sci. 2013;54:5520-5526.
16. Tapas A, Kawtikwar P, Sakarkar D. Enhanced dissolution rate of felodipine using spherical agglomeration with Inutec SP1 by quasi emulsion solvent diffusion method. Res Pharm Sci. 2009;4:77-84.

17. Nili SF, N Bolourchian M. Crystal habit modification of meloxicam utilizing different alcoholic solvents and crystallization conditions. Res Pharm Sci. 2012;7:S317.
18. Patel A, Jones SA, Ferro A, Patel N. Pharmaceutical salts: a formulation trick or a clinical conundrum. Br J Cardiol. 2009;16:281-286.
19. Shukla V. Techniques for solubility enhancement of poorly soluble drugs: an overview. J Med Pharm App Sci. 2012;1:18-38.
20. Ajay S, Harita D, Tarique M, Amin P. Solubility and dissolution rate enhancement of curcumin using kollidon VA64 by solid dispersion technique. Int J Pharm Tech Res. 2012;4:1055-1064.
21. Ismail S, El-Mahdy M, Al-Kubati S. Enhancement of solubility and dissolution of nimesulide using solubilization, solid dispersion and complexation techniques. Bull Pharm Sci, Assiut University. 2009;32:321-338.
22. Joshi HN, Tejwani RW, Davidovich M, Sahasrabudhe VP, Jemal M, Bathala MS, *et al*. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture. Int J Pharm. 2004;269:251-258.
23. Kakran M, Sahoo N, Li L. Dissolution enhancement of quercetin through nanofabrication, complexation, and solid dispersion. Colloids Surf B Biointerfaces. 2011;88:121-130.
24. Ramakrishna GS, AnjiReddy K, P BJRD, Rao PR, Bhavanam PR. Enhancement dissolution rate of iboprofen by solid dispersion method. J Innovative Trends Pharm Sci. 2010;1:204-206.
25. Roul L, Manna N, Parhi R, Sahoo S, Suresh P. Dissolution rate enhancement of alprazolam by solid dispersion. Indian J Pharm Educ Res. 2012;46:38-44.
26. Tabbakhian FH, Tavakoli N, Z Jamshidian . Dissolution enhancement of glibenclamide by solid dispersion: solvent evaporation versus a supercritical fluid-based solvent-antisolvent technique. Res Pharm Sci. 2014;9:337-350.
27. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm. 2007;341:26-34.
28. Javadzadeh Y, Musaalrezaei L, Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm. 2008;362:102-108.
29. Rajesh K, Rajalakshmi R, Umamaheswari J,Ashok Kumar CK. Liquisolid technique a novel approach to enhance solubility and bioavailability. Int J Biopharmaceutics. 2011;2:8-13.
30. Thadkala K, Voruganti S, Badari SR, Padman SC. Enhancement of Dissolution rate of nimesulide by liquisolid compaction technique. Int J Pharm Tech Res. 2012;4:1294-1302.
31. Javadzadeha Y, Siahi-Shadbada M, Barzegar-Jalalia M, Nokhodchia A. Enhancement of dissolution rate of piroxicam using liquisolid compacts. Farmaco. 2005 60:361–365.
32. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad M, Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci. 2005;12;8:18-25.
33. Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm. 1995;125:91-97.
34. Möschwitzer J. Particle size reduction technologies in the pharmaceutical development process. Am Pharm Rev. 2010;2010:54-59.
35. Mohammadi G, Nokhodchi A, Barzegar-Jalali M, Lotfipour F, Adibkia K, Ehyaei N, *et al*. Physicochemical and anti-bacterial performance characterization of clarithromycin nanoparticles as colloidal drug delivery system. Colloids Surf B Biointerfaces. 2011;88:39-44.
36. Javadzadeh Y, Ahadi F, Davaran S, Mohammadi G, Sabzevari A, Adibkia K. Preparation and physicochemical characterization of naproxen-PLGA nanoparticles. Colloids Surf B Biointerfaces. 2010;1;81:498-502.
37. Sahu BP, Das MK. Nanosuspension for enhancement of oral bioavailability of felodipine. App Nanosci. 2014;4:189-197.
38. Kesisoglou F, Panmai S, Wu Y. Nanosizing Oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev. 2007;59:631-644.
39. Homayouni FS, Varshosaz J, H Garekani A. Soluplus®; a novel excipient to improve dissolution rate of poorly water soluble drug, celecoxib. Res Pharm Sci. 2012;7:S386.
40. Sigfridsson K, Lundqvist AJ, Strimfors M. Particle size reduction and pharmacokinetic evaluation of a poorly soluble acid and a poorly soluble base during early development. Drug Dev Ind Pharm. 2011;37:243-251.
41. Nekkanti V, Vabalaboina V, Pillai R. Drug Nanoparticles–An Overview. In: Hashim AA, editor. The delivery of nanoparticles. Rijeka: INTECH; 2012. p. 111-132.
42. Li X, Gu L, Xu Y, Wang Y. Preparation of fenofibrate nanosuspension and study of its pharmacokinetic behavior in rats. Drug Dev Ind Pharm. 2009;35:827-833.
43. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm. 2006;62:3-16.
44. Robertson A. The development of ideas on heterogeneous catalysis. Platinum Metals Rev. 1983;27:31-39.
45. D'Addio SM, Prud'homme RK. Controlling drug nanoparticle formation by rapid precipitation. Adv Drug Deliv Rev. 2011;63:417-426.
46. Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly-water-solublecompounds. Eu J Pharm Sci. 2003;18:113-120.
47. Adibkia K, Barzegar- Jalali M, Nokhodchi A, Siahi Shadbad M, Omidi Y, Javadzadeh Y, *et al*. A review

on the methods of preparation of pharmaceutical nanoparticles. Pharm Sci. 2010;15:303-314.
48. Sabzevari A, Adibkia K, Hashemi H, Hedayatfar A, Mohsenzadeh N, Atyabi F, *et al*. Polymeric triamcinolone acetonide nanoparticles as a new alternative in the treatment of uveitis: *in vitro* and *in vivo* studies. Eur J Pharm Biopharm. 2013;84:63-71.
49. Dizaj SM, Lotfipour F, Barzegar-Jalali M, Zarrintan MH, Adibkia K. Antimicrobial activity of the metals and metal oxide nanoparticles. Mater Sci Eng. 2014;44:278-284.
50. Gulsun T, Gursoy R, Levent O. Nanocrystal technology for oral delivery of poorly water-soluble drugs. FABAD J Pharm Sci. 2009;34:55-65.
51. Rasenack N, Müller BW. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm Res. 2002;19:1894-1900.
52. Nighute A, Bhise S. Enhancement of Dissolution rate of rifabutin by preparation of microcrystals using solvent change method. Int J Pharm Tech Res. 2009;1:142-148.
53. da Costa MA, Seiceira RC, Rodrigues CR, Hoffmeister CRD, Cabral LM, Rocha HVA. Efavirenz dissolution enhancement I: co-micronization. Pharmaceutics. 2012;5:1-22.
54. Chingunpituk J. Nanosuspension technology for drug delivery. Walailak J Sci & Tech. 2007;4:139-153.
55. Yu X, Valmikinathan CM, Wang J, Rogers A, Hoffman J, Nalwa HS. Electrospun nanofibers for bioengineering applications. Encyclopedia of nanoscience and nanotechnology. 2011;13;559-583.
56. Saffie-Siebert R, Ogden J, Parry-Billings M. Nanotechnology approaches to solving the problems of poorly water-soluble drugs. Drug Dis World. 2005;2:1-71.
57. Parboosing R, Maguire GE, Govender P, Kruger HG. Nanotechnology and the treatment of HIV infection. Viruses. 2012;4:488-520.
58. Thassu D, Pathak Y, Deleers M. Nanoparticulate drug-delivery systems: an overview. Boca Raton, Florida:CRC press; 2007. p. 1-4.
59. Dizaj SM, JafarI S, Yari- Khosroshahi A. A sight on the current nanoparticle-based gene delivery vectors. Nanoscale Res Lett. 2014;9:252.
60. Adibkia K, Javadzadeh Y, Dastmalchi S, Mohammadi G, Niri FK, Alaei-Beirami M. Naproxen–eudragit RS100 nanoparticles: Preparation and physicochemical characterization. Colloids Surf B Biointerfaces. 2011;83:155-159.
61. Cavalli R, Leone F. Nanosuspensions A versatile drug delivery platform. Chim Oggi. 2013;31:46-49.
62. Mansouri M, Pouretedal HR, Vosoughi V. Preparation and characterization of Ibuprofen nanoparticles by using solvent/antisolvent precipitation. Open Confere. Proc. J. 2011;2:88-94.
63. Beg S, Swain S, Rizwan M, Irfanuddin M, Shobha Malini D. Bioavailability enhancement strategies: basics, formulation approaches and regulatory considerations. Curr Drug Deliv. 2011;8:691-702.
64. De Villiers MM, Aramwit P, Kwon GS. Nanotechnology in drug delivery. New York City: Springer; 2009. p. 3-105.
65. Gupta RB, Kompella UB. Nanoparticles technology drug delivery. New York: Taylor & Francis; 2006. p. 1-20.
66. Junghanns J-UA, Müller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008;3:295-310.
67. Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. Expert Opin Drug Deliv. 2007;4:403-416.
68. Wu Y, Loper A, Landis E, Hettrick L, Novak L, Lynn K, *et al*. The role of biopharmaceutics in the development of a clinical nanoparticle formulation of MK-0869: a Beagle dog model predicts improved bioavailability and diminished food effect on absorption in human. Int J Pharm. 2004;285:135-146.
69. Rezaei Mokarram A, Kebriaee zadeh A, Keshavarz M, Ahmadi A, Mohtat B. Preparation and in-vitro evaluation of indomethacin nanoparticles. DARU. 2010;18:185-192.
70. Liu Y, Sun C, Hao Y, Jiang T, Zheng L, Wang S. Mechanism of dissolution enhancement and bioavailability of poorly water soluble celecoxib by preparing stable amorphous nanoparticles. J Pharm Pharm Sci. 2010;13:589-606.
71. Badawi AA, El-Nabarawi MA, El-Setouhy DA, Alsammit SA. Formulation and stability testing of itraconazole crystalline nanoparticles. AAPS Pharm Sci Tech. 2011;12:811-820.
72. Koradia DK, Parikh HR. Dissolution enhancement of albendazole through nanocrystal formulation. J Pharm Bioallied Sci. 2012;4:S62.
73. Sun J, Wang F, Sui Y, She Z, Zhai W, Wang C, *et al.* Effect of particle size on solubility, dissolution rate, and oral bioavailability: evaluation using coenzyme Q10 as naked nanocrystals. Int J Nanomedicine. 2012;7:5733-5744.
74. Ravichandran R. Development of an oral curcumin nanocrystal formulation. J Nanotech Eng Med 2012;3:ID:041007.
75. Schöler N, Krause K, Kayser O, Müller RH, Borner K, Hahn H, *et al*. Atovaquone nanosuspensions show excellent therapeutic effect in a new murine model of reactivated toxoplasmosis. Antimcrob Agents Chemother. 2001;45:1771-1779.
76. Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm. 2005;299:167-177.
77. Jinno J, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, *et al*. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J Control Release. 2006;111:56-64.
78. Quan P, Xia D, Piao H, Piao H, Shi K, Jia Y, *et al*. Nitrendipine nanocrystals: its preparation, characterization, and *in vitro–in vivo* evaluation. AAPS Pharm Sci Tech. 2011;12:1136-1143.

79. Lai F, Pini E, Angioni G, Manca M, Perricci J, Sinico C, *et al*. Nanocrystals as tool to improve piroxicam dissolution rate in novel orally disintegrating tablets. Eur J Pharm Biopharm. 2011;79:552-558.
80. Wang L, Hao Y, Liu N, Ma M, Yin Z, Zhang X. Enhance the dissolution rate and oral bioavailability of pranlukast by preparing nanosuspensions with high-pressure homogenizing method. Drug Dev Ind Pharm. 2012;38:1381-1389.
81. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. J Adv Pharm Technol Res. 2011;2:81-87.
82. Adibkia K, Omidi Y, Siahi MR, Javadzadeh AR, Barzegar-Jalali M, Barar J, *et al*. Inhibition of endotoxin-induced uveitis by methylprednisolone acetate nanosuspension in rabbits. J Ocul Pharmacol Ther. 2007;23:421-432.
83. Athul PV. Preparation and characterization of simvastatin nanosuspension by homogenization method. Int J Pharm Tech Res. 2013;5:193-197.
84. Cerdeira AM, Mazzotti M, Gander B. Formulation and drying of miconazole and itraconazole nanosuspensions. Int J Pharm. 2013;443:209-220.
85. Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: a formulation approach for poorly-water-soluble compounds. Eu J Pharm Sci. 2003;18:113-120.
86. Nakarani M, Misra A, Patel J, Vaghani S. Itraconazole nanosuspension for oral delivery: Formulation, characterization and *in vitro* comparison with marketed formulation. Daru. 2010;18:84-90.
87. Jain V, Kare P, Jain D, Singh R. Development and characterization of mucoadhesive nanosuspension of ciprofloxacin. Acta Pol Pharm. 2011;68:273-278.
88. Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. J Pharm Bioallied Sci. 2011;3:426-434.
89. Hou CD, Wang JX, Le Y, Zou HK, Zhao H. Preparation of azithromycin nanosuspensions by reactive precipitation method. Drug Dev Ind Pharm. 2012;38:848-854.
90. Pandya VM, Patel JK, Patel DJ. Formulation and optimization of nanosuspensions for enhancing simvastatin dissolution using central composite design. Dissolution Tech. 2011;18:40-45.
91. Saltiel E, Ellrodt A, Monk J, Langley M. Felodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs. 1988;36:387–428.
92. Tsuji JS, Maynard AD, Howard PC, James JT, Lam C-w, Warheit DB, *et al*. Research strategies for safety evaluation of nanomaterials, part IV: risk assessment of nanoparticles. Toxicol Sci. 2006;89:42-50.
93. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008;3:133-149.
94. Zimper U, Aaltonen J, Krauel-Goellner K, Gordon KC, Strachan CJ, Rades T. The influence of milling on the dissolution performance of simvastatin. Pharmaceutics. 2010;2:419-431.