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# SIGNIFICANCE OF NANOCRYSTALS IN DRUG DELIVERY

**N.B. GUPTA*, K. SINGH, N. BHANDARI, P. SHARMA**

**Department of pharmaceutics, Sri Sai College Of Pharmacy, Badhani, Pathankot, Punjab, India.**

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**Corresponding Author**

Nitan Bharti Gupta

Asistant Professor, Sri Sai College of Pharmacy, Badhani, Pathankot, Punjab, India-145001

## Abstract

For the past few decades, there has been a considerable research interest in the area of drug delivery by using particulate delivery systems as carriers for small and large molecules. Significance of nanocrystal drugs is mentioned in this review. Nanocrystals are aggregates anywhere from a few hundred to tens of thousands of atoms that combine into a crystalline form of matter known as a "cluster". They are used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They have been used in vivo to protect the drug entity in the systemic circulation. The method of preprations of nanocrystal is bottom up, top down, top down and bottom up, spray drying and some new techniques. These approaches are paving the way to the development of nanosized objects which are able to perform multiple technological tasks. There are several important advantages of nanocrystal formulations such as, enhanced oral bioavailability, improved dose proportionality, reduced food effects, suitability for administration by all routes and possibility of sterile filtration due to decreased particle size range. The drug selection depends upon the sites and to deliver the drug at a controlled and sustained rate to the site of action. Here, we review various aspects of nanocrystals formulation, characterization, effect of their characteristics and their pharmaceutical applications in delivery of drug molecules and therapeutic genes.

## INTRODUCTION

At present about 40% of the drugs being in the development pipelines are poorly soluble, even up to 60% of compounds coming directly from synthesis are poorly soluble. Poor solubility has poor bioavailability. According to the Noyes-Whitney law the dissolution velocity dc/dt depends on the saturation solubility $c_s$. There are two basic approaches to overcome the bioavailability problems of these drugs:

1. Increase of saturation solubility (e.g. by formation of complex)

2. Increase of dissolution velocity[1].

Drug nanocrystals are pure solid drug particles with a mean diameter below 1000 nm. The term drug nanocrystal implies a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous[2].

There are many advantages of nanocrystal formulations designed for oral administration and they are as follows:

- Increased rate of absorption,
- Increased oral bioavailability,
- Rapid effect,
- Improved dose proportionality,
- Reduction in required dose,
- Applicability to all routes of administration in any dosage form. Contrary to micronized drugs, nanocrystals can be administered via several routes. Oral administration is possible in the form of tablets, capsules, sachets or powder; preferably in the form of a tablet. Nano suspensions can also be administered via the intravenous route due to very small particle size, and in this way, bioavailability can reach 100 %.
- Reduction in fed/fasted variability,
- Rapid, simple and cheap formulation development
- Possibility of high amounts (30-40 %) of drug loading,
- Increased reliability. Usually side effects are proportional to drug concentration, so decreasing the concentration of active drug substances leads to an increased reliability for patients.
- Sustained crystal structure. Nanocrystal technology leads to an increase in

dissolution rate depending on the increase in surface area obtained by reduction of the particle size of the active drug substance down to the Nano size range preserving the crystal morphology of the drug.

- Improved stability. They are stable systems because of the use of a stabilizer that prevents re-aggregation of active drug substances during preparation. Suspension of drug nanocrystals in liquid can be stabilized by adding surface active substances or polymers.
- Applicability to all poorly soluble drugs because all these drugs could be directly disintegrated into nanometre-sized particles[4].

**SPECIAL PROPERTIES OF NANONISED DRUGS**

Drug nanoparticles are a formulation principle for all poorly soluble drugs for which the dissolution velocity is the rate limiting step for absorption and thus the reason for a too low oral bioavailability. The increase in surface area leads to an increase in the dissolution velocity according the Noyes-Whitney equation. A fact in the past often overlooked is the increase in the saturation solubility of nanonised compounds compared to micrometre particles, precisely the kinetic saturation solubility increases. The basis for this is the Kelvin equation describing the vapour pressure as a function of the curvature of liquid droplets in a gas phase. Compared to micrometer crystals the nanocrystals lead to a supersaturated solution. This situation is metastable, that means as a function of time crystallisation will be initiated, large crystals will precipitate and the system returns to the thermodynamically stable state of the saturation solubility of micrometer crystals. However, in general duration of this supersaturated state is sufficient for oral absorption. In general amorphous material possesses a higher saturation solubility compared to crystalline material; e. g. itraconazole amorphous has a 60 times higher solubility than in the crystalline state. Therefore, to achieve highest supersaturating, the ideal drug nanoparticles should not be crystalline (drug nanocrystals) but amorphous. The prerequisite for using this approach is that the amorphous state can be preserved. However, it has been shown that preservation of amorphous conditions or

solid solutions for the shelf-life of pharmaceutical products is possible (e. g. the SDD technology by Pfizer)[5].

**Nanocrystal Preparation Methods:** Several preparation methods devolpe today, implemented preparation methods of Nanocrystal formulations can be classified as "bottom up", "top-down", "top down and bottom up" and "spray drying". "Bottom up" technology begins with the molecule; active drug substance is dissolved by adding an organic solvent, and then, solvent is removed by precipitation. "Top-down" technology applies dispersing methods by using different types of milling and homogenization techniques. "Top down" technology is more popular than "Bottom up" technology; it is known as "nanosizing". In other words, it is a process which breaks down large crystalline particles into small pieces. In "top down and bottom up" technology, both methods are utilized together. Spray drying is also a method for preparing drug nanocrystals, which is faster and more practical compared to the other methods[4].

1. **Bottom up**

a) Nanoprecipitation

2. **Top down**

a) Milling

b) Homogenization

3. **Top down and Bottom up**

4. **Spray drying**

5. **Other Techniques used for the Production of Drug Nanocrystals:**

a) Rapid expansion from a liquefied-gas solution (RESS)

b) Nanopure® XP technology

c) Spray Freezing into Liquid (SFL) technology

**1. Bottom up technology**: The principle of this method is based on the dissolution of the active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated. Basic advantage of the precipitation technique is that it is simple and has a low cost. Also, scale up is simple in this method. It should be kept in mind that several parameters; such as stirring rate, temperature, solvent/ nonsolvent rate, drug concentration, viscosity, type of solvent and stabilizer should be controlled in order to obtain homogenous nanocrystals by this technique[3].

a) **Precipitation methods:** The drug is dissolved in a solvent and subsequently added to a nonsolvent, leading to the precipitation of finely dispersed drug nanocrystals. One must consider in mind that these nanocrystals need to be stabilized in order when they are not allowed to grow to the micrometre range. In addition, the drug needs to be soluble in at least one solvent, which creates problems for newly developed drugs that are insoluble in both aqueous and organic media. Due to some of these reasons as reported, this technology has not been applied to a product as yet. A solution of the carotenoid, together with a surfactant in digestible oil, is mixed with an appropriate solvent at a specific temperature. To obtain the solution a protective colloid is added. This leads to an O/W two phase system. The carotenoid stabilized by the colloid localizes in the oily phase. After Lyophilisation X-ray analysis shows that approximately 90% of the carotenoid is in an amorphous state[6].

**2. Top down technology:** "Top-down" technology applies dispersing methods by using different types of milling and homogenization techniques. "Top-down" technology is more popular than "Bottom up" technology; it is known as "nanosizing". In other words, it is a process which breaks down large crystalline particles into small pieces. In "top down and bottom up" technology, both methods are utilized together. Top-down technology can be applied by either homogenization or milling [4].

a) **Milling methods:** The classical Nanocrystal® technology uses a bead or a pearl mill to achieve particle size diminution. Ball mills are already known from the first half of the 20th century for the production of ultra fi ne suspensions. Milling media, dispersion medium (generally water), stabilizer and the drug are charged into the milling chamber. Shear forces of impact, generated by the movement of the milling media, lead to particle size reduction. In contrast to high pressure homogenization, it is a low energy milling technique. Smaller or larger milling pearls are used as milling media. The pearls or balls consist of ceramics (cerium or yttrium stabilized zirconium dioxide), stainless steel, glass or highly cross-linked polystyrene resin-coated beads. Erosion from the milling material during the milling

process is a common problem of this technology. To reduce the amount of impurities caused by erosion of the milling media, the milling beads are coated. Another problem is the adherence of product to the inner surface area of the mill. There are two basic milling principles. Either the milling medium is moved by an agitator, or the complete container is moved in a complex movement leading consequently to a movement of the milling media. When one assumes that 76% of the volume of the milling chamber is to be filled with milling material, larger batches are difficult to produce when moving the new container, so mills using agitators are used for large sized mill for large batches. The milling time depends upon many factors such as the surfactant content, hardness of the drug, viscosity, temperature, energy input, size of the milling media. The milling time from about 30 minutes to hours or several days. This new technology is an important particle size reduction which is proven by four FDA-approved drugs using it, which will the subject later in this text[7].

b) **Homogenization methods:** (IDD-P™ technology) The Micro fluidizer is a jet stream homogenizer of two fluid streams collide frontally with high velocity (up to 1000m/sec) under pressures up to 4000 bar. There is a turbulent flow, high shear forces and particles collide leading to particle diminution to the nanometre range. The high pressure applied and the high streaming velocity of the lipid can also lead to cavitations additionally, contributing to size decreased. To prevent the particle size, stabilization with phospholipids or other surfactants and stabilizers is required. In many cases, 50 to 100 time- consuming passes are necessary for a sufficient particle size reduction.

- **Piston-gap homogenization in water (Dissocubes®):** Drug nanocrystals can also be produced by high-pressure homogenization using piston gap homogenizers. Depending on the homogenization temperature and the dispersion media, there is a difference between the Dissocubes® technology and the Nanopure® technology. Dispersion medium of the suspensions was water. A piston in a large bore cylinder creates pressure up to 2000 bar. The suspension is pressed through a very narrow ring gap. The gap width is typically in the range of 3-15 micrometres at pressures between 1500-

150 bar. There is a high streaming velocity in the gap according to the Bernoulli equation. Due to the reduction in diameter from the large bore cylinder to the homogenization gap which increases the dynamic pressure (streaming velocity) and simultaneously decreases the static pressure on the liquid. When the liquid starts boiling at that time gas bubbles occur which subsequently implode, when the suspension leaves the gap and is again under normal pressure (cavitation). Gas bubble formation and implosion lead to shock waves which cause particle diminution. The patent describes cavitation as the reason for the achieved size diminution. Piston gap homogenizers which can be used for the production of Nano-suspensions are e.g. from the companies APV Gaulin, Avestin or Niro Soavi. The technology was acquired by Skye pharma PLC at the end of the 90s and employed in its formulation development. The use of water as dispersion medium is associated with some disadvantages. Hydrolysis of water-sensitive drugs can occur, as well as problems during drying steps. In cases of thermo labile drugs or drugs possessing a low melting point, a complete water removal requires relatively expensive techniques, such as Lyophilization. For these reasons, the Dissocubes® technology is particularly suitable if the resulting nanosuspension is directly used without modifications, such as drying steps. Many different drugs have been processed by high-pressure homogenization to product DissoCubes. Up to now each drug investigated could be converted into a nanosuspension[8].

**3 Top down and bottom up technology:** In "top down and bottom up" technology, both methods are used together. Nano-Edge® is a product obtained by such a combination technology. Nano-edge technology described the formulation method for poorly water-soluble drugs. It is a useful technology for active ingredients that have high melting points and high n-octanol-water partition coefficients. It is based on direct homogenization, micro precipitation, and lipid emulsions. In micro precipitation, the drug first is dissolved in a water-miscible solvent to form a solution. Then, the solution is mixed with a second solvent to form a pre suspension and energy is added to the pre suspension to form particles having an average effective

particle size of 400 nm to 2 µ. The energy-addition step involves adding energy through sonication, homogenization, counter current flow homogenization, micro fluidization, or other methods of providing impact, shear, or cavitation forces. A drug suspension resulting from these processes may be administered directly as an injectable solution, provided water-for-injection and sterile is used in the formulation. Nano-edge technology facilitates small particle sizes (<1000 nm [volume weighted mean]), high drug loading (10–200 mg/mL), long-term stability (up to 2 years at room temperature or temperatures as low as 5 °C), the elimination of co solvents, reduced levels of surfactants, and the use of safe, well-tolerated surfactants NANO-EDGER process is particularly suitable for drugs that are soluble in non-aqueous media possessing low toxicity, such as N-methyl-2-pyrrolidinone[9].

**4. Spray Drying:** One of the preparation methods of nanocrystals is spray drying. This method is usually used for drying of solutions and suspensions. In a conical or cylindrical cyclone, solution droplets are sprayed from top to bottom, dried in the same direction by hot air and spherical particles are obtained. Spraying is made with an atomizer which rapidly rotates and provides scattering of the solution due to centrifugal effect. The solution, at a certain flow rate, is sent to the inner tube with a peristaltic pump, nitrogen or air at a constant pressure is sent to the outer tube. Spraying is provided by a nozzle. Droplets of solution become very small due to spraying; therefore, surface area of the drying matter increases leading to fast drying. Concentration, viscosity, temperature and spray rate of the solution can be adjusted and particle size, fluidity and drying speed can be optimized. The dissolution rate and bioavailability of several drugs, including hydrocortisone, COX-2 Inhibitor (BMS-347070) were improved utilizing this method[6].

**3. Other technologies:**

**a) Rapid expansion from a liquefied-gas solution (RESS):** This process is applicable to the substances those are soluble in supercritical fluids. In this process, the solute is first dissolved in a supercritical fluid then it is passed through a nozzle at supersonic speed. Pressure reduction of solution in a nozzle leads to a rapid

expansion. This RESS leads to super saturation of the solute and subsequent precipitation of solute particles with narrow particle size distributions applied SCF processing technique *i.e.* rapid expansion of super critical solution in a liquid solvent (RESOLV) for the nanosizing of water insoluble drug particles. The drugs used for nanosizing were anti-inflammatory Ibuprofen and Naproxen for which CO2 and CO2–co solvent system were used due to its favorable processing characteristics' like its low critical temp (TC=31.1-C) and pressure (PC=73.8 bar). The RESOLVE process produced exclusively nanoscale (less than 100nm) Ibuprofen and Naproxen particles suspended in aqueous solution and the aqueous suspension of the drug nanoparticle are protected from agglomeration and precipitation by using common polymeric and oligomeric stabilizing agents although particles are obtained by the RESS recently nanometre particles production has been reported in most cases micrometre and sub micrometre sized[10].

**b) Nanopure® XP technology:** This is the registered trade name given by the company PharmaSol GmbH/Berlin. Similar effective particle size reduction can also be obtained in nonaqueous or water reduced media. The production of nanocrystals in non-homogenization media is a very effective method to obtain direct formulation. The nanocrystals of the drug dispersed in liquid polyethylene glycol (PEG) or various oils can be directly filled as drug suspensions into HPMC capsules or gelatin. Cavitation is the major force in particle size reduction. Against this theory, this technology was developed. Even in non-aqueous media, the particle size diminution can be achieved. Tablets, pellets and capsules must be formed. The advantages of this method are that the dispersion medium need not be removed. Evaporation is faster and under milder conditions (when water and water miscible liquids are used). This is useful for temperature sensitive drugs. For i.v. injections, isotonic nanosuspension is obtained by homogenizing in water-glycerol mixtures. Water reduction causes decrease in the energy required for the various steps carried out such as fluidized bed drying, spray drying or layering of suspension onto the sugar spheres. The IP owned by Pharmasol covers water mixtures and water

– free dispersion media (e.g. PEG, oils). When developing the second generation of drug nanocrystals Nanopure, just opposite was done as described in the literature. Suspensions of the drug in the non-aqueous media were homogenized. This process was done at 0˚C as well as below freezing point (e.g. -20˚C), along with performing it at room temperature. This was, hence, also called as the 'deep-freeze homogenization'. Against the literature findings, the result obtained that the particle disintegration was similarly effective in the nonaqueous media. Hence, the chances for further preparing the non-aqueous formulations to oral preparations has increased manifold. Also, the process of homogenization was performed below the freezing point of water. So this should be less effective as per the theory because the vapour pressure of liquid decreases with reduction in temperature, thus leading to even very less cavitation or no cavitation may also be there. The results obtained were compared with the results of homogenization in water [11]. Hence, chemically labile drugs can also be processed at very milder conditions. As the homogenization process is very fast, temperature peaks occur only for a few milliseconds. Till now, decomposition was observed during homogenization at room temperature of only one compound namely, azodicarbonamide (ADA). But when the same process was carried out using second generation technique and carrying the homogenization at 0˚C, the compound was found to be chemically stable and no foamy nanosuspension was formed here[10].

The NANOPURE® XP technology has the main features of scaling up and ability to produce on a large scale, with the application of mild and normal conditions. Pharmasol utilizes a pre-treatment step of subsequent homogenization, along with its NANOPURE® XP technology. This gives rise to particles below the size range of 100 nm. The final nanosuspension is translucent in appearance because the particle size is about 50 nm which is smaller than the wavelength of visible light[12].

**c) Spray Freezing into Liquid (SFL):** The University of Texas (Austin) was the first to develop and patent the SFL method in the year 2003. This technique was first commercialized by Dow Chemical Company (Midland, MI). Here in, the atomization of an aqueous, organic, aqueous organic co-

solvent solution, aqueous–organic emulsion or suspension containing drug occurs directly into either a compressed gas (i.e. CO2, propane, ethane or helium), or a cryogenic liquid (i.e. argon, nitrogen or hydrofluoroethers). These frozen particles are then lyophilized to obtain free flowing and dry micronized powders. The drying time for lyophilisation was decreased by acetonitrile and also it increased the drug loading. Better results were obtained, i.e. highly effective wettability and high surface area, enhanced dissolution rates were obtained from the SFL powder which contained the amorphous nanostructured aggregates. The micronized bulk danazol exhibited a slow dissolution rate; only 30% of the danazol dissolved in 2 minutes. Then 95% of the danazol was dissolved in only 2 minutes for the SFL highly potent powders. In a study, SFL danazol/PVP K-15 powders with high surface areas and high glass transition temperatures remained amorphous and exhibited rapid dissolution rates even after 6 months long storage[13].

**Characterization of Nanocrystals**

**1. Particle size analysis:** Size and size distribution of the crystals in dried form was determined following redispersion in water containing 0.1% polyvinyl alcohol (PVA&403) by dynamic light scattering through particle size analyser Nanotrac 150 (Japan) with a wet sampling system and the diameters reported were calculated using mean particle size distribution[14].

**2. Determination of drug content:** The drug content of freeze dried samples was checked by UV & spectrophotometer to confirm the purity of the prepared samples. For quantitative determination of drug content in formulations aqueous dispersions of formulations (25mg/10ml distilled water) were passed through 0.8 <m filter. The filtrates containing fine particles smaller than 0.8 <m were dissolved in 4% sodium lauryl sulphate solution and the concentration of drug was determined spectrophotometrically at a wavelength of 291 nm. The amount of drug in filtrate relative to the total amount of drug in the dispersion was calculated and expressed as nanocrystal yield.

**3. Scanning electron microscopy:** The surface morphology of the commercial drug powder and the freeze-dried formulation samples was examined by SEM. Before

examinations the samples were mounted on top of double sided sticky carbon tape on metal discs and coated with 80 nm gold/palladium in Blazers 120B sputtering device[15].

**4. Powder X-ray diffraction (PXRD):** The PXRD was carried out using Philips Analytical XRD B.V. at the scanning rate of 4 0 /min 2θ range of 10&70 0.

**5. Differential scanning calorimeter:** DSC, equipped with a liquid nitrogen cooling system was used to measure the thermal behaviour of the commercial griseofulvin powder and the freeze dried samples. In DSC analysis, 2&5 mg of sample was put in aluminium pan and examined at a scanning rate of 100 C/min from 25 to 300 $^0$C.

**6. Solubility:** Saturation solubility measurements were assayed through ultraviolet absorbance determination at 291 nm using an UV spectrophotometer. An excess amount of griseofulvin powder and formulations were added to 150 ml of 4% SLS solution the mixture were stirred in mechanical shaker for 24 hours at a temperature of 37+ .05 0 C using GLF 1086 shaker. Visual inspection was carefully made to ensure there was excess sample in solid state indicating that saturation had been reached. The mixtures were filtered using 0.2<m filter and filtrates were diluted suitable to determine the solubility of griseofulvin from each formulation.

**7. Dissolution test:** A dissolution test for commercially available griseofulvin and formulations was carried out by filling them in hard gelatine capsules (Zydus Cadilla, Goa, India). The prepared samples and the drug powder were filled in capsules (125mg) and subjected to dissolution studies with 900 ml 4% SLS solution as dissolution medium preheated and maintained at 37 + 0.5 0 C. The baskets were rotated at a speed of 75 rpm/min. 10ml samples were withdrawn at specified time intervals, filtered through 0.2<m filter, and the concentration of was determined by UV& spectrophotometer.

**8. Stability studies:** All the formulations were subjected to stability study as per ICH guidelines the formulations were divided into two parts and stored at 30 o ± 2 o C and 65% ± 5% RH and 40 o ± 2 o C and 70% ± 5% RH. The drug release and the drug content were estimated after specified intervals of time [16].

**Pharmaceutical application of drug nanocrystals in drug delivery:**

1. Parental administration
2. Per oral administration
3. Ophthalmic drug delivery
4. Pulmonary drug delivery
5. Target drug delivery
6. Dermal drug delivery

**1. Parenteral administration:** Drug nanocrystals in the form of nanosuspensions can be administered via Different parenteral administration route ranging from intra articular via. Intra-peritoneal to intravenous injection. Nanosuspension has been found to increase the efficacy of Parenteral administered drugs. Clofazimine nanosuspension, poorly water soluble anti leprosy drug, reveals an improvement in stability and efficacy over the liposomal clofazimine.[17]

**2. Per oral administration:** Nanosizing of drug leads to dramatic increase in their oral absorption and subsequent bioavailability. Aqueous nanosuspension can be used directly in liquid dosage form such as tablets and hard gelatine capsule with pellets[21].

**4. Pulmonary drug delivery:** Aqueous nanocrystals can be nebulizer using mechanical and ultrasonic nebulizers for lung delivery. The dispersion can be high concentration due to the presence of many small particles instead of a few micro particles; all aerosols droplets are contain drug nanocrystals. Budesonide, poorly water soluble corticosteroid, has been successfully prepared as nanosuspension is formulated by treatment of lungs infections by using nebulisation[20].

**5. Target drug delivery:** Nanocrystals can be used for target delivery. Targeting of cryptosporidium partum, the organism responsible for cryptosporidiosis was achieved by using surface modification mucoadhesive nanosuspension of bupravauone. Similarly, condition such as pulmonary aspergillosis can easily targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspension instead of using stealth liposome[23.]

**6. Dermal Drug Delivery:** Dermal nanosuspension are mainly of interest if conventional formulation approaches fail the use of drug nanocrystals leads to an

increased concentration gradient between the formulation and the skin. The increased saturation solubility leads to supersaturated formulations, enhancing the drug absorption through the skin [18]. This effect can further be enhanced by the use of positively charged polymers as stabilizers for the drug nanocrystals. The opposite charge leads to an increased affinity of the drug nanocrystals to the negatively charged stratum conium[19].

## CONCLUSION

Poor solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds and leads to employment of novel formulation technologies.

The use of drug nanocrystals is a universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. Almost any drug can be reduced in size to the nanometer range. Many insoluble drug candidates are in clinical trials formulated as drug. The striking advantages are that the drug nanocrystal can be applied to various administration routes. That means oral but also parenteral especially intravenous administration, other administration like dermal delivery to create super-saturated system with high thermodynamic activity. Ophthalmic administration to create systems with prolonged retention time, nasal administration to stick nanocrystal to the nasal mucosa, vaginal administration to create system evenly spreading throughout the therapeutic area and aerosol containing drug nanocrystal for pulmonary delivery based on their criteria. The drug nanocrystal technology is successful emerging technology.

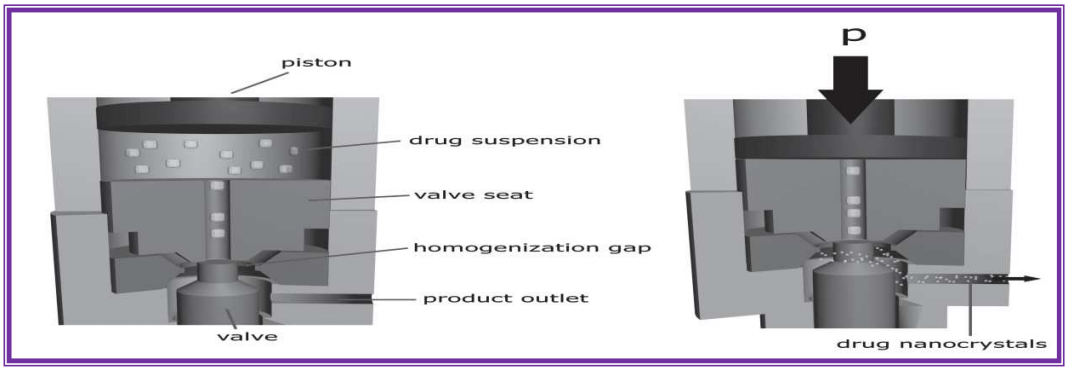

**Figure 1 Basic principle of high pressure homogenization using a piston gap homogenizer[6]**

**Table 1**

**FDA products on the pharmaceutical market approved nanocrystal[4].**

| Product | Drug | Indication | Year of FDA approval |
|---|---|---|---|
| Rapamune® | Sirolimus | Immunosuppressant | 2000 |
| Emend® | Aprepitant | Antiemetic | 2003 |
| Tricor® | Fenofibrate | Treatment of high cholesterol and high triglyceride levels | 2004 |
| Megace ES® | Megestrol Acetate | Palliative treatment of some breast and uterine cancers | 2005 |
| Triglide® | Fenofibrate | Treatment of high cholesterol and high triglyceride levels | 2009 |
| Invega Sustenna® | Paliperidone palmitate | Treatment of schizophrenia | 2009 |

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