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PHARMACEUTICAL PARTICLE SIZE REDUCTION TECHNIQUES: AN APPROACH TO IMPROVE DRUG SOLUBILITY, DISSOLUTION AND BIOAVAILABILITY

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ABSTRACT

Poorly soluble molecules have been successfully formulated by employing a variety of techniques to modify the physico-chemical and biopharmaceutical properties of drugs such as: (i) solubilization in surfactant solutions; (ii) use of co-solvents, salt formation, complexation with cyclodextrins, crystallization, amorphization, milling, etc. Among various techniques for solubility enhancement, physical modifications of drug products such as reducing the particle size and modifying crystal habit are common approaches to increase drug solubility. According to the Noyes-Whitney equation, the reduction of the particle sizes of drug crystals increases the specific surface area, which can improve the rate of dissolution of the drug. With a reproducible and controlled particle size of active pharmaceutical ingredients and excipients, manufacturing of finished dosage form could be improved. The present review deals with the different particle size reduction technologies commonly applied to produce micro or nanosized drug crystals in order to increase the dissolution rate and absorption, and hence the bioavailability of poorly-soluble materials and allowing to optimize the formulation of the product and reduce the therapeutic dose.

KEYWORDS: Particle size reduction, poorly soluble drugs, Solubility enhancement, Micronization, Nanosization.

INTRODUCTION

Drug solubility, dissolution and gastrointestinal permeability are fundamental parameters that control rate and extent of drug absorption and its bioavailability. Oral bioavailability of a

drug depends on aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and susceptibility to efflux mechanisms. Aqueous solubility and drug permeability are two important parameters attributed to oral bioavailability. In drug discovery, the number of insoluble drug candidates has increased in recent years. Almost 70% of new drug candidates are showing poor water solubility. Poorly water-soluble drug properties can impede the effective delivery of these drugs into humans, and affect their dissolution rate and subsequent absorption at the site of activity. For these drug candidates, poor aqueous solubility and poor dissolution in the GI fluids is a limiting factor to the in vivo bioavailability after oral administration. Many drugs exhibit poor solubility in water, and absorption rate in the gastrointestinal tract are very low because of its big size. In the pharmaceutical industry, many micronization techniques are used to improve dissolution rates of drugs into the biological environment. Apart from conventional micronizing techniques, particle technology now deals with various particle and nanoparticle engineering processes as promising methods of improving drug solubility.[1] This review discusses about the various particle technologies, from conventional size reduction methods to recent novel methods that can be used for improving the aqueous solubility hydrophobic drugs.

Particle size reduction

Particle size reduction technologies are routinely used to increase the bioavailability of poorly soluble drugs. When the particle size is decreased, the larger surface area of the drug allows the increase in the surface area to volume ratio thus increasing the surface area available for solvation. Many strategies like polymorphism, salt formation, co-crystal formation and addition of excipients also marginally increase the solubility of the insoluble drugs but their use is mainly limited due to low success rates for increasing bioavailability and in some cases, being undesirable due to production of toxic side effects. The conventional particle size reduction still remains a basic size reduction procedure but particle size reduction techniques now involve nanotechnology and nanosization, which are being widely studied for the formulation approaches to drugs with poor aqueous solubility.[1]

Methods for the preparation of micronized drug

Conventional size reduction of pharmaceuticals is accomplished by mechanical comminution such as crushing, grinding and milling of previously formed larger particles. The size reduction in these processes takes place by compression, friction, attrition, impact or shearing. Jet mills and ball mills are commonly used for mechanical micronization of drugs.

Fluid energy mill (jet mill) is the most preferred micronization technique. All of these methods of size reduction have been reported in various studies to have increased the dissolution and bioavailability of poorly aqueous soluble drugs by decreasing their size and increasing the surface area of the drugs.

1. Jet milling

A fluid jet mill uses the energy of the fluid (high pressure air) to achieve ultra fine grinding of pharmaceutical powders. Fluid energy milling has been successfully employed for the micronization of many drugs for the purpose of improving their dissolution and solubility characteristics. Some examples include ibuprofen, salbutamol sulfate and fenoterol hydrobromide.[5] Jinno et al. reported that the in vitro dissolution rate of a poorly soluble drug cilostazol was improved by milling and a moderate enhancement of bioavailability was observed in absorption from cilostazol suspension produced by jet milling. In another study, ibuprofen powders were micronized to the particle size range of 5-10 microns through the process of simultaneous micronization using continuous fluid energy milling, resulting in the improvement of dissolution rate.[1]

It was reported that fluid energy milling of a blend of fenofibrate, together with a mixture of hydrophilic excipients resulted in faster drug dissolution rates compared to a powder formulation of identical composition prepared by mixing pre-milled fenofibrate with the excipient mixture. In a study to improve the bioavailability, Vogt et al. found that co-grinding a mixture of EMD 57033, a poorly water-soluble calcium sensitizing agent with lactose and hydroxyl propyl methyl cellulose using a fluid energy mill was more effective than micronizing the drug alone or spray drying a nanosuspension of the drug.[5]

2. Ball milling

Ball milling is another popular size reduction technique used for the production of microparticles, especially in research laboratories. A pharmaceutical ball mill is usually a cylindrical crushing device that is used for grinding of pharmaceutical powders by rotation around a horizontal axis. The device is partially filled with the material to be ground and the grinding medium usually ceramic balls, flint pebbles or stainless steel balls.

The use of ball milling as a micronization technique for enhancing drug solubility is well supported by literature dating as far back as the 1970s. Apart from its comminution function, ball milling also serves as an intensive mixing technique capable of producing co-ground

drug-excipient mixtures comprising amorphous drug forms intimately mixed with suitable hydrophilic excipients at the molecular level. This interaction between the drug and hydrophilic excipient enhances the wetting and dissolution of the drug.[5]

In 1995, Liversidge and Cundy reported that ball milling could be used for preparing nanoparticulate formulation of a poorly water soluble drug, danazol, which showed enhanced bioavailability in beagle dogs when compared to that of aqueous suspension of conventional danazol particles. In 2006 Patterson et al. suggested ball milling technique is also essential in preparing amorphous powders of drugs if milled together with polymeric compounds. Preparing amorphous form is an essential approach to improve dissolution of drugs since the amorphous state are more readily soluble than the crystalline form.[1]

Studies showed that vibrational ball milling of griseofulvin and phenytoin in combination with microcrystalline cellulose resulted in amorphization of the drug, enhancing its dissolution and bioavailability. In a study it was reported that ball milling of ibuprofen and aluminium hydroxide facilitate complex formation and drug amorphization enhanced the dissolution of ibuprofen. It was reported that the co-milling of salbutamol sulfate with crystalline excipients (α-lactose monohydrate, adipic acid, magnesium stearate) in a ball mill was effective in reducing milling-induced amorphization or structural disorder of salbutamol sulfate. In another study it was reported that ball milling of a combination of two BCS Class II drugs, simvastatin and glipizide, resulted in the formation of stable co-amorphous mixtures.[5]

3. In-situ micronization

In-situ micronization is a novel particle engineering technique where micron sized crystals are obtained during its production itself without the need for any further particle size reduction. In contrast to other techniques where external processing conditions like mechanical force, temperature and pressure are required, the drug is obtained in micron size during the crystal formation. Hence this technique is described as in situ micronization. Solvent change method and pH shift method are to be used in in situ micronization technique. These methods are proved to be promising to enhance flow properties, dissolution rate and stability of poorly water soluble substances and to enhance flow properties of water-soluble drugs.[3]

Methods for the preparation of nanonized drugs

When the solubility of a drug is very low, down-sizing it to the micrometer range is insufficient to increase its dissolution rate and gastrointestinal absorption. In the last decade, significant advancements and evolutions in milling processes have enabled the production of submicron-sized or nanoparticles. This process may be termed as nanonization. Nanoparticles, sometimes termed as nanocrystals, are typically 200 -500 nm in size, and are particularly suited for the formulation of parenteral preparations. Nanoparticles possess significant advantages over microparticles in enhancing drug solubility. It was reported that orally-delivered nanoparticles displayed strong adhesive properties to the mucosal surfaces of the gastro-intestinal tract, arising from the increased van der Waals forces of attraction between the nanoparticles and the gut wall. This would further contribute to the increased absorption and bioavailability of drugs administered as nanoparticles.[5]

1. Nanoprecipitation

Nanoprecipitation is also called solvent displacement method. It involves precipitation of a preformed polymer from an organic solution and diffusion of organic solvent in aqueous medium in the presence or absence of a surfactant. In precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good. The solution with the drug is then injected into water, which acts as a bad solvent, at the time of injection; the water has to be stirred efficiently so that the substance will precipitate as Nano crystals. Nanocrystals can be removed from the solution by filtering and then dried in air. In Nanoprecipitation the polymer generally PLA, is used, this method is also called solvent displacement method. The solvent displacement technique allows the preparation of nanocapsules when a small volume of oil incorporated in organic phase.[4]

This technique was well adapted for the incorporation of cyclosporin A, because entrapment efficiencies as high as 98% were obtained. Highly loaded nanoparticulate systems based on amphiphilic h-cyclodextrins to facilitate the parenteral administration of the poorly soluble antifungal drugs Bifonazole and Clotrimazole were prepared according to the solvent displacement method.[7]

2. Supercritical fluid technology

Super-critical fluids can be defined as fluids that are in a state where their temperature and pressure are greater than their critical temperature and pressure causing them to possess properties vacillates between those of a liquid and a gas. Rapid expansion of supercritical

solutions (RESS) was developed for micronization of particles. In the RESS process, solutes are dissolved in a supercritical fluid, resulting in a solute-laden supercritical phase. By reduction of the pressure by an expansion device, fine particles with a narrow size distribution can be obtained. In this process, free-flowing small particles with a large surface area are produced with small amounts of organic solvents as by-products. The use of this process to form nanonized drug particles is a considerable example for the universality of the process. CO_2 is the most common gas used due to its low critical temperature and pressure (Tc = 31.1ºC and Pc = 73.8 bar respectively).[6]

Studies reported that Dexamethasone phosphate drug nanoparticles and griseofulvin nanoparticles were prepared by using this method**.** Griseofulvin (GF) is a pharmaceutical aid with a powerful antifungal action. The bioavailability of GF compared to the initial dose, is low. Moreover, its toxicity threshold is close to the actual therapeutic dosage. Therefore, it should be safer and better to use GF if it were possible to reduce the dose through an increase in its bioavailability. Bioavailability should be improved by a further comminution with regard to the particle size usually used. In a study, Chen Hongyan used CO_2 as supercritical solvent, but the solubility of GF in supercritical CO_2 was very low. In other study, the supercritical fluid was carbon dioxide with co solvent acetone. The co solvent acetone is to increase the solubility of GF in supercritical CO_2**.**[11]

3. High Pressure Homogenization

High pressure homogenization (HPH), is a widely used technique for preparing nanosuspensions of drugs with poor water solubility. Its use has been reported to improve the dissolution rate and bioavailability of several poorly water soluble drugs such as spironolactone, budesonide and omeprazole by effective size reduction to the nanosize range. HPH has also been known to overcome the drawbacks of conventional size reducing methods such as amorphization, polymorph transformation and metal contamination due to high mechanical energy associated with conventional milling processes. Due to this reason, HPH is particularly advantageous for comminution of drug particles. In HPH, the solid to be comminuted is first dispersed in a suitable fluid and then forced under pressure through a nanosized aperture valve of a high pressure homogenizer, which is essentially a bottleneck through which the suspension passes with a high velocity, and then suddenly experiences a sudden pressure drop, turbulent flow conditions and cavitation phenomena. Thus comminution of particles is achieved by collision of particles with each other, collision with

the homogenizer and by cavitation and the two factors that influence homogenization in this process are the pressure drop and the number of passes across the homogenizer. HPH is compatible for use in both aqueous as well as non-aqueous fluid media and attempts have been made to use different pressurized fluids like carbon dioxide and 1,1,1,2-tetrafluoroethane so that these fluids can undergo residue-free evaporation upon pressure release and the micronized products can be directly recovered in the form of a dry powder as suggested by Kluge et al. in their study.

HPH has also been widely used in formulating parenteral formulations of poorly water soluble drugs. This process is considered suitable for parenteral formulations since there is no risk of contamination from milling media and the high pressure environment is able to protect from microbial contamination by eliminating potential contaminants. It was successfully demonstrated by Muller and Peters in 1998 that HPH can be used to formulate nanosuspensions of poorly soluble drugs like prednisolone and carbamazepine that could be consid-ered acceptable for parenteral administration.

Hecq et al. have reported that HPH was successful in formulating nifedipine as nanoparticles, which showed enhanced dissolution as well as improved saturation solubility and have suggested HPH as a simple, adequate and easily scaled up technique that can have general applicability to many poorly water soluble drugs. This technique is thus useful in oral as well as parenteral drug formulations and is remarkably efficient in enhancing saturation solubility, dissolution as well as bioavailability of poorly soluble drugs.[1]

4. Wet Chemical Processes

Most of the solution based nanoparticles use surfactant or polymer as protective agents for defined control of the particle size and size distribution. Solutions of different ions are usually mixed in well-defined quantities and under controlled conditions of heating, temperature, and pressure to promote the formation of insoluble compounds, which precipitate out of solution. These precipitates are then collected through filtering and /or spray drying to produce a dry and fine powder. The advantages of the wet chemical processes are that a variety of compounds can be fabricated, including inorganic and organic compounds, and some metals, in fairly inexpensive equipment and significant quantities. Another important advantage of these processes is the ability to control particle size and to produce highly mono-disperse materials.[8]

5. Wet milling

Both fluid energy and ball milling techniques involve size reduction of drug particles in their dry state. The extent of size reduction achievable in these dry milling techniques is limited to a few micrometers. Drug nanoparticles are most commonly produced by wet milling. As the name suggests, wet milling involves size reduction of drug particles suspended in a liquid medium that may be aqueous or non-aqueous in nature. Wet milling is particularly suited for potent drugs and drugs which possess high residual moisture contents (>50% moisture) because dry milling may be problematic for drugs of this nature. In wet milling, a drug nanosuspension is produced as the end product although for improved product stability, patient convenience and the drive towards sustainable manufacturing processes.[5,10]

Media Milling

Media milling can be considered a modernized version of the ball mill. This technology, first developed by Liversidge and co-workers, is a classical wet milling technique where in a sufficiently concentrated dispersion of drug particles in an aqueous or non-aqueous liquid medium is subjected to a traditional ball milling operation**.** The liquid medium prevents adhesion and subsequent compaction of the milled drug particles on the wall of the vessel and/or the surfaces of the milling balls, which is a common occurrence when the drug is milled in its dry state. This improves the yield of nanoparticles.[5]

In this method the nanoparticles are produced using high-shear media mills or pearl mills. The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticle drug into nanoparticles. The milling medium is composed of glass, zirconium oxide, or highly cross-linked polystyrene resin. They are considered as nontoxic.[8]

Media milling has been employed for particle size reduction of loviride, ezetimibe, alpha-lipoic acid, ibuprofen, cinnarizine, naproxen, ketoconazole, phenytoin and candesartan cilexetil. The majority of these cited studies involve the conversion of the resultant drug nanosuspension into a suitable solid dosage form like dry powders and tablets. Less conventionally, stable nanoparticles of naproxen, fenofibrate and griseofulvin produced from wet-stirred media milling have also been incorporated into hydroxypropylmethyl cellulose polymer films. The dissolution rates of the drugs were improved by nanonization. Another interesting example is the incorporation of crystalline nanoparticles of indomethacin,

prepared by media milling, into coated mannitol microparticles using an aerosol flow reactor method. The nanostructured microparticles produced exhibited rapid dissolution properties.

The Ultra Apex Mill (Kotobuki Industries) is an example where centrifugal technology has been integrated into the design of the mill to effectively separate the milling media, which can range from 15 to 100 mm, from the milled product. This mill has been successfully employed for the production of nanoparticles of albendazole, danazol and omeprazole as well as probucol for the enhancement of their dissolution and absorption properties.[5]

6. Dry Co-Grinding

While media milling is a wet-grinding technique, nanonization can be achieved via dry milling techniques as well. Nanosuspensions in this case are prepared by dry grinding of poorly soluble drugs with soluble polymers and copolymers. Polymers and co-polymers like polyvinylpyrrolidone (PVP), sodium dodecylsulfate (SDS), polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives are used in dry co-grinding techniques for preparation of nanosuspensions.

The dry co-grinding process enables improvements in surface polarity and aids transformation from a crystalline to an amorphous form. This is important because amorphous forms of drug candidate is how better solubility than crystalline forms in aqueous phase. Drugs prepared using this method includes: Clarithromycin, Glibenclamide and Griseofulvin, Glisentide, Naproxen, Phenytoin, Nifedipine, Indomethacin, Pranlukast, Fenofibrate etc.[6]

7. 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 drying matter increases leading to fast drying. The dissolution rate and bioavailability of several drugs, including hydrocortisone, COX-2 Inhibitor were improved utilizing this method.[4]

8. Gas-Phase Synthesis

These include flame pyrolysis, laser ablation, and high temperature evaporation techniques. Flame pyrolysis has been used for many years in the fabrication of simple materials such as carbon black and fumed silica, and is being used in manufacturing many more compounds. In laser ablation, a solid target is irradiated and the ejected material forms nanoparticles in the surrounding liquid. Laser ablation is capable of making almost any nanomaterial since it utilizes a mix of physical erosion and evaporation. High temperature evaporation has been used successfully to make a wide range of materials. The heat source is very clean and controllable, which means that even highly refractory materials can be processed. The production of fullerences and carbon nanotubes is a specific subset of gas-phase synthesis techniques.[8]

9. Laser fragmentation

Laser fragmentation in liquids is increasingly popular techniques for the rapid and simple production of inorganic and organic nanoparticles. In laser fragmentation, a stirring suspension of microparticles is irradiated breaking them into nanoparticles. Previously, nanosecond (ns) or picoseconds (ps) laser fragmentation were used for the nanonization of organic materials such as phthalocyanines, quinadrone, buckminsterfullerene (C60), 3,4,9,10 perylenetetracarboxylicdianhydride and melamine cyanurate.

Alternatively, femtosecond (fs) laser technology has been shown to generate smaller sized organic particles than ns-laser, and offers the advantage of irradiating materials with less energy, thus limiting the possible alteration of the ablated drugs nanocrystals. All the above studies were, however, not intended for applications in drug delivery and reported very little information on the degradation and on the polymorphic transformation of the organic material upon laser fragmentation.

Recently, fs laser fragmentation was investigated for the nanonization of the anticancer agent paclitaxel. The method was found to be particularly well-suited for the treatment of small quantities of drug, therefore suggesting its application as a preclinical screening tool. When it is established that nanocrystal formulation is suitable and greater quantities of the lead compounds become available, than conventional techniques (such as media milling) may take the relay in the drug development process. Paclitaxel being a labile molecule and prone to polymorphic transformation in presence of water, the laser process was however accompanied by significant chemical degradation.[9]

10. Form-in-Place Processes

These include lithography, vacuum deposition processes such as physical vapor deposition, chemical vapour deposition, and spray coatings. Synthesis of carbon nanotubes by chemical vapor deposition over patterned catalyst arrays leads to nanotubes grown from specific sites on surfaces. The growth directions of the nanotubes can be controlled by van der Waals self-assembly forces and applied electric fields. Controlled synthesis of nanotubes opens up exciting opportunities for coupling single-walled carbon nanotubes with peptide nucleic acid enzymes and proteins. These processes are more geared to the production of nanostructured layers and coatings, and can be used to fabricate nanoparticles by scraping the deposits from the collector.

It is desirable that nanoparticles are stable as aqueous dispersions without having the need to make a lyophilized or spray-dried product. Lyophilization (also called hydrosols) can make products stable longer. Insufficient stability of suspensions can lead to crystal growth and/or particle aggregation. To avoid the growth of the nanoparticle, an appropriate surfactant such as Tween 80 and Phospholipon (0.6%), is needed to stop particle agglomeration. Utilizing electrostatic and steric stabilizers and coating the nanoparticles can prevent them from agglomeration and ensure pharmaceutical stability.[8]

11. Cryo-vaccum method or Cryogenic milling

In this method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution**.** The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 °C). Rapid cooling causes a very fast rise in the degree of saturation based on decrease of solubility and development of ice crystals when the temperature drops below 0°C. This leads to a fast nucleation of dissolved substance at the edges of ice crystals. The solvent must be completely frozen before the vessel is removed from liquid nitrogen. Next the solvent is removed by sublimation in a lyophilization chamber where the temperature is kept at constant - 22°C and pressure is lowered to 10-2 m.bar. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of particles produced, so as to remain crystalline. The method yields very pure nanocrystals and there is no need to use surfactants or harmful reagents.[4]

Salazar et al. studied media milling and high pressure homogenization of glibenclamide that was first pre-treated by freeze-drying. Freeze-drying rendered the drug brittle and porous, facilitating the subsequent milling process. This combination approach reduced milling time

and improved milling efficiency. In a study Sugimoto et al. performed the cryogenic co-milling of phenytoin and polyvinylpyrrolidone as a means to improve the dissolution rate of the drug. In another study, pluronic F-68, a soft and meltable material that may be used both as an excipient and active ingredient in inhalable dry powder formulations, was subjected to a micro-ball milling technique using stainless steel ball bearings as the grinding agent. Ball milling was carried out in the presence of liquid nitrogen vapor. Apart from chilling the chamber, the liquid nitrogen also prevented plastic deformation of the material and improved the particle fracture process. Jayasankar et al, in a study on co-crystal formation between carbamazepine and saccharin, reported that cogrinding the drug and excipient under cryogenic conditions was necessary to prevent the reaction from proceeding through the melt phase which commonly occurs when cogrinding is carried out at ambient conditions.

Cryogenic cogrinding also led to higher levels of amorphization than cogrinding at room temperature. These results are echoed in another study involving the ball milling of different crystalline forms of piroxicam. Differing extents of drug amorphization was achieved by ball milling the drug under different temperature conditions (ambient and cryogenic conditions), with cryogenic ball milling being more effective in inducing drug amorphization. This is because milling at cryogenic temperatures effectively 'traps' the milled material in its amorphous state by removing the thermal energy required for re-crystallization to occur. In this regard, cryogenic milling is advantageous as it enables the production of amorphous material without the deleterious effects of solvents or heating.

Crowley and Zografi studied the cryogenic grinding of 5 crystal forms of indomethacin and found that amorphization occurred for one of the solvates (indomethacin methanolate) and all the three polymorphs (ϒ, α and δ) studied. Recently,ϒ -indomethacin was subjected to cryomilling and it was reported that the amorphous indomethacin produced exhibited enhanced dissolution rates which was positively related to the duration of cryomilling.

Cryogenic grinding was successfully used to convert crystalline glibenclamide to its amorphous form, averting possible chemical degradation during the process. The crystalline-amorphous conversion was shown to be connected with the amide-imidic acid tautomerism of glibenclamide. Chieng and co-workers investigated the effect of cryomilling on 2 polymorphic forms of ranitidine hydrochloride and evaluated the physical stability of the milled amorphous drug under different storage conditions. High impact cryomilling thus enables the production of completely amorphous drugs that may otherwise be difficult to

obtain by milling at room temperature. However, drug amorphization may not always be advantageous from a stability point of view. In a recent study on the cryomilling of furosemide, it was reported that the duration of cryomilling and resultant drug amorphization were factors responsible for the chemical decomposition of the drug . Drug amorphization may not occur in all cases. In a study by Niwa et al., the nanocrystals of phenytoin, ibuprofen and salbutamol sulfate produced from an optimized cryomilling process retained their crystalline character. This was explained by the mild processing conditions that prevailed during cryomilling. Feng et al. reported that cryogenic milling of griseofulvin led to a reduction in drug crystallinity due to the increase of crystal defects, rather than the formation of amorphous drug. A body of research on the use of cryomilling to process molecular materials, including model pharmaceutical compounds, has been carried out by Willart and Descamps.

Cryomilling minimizes the degradation of thermolabile drug substances and loss of volatile drug compounds. It also reduces the risk of explosion, oxidation of formulation constituents and particle aggregation during the milling. Cryomilling decreases the effect of temperature-induced changes during milling.[5]

CONCLUSION

Poor aqueous solubility of a drug entity can be addressed with various pharmaceutical particle size reduction technologies. The conventional methods of size reduction involve mechanical micronization techniques that are simple and convenient methods to reduce the drug particle size and increase the surface area and thus enhance the solubility and dissolution of poorly soluble drugs. The conventional particle technologies are limited for some drugs due to their low efficiency, sometimes leading to thermal and chemical degradation of drugs, and resulting in non-uniform sized particles. Down-sizing poorly soluble drugs to the micrometer range is insufficient to increase its dissolution rate and gastrointestinal absorption. Significant advancements and evolutions in milling processes have enabled the production of submicron-sized or nanoparticles. Nanoparticles possess significant advantages over microparticles in enhancing drug solubility. The novel methods are developed from conventional methods where the basic principle remains the size reduction for solubility improvement. Each particle technology has its own importance and applicability in enhancing water solubility of poorly aqueous soluble drugs. An appropriate method can be selected by considering the properties of drug to be formulated and the properties of desired dosage form.

Other possible methods are yet to be explored in the field of pharmaceutical particle technology that can be used to formulate various drugs with poor aqueous solubility.

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