A REVIEW ON MECHANICAL MICRONIZATION: A TOOL FOR INCREASING SOLUBILITY

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Abstract : Micronization is a conventional technique for the particle size reduction and is a commonly used method for increasing solubility of BCS class II drugs Particle technology in pharmaceutics is a technique to modify physicochemical, micrometrics and biopharmaceutical properties of the poorly soluble drugs, thereby improving their solubility. 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 Apart from conventional micronizing techniques, particle technology now deals with various particle and nanoparticle engineering processes as promising methods of improving drug solubility. This review focuses primarily on various particle technologies, from conventional size reduction methods torecent novel methods that can be used for formulating drugs with poor aqueous solubility .

Keywords - Particle Size Reduction, Increasing Solubility, Mechanical Micronization

Introduction

Micronization is a term used to describe size reduction where the resulting particle size is less than 10 microns. Micronization size reduction involves acceleration of particles so that grinding occurs by particle-to-particle impact or impact against a solid surface.It is a simple technique that refers to transfer of coarse drug powder to an ultrafine powder with the mean particle size in the range of 2-5 mm and only a very little fraction of the particles lie below 1 mm size range [2]. Micronization does not increase the equilibrium solubilityof the drug itself but it increases the dissolution rate by increasing the surface area to drug ratio by which the active ingredient can dissolve or diffuse from the drug particles. 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 pressure, friction, attrition, impact or shearing. Jet mills, ball mills and high-pressure homogenization are commonly used for mechanical micronization of drugs and dry milling in a fluid energy mill (jet mill) is the most preferred micronization technique [3]. 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.

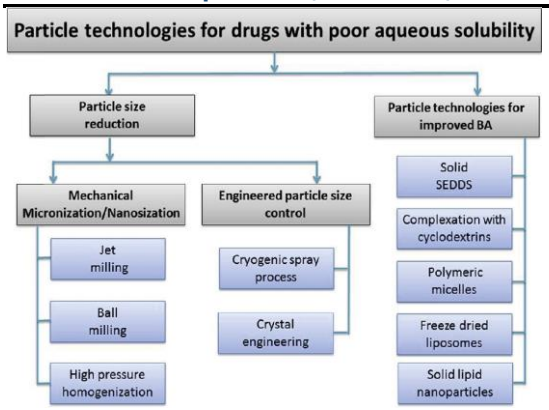


Fig. 1-Pharmaceutical particle technologies for improved solubility, dissolution, and bioavailability of drugs

Advantages

- The micronization is used to increased surface area for dissolution
- Micronization increases the dissolution rate of drugs through increased surface area.

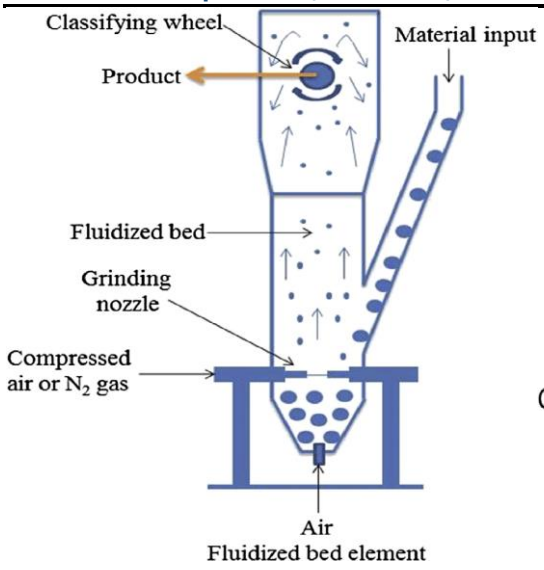
Disadvantages

- It does not increase equilibrium solubility
- Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [15].

Particle technology	Method	Example drugs
Mechanical micronization	Jet milling	Cilostazol, Ibuprofen
	Ball milling	Danazol,carbamazepine, dipyridamole, indomethacin
	HPH	Prednisolone,carbamazepine, nifedipine

Jet milling

A fluid jet mill uses the energy of the fluid (high pressure air) to achieve ultra fine grinding of pharmaceutical powders (Fig. 2).



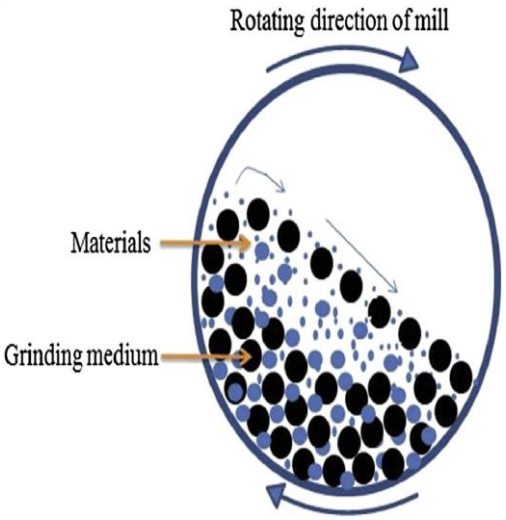


Fig. 2-Schematic diagram of a pharmaceutical jet mill. Fig. 3-Schematic diagram of a ball mill.

It has several advantages of being a dry process, size reduction of micron-sized particles with narrow size distributions, absence of contamination and is suitable for heat sensitive drugs [4]. In a study conducted by Jinno et al., 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 [5]. However in the same study, remarkably higher enhancements in bioavailability were observed for a nano crystal suspension of cilostazol, suggesting that reduction of drug particle size to the nanometer- size range is more effective in enhancing the bioavailability of drugs with poor aqueous solubility. In another study, a BCS class II drug, ibuprofen was also subjected to simultaneous micronization through continuous fluid energy milling, resulting in the improvement of dissolution rate while avoiding disadvantages of conventional micronization such as agglomeration, poor flowability, loss of expected large surface area, low bulk density and insignificant or no dissolution improvement [6]. In this process, ibuprofen powders were micronized to the particle size range of 5-10 mm through the process of simultaneous micronization. The increase in dissolution behavior is attributed to the increased particle surface area, as per the Noyese Whitney equation.

Fluid-energy impact milling & micronization techniques:

1. Spiral jet mill micronization

The spiral jet mill is suitable for the fine and ultra fine size reduction of materials up to a Moh's hardness of 3 that display brittle crystalline grinding characteristics. They are typically used in applications where a ultrafine portion is required. The spiral jet mill is simple in design, consisting of a flat cylindrical grinding chamber with several nozzles arranged tangentially in the peripheral wall, a pneumatic feed injector, and a feed funnel. Operation is just as simple. The feed is accelerated into the grinding chamber through the feed injector. The material inside the grinding chamber is subjected to two opposing force :the free vortex created by centrifugal force(mass force)imparted on the particle by the nozzles, and the drag force created by the airflow as it spirals toward the center of the mill. The larger particles are affected to a greater degree by the mass force, circulating around the periphery of the mill and colliding with other particles. As the particles become finer, the drag force exerts greater effects, drawing the particles with the airstream to the

central outlet of the mill. Feed particle size is critical, restricted by the size of the feed injector, for mills of 200-300, the feed size can be a maximum of 1.5mm, the smaller –size mills, the feed size is correspondingly finer. There are several factors, both operational and physical, which affect the fineness of the end product, such as feed rate, nozzle pressure, nozzle angle, air flow rate, feed particle size, chamber diameter and width, and product outlet diameter. All of these variables can be adjusted during operation, but it is more likely that once operation has begun, only feed rate will be varied to meet the required particle size distribution. The size range of spiral jet mills employed in size reduction of pharmaceutical poders includes units from 50mm to 500mm, but most are in the 100mm and 200mm size range.Table 1 shows some typical mill sizes with their relative fineness and throught ranges.

There are several manufacturer of spiral jet mills which meet the general design and performance criteria outlined above. There may be slight differences in design, manufacturing methods, and product collection requirements. There are two types of spiral jet mill designs, with single or dual product collection points. A jet mill system with a single product collection point is easier to clean and sterilize, is more compact, and does not split product into two fractions. It is also easier to design in 10 BAR PSR constructions. Spiral jet mills are effective tools for micronization, especially in the pharmaceutical industry, but they have several limitations. First, as mentioned above, is the limitation in feed size due to the method of product injection. Oversized feed particle can cause blockage in the feed hopper and result in variations in particle size distribution caused by fluctuating feed rates. This can be controlled by presizing the feed, using a properly designed feed system, and applying vibration to dislodge buildup in the feed chute. There is also possibility of buildup and scaling in the mill due to the impact which occurs on the mill walls, this is especially problem with sticky substances such as steroids. But perhaps the most serious drawback is the lack of control of particle size distribution, especially top size limitations. These limitations led to the development of fluidized-bed jet mill.[15]

2. Fluidised-bed jet mill micronization

The fluidized-bed jet mill is suitable for the fine and ultrafine size reduction of any material up to a Moh's hardness of 10 that can be fluidized by the expanded compressed gas in the grinding chamber. They are typically used in applications where a fine to ultrafine micronization is required, and they are not limited for feed size, heat sensitivity of material, or abrasive characteristics. They are characterized by decreased energy consumption, reduced wear and buildup grinding chamber, steeper particle size distribution, and low noise emission. The fluidized-bed jet mill actually consists of two distinct segments and thus processes. The lower grinding section comprises the actual grinding chamber with several nozzles arranged radially in the chamber wall and gravity feed inlet.

The upper classifier section is a centrifugal forced vortex air classifier which is responsible for particle-size control. The two processes together to give the fluidized-bed jet mill its characteristics steep particle-size distribution and sharp top size control. Operation of the fluidized-bed jet mill is quit simple. Feed material is introduced to the grinding chamber through a large cavity feed inlet. During normal operation, there is fluidized bed of material inside the grinding chamber .Material is entrained by the high velocity gas streams created by the nozzles, and size reduction occurs as a result of particle-to-particle collision in the gas stream

and at the local point of the nozzles. The expanded gas conveys ground particles upward towards the centrifugal air classifier. The classifier allows material of a given fineness to exit the mill while rejecting oversized particles back into the grinding chamber for additional size reduction. Equilibrium is established with an internal recirculation: the introduction of fresh feed material and constant discharge of ground material from the mill. The key to maintaining a consistent particle-size distribution is the integral air classifier. Air classification is defined as the separation of the bulk material according to the settling velocity in a gas. As in the spiral jet mill, the same two opposing force –mass force and drag force-are acting on the particles. Mass force is the force exerted on the particle by acceleration due to gravity, inertia, or centrifugal force. Drag force is the force exerted on a particle by the surrounding medium as affected by its aerodynamic properties. In the centrifugal air classifier the mass force is exerted by the peripheral velocity of the classifier wheel. The drag force is exerted on the particle by the carrying fluid, which in the case of a jet mill is the expanded grinding gas. The particle size at which the mass force and drag force act equally on the particle is defined as the cut point. As in the spiral jet mil, the mass force

exerts a greater influence on the particles which are coarser than the cut size, and they are returned to the grinding zone of the jet mill. The drag force acts upon the particles which are finer than the cut size, and carried through the classifier wheel and recovered as product.

Most of the limitations inherent in the spiral jet mill do not exist in the fluidized-bed jet mill. There is no real limitation on feed size as the gravity feed inlet varies in size from two to six inches. The problem of the material buildup and scaling in the mill is also virtually nonexistent. Material does not circulate or impact against the mill walls; in fact, the vertical velocity of air and product in the chamber is only about 1.5 meters per second. The most improvement in the fluidized-bed jet mill process is the ability to control the particle-distribution of the product. The upper particle size of the product is strictly controlled by adjustment of the integral air classifier .By increasing the rotational velocity of the classifier wheel, a greater mass force is exerted on the particles, and smaller particles will be rejected and returned to the grinding zone. The end result is a finer particle size distribution. Conversely, decreasing the classifier speed will allow larger particles to pass through the classifier wheel, the end result being a coarser particle size distribution. Airflow also has an effect. A higher airflow through the classifier wheel result in an increased drag force and a coarser particle-size distribution. With this degree of control, a fluidized-bed jet mill is able to produce an infinitely adjustable particle-size distribution.

Because of the integrated classifier, spatter grain particle are virtually eliminated from the finished product. Control of the upper particle size also reduces the possibility of overgrinding the product in order to ensure a top size. The first graph, comparing the resulting particle-size distribution from a fluidized-bed jet mill to that from a spiral jet mill clearly shows a more precise cut point and a reduction in the ultrafine fraction.

Ball milling

A pharmaceutical ball mill is usually a cylindrical crushing device that is used for grinding of pharmaceutical powders byrotation around a horizontal axis. The device is partially filled with the material to be ground plus the grinding mediumusually ceramic balls, flint pebbles or stainless steel balls (Fig. 3). Back 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 [7].Ball milling technique for size reduction is also essential in preparing amorphous powders of drugs if milled together with polymeric compounds as suggested by Patterson et al. in 2006. Preparing amorphous form is an essential approach to improve dissolution of drugs since the amorphous state are more readily soluble than the crystalline form because of higher Gibbs free energy in the amorphous form [8]. In their work, Patterson et al. used three poorly water soluble drugs (carbamazepine, dipyridamole and indomethacin) with a polymer polyvinyl pyrrolidone K30 (PVP K30) at a 1:2 drug polymer ratio to prepare glass solutions of the drugs. The glass solution was referred to an amorphous solid in which the solute (drug) was dispersed in the solid solvent (polymer) on a molecular level [9]. Use of a ball mill to prepare the glass solutions was found to be effective in producing a single homogenous amorphous phase, and the dissolution rates were also found to be higher when compared to the glass solutions of the same drugs prepared by spray drying. This suggests the applicability of ball milling technique to produce homogenous amorphous preparations of poorly soluble drugs, and can be an important approach to improve the solubility of such drugs.

High pressure homogenization

High pressure homogenization (HPH), a top down technology, 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 [10]. 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 [11]. 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 (Fig. 3).

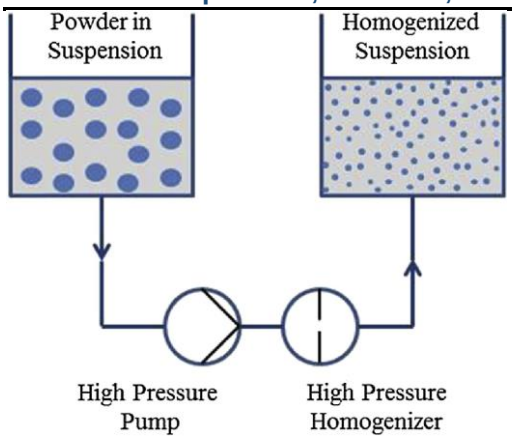


Fig. 4 e Scheme of high pressure homogenization process [11].

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[10,11,12]. 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 residuefree 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 [11]. Together with their applicability in oral dosage forms, 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 [12]. 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 considered acceptable for parenteral administration [13]. 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 [14]. 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.

Drugs used in Mechanical Micronization:

1. **Cilostazol[16]:**

   In a study conducted by Jinno et al., 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. However in the same study, remarkably higher enhancements in bioavailability were observed for a nano crystal suspension of cilostazol, suggesting that reduction of drug particle size to the nanometer- size range is more effective in enhancing the bioavailability of drugs with poor aqueous solubility.

2. **Ibuprofen[17]:**

In another study, a BCS class II drug, ibuprofen was also subjected to simultaneous micronization through continuous fluid energy milling, resulting in the improvement of dissolution rate while avoiding disadvantages of conventional micronization such as agglomeration, poor flowability, loss of expected large surface area, low bulk density and insignificant or no dissolution improvement.

3. **Danazol[18]:**

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.

4. **Spironolactone, Budesonide and Omeprazole:**

High pressure homogenization 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.

5. **Prednisolone and Carbamazepine:**

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 considered acceptable for parenteral administration.

6. **Nifedipine**

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.

7. **Fenofibrate:**

Several techniques were compared for improving the dissolution of fenofibrate, a poorly soluble drug. Particle size reduction was realized by jet milling (micronization; cogrinding with lactose, polyvinylpyrrolidone or sodium lauryl sulphate) and by media milling using a bead mill (nanosizing) with subsequent spray-drying. Solid state characterization by X-ray diffraction and Differential Scanning Calorimetry verified the maintenance of the crystalline state of the drug after dry milling and its conversion to the amorphous state during spray-drying. Micronization of fenofibrate enhanced its dissolution rate in biorelevant media (8.2% in 30 min) compared to crude material (1.3% in 30 min). Coground mixtures of the drug increased the dissolution rate further (up to 20% in 30 min). Supersaturated solutions were generated by nanosizing combined with spray-drying, this process converted fenofibrate to the amorphous state. Fenofibrate drug products commercially available on the German and French markets dissolved similarly to crude or micronized fenofibrate, but significantly slower than the coground or spray-dried fenofibrate mixtures. The results suggest

that cogrinding and spray-drying are powerful techniques for the preparation of rapidly dissolving formulations of fenofibrate, and could potentially lead to improvements in thebioavailability of oral fenofibrate products.

8. **Levonorgestrel[19]:**

Levonorgestrel is a synthetic progestogen. In this study Levonorgestrel Tablet 1.5 mg is being developed for prevention of pregnancy, following unprotected intercourse or a known or suspected contraceptive failure. Micronization is a process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by use of attrition methods (Fluid energy or Air Jet Mill). Micronization is a technique for improving the dissolution of poorly soluble drugs. Particle size reduction was realized by Air JetMilling. Micronization of Micronization of Levonorgestrel enhanced its dissolution rate in 0.1N HCl with 0.1% Sodium lauryl sulphate compared to nonmicronized material. Levonorgestrel drug products commercially available in USA, German and French markets dissolved similarly to micronized Levonorgestrel, but significantly higher than the nonmicronized Levonorgestrel. The results suggest that micronization technique for the preparation of rapidly dissolving formulations of Levonorgestrel, and could potentially lead to improvement in the bioavailability of oral Levonorgestrel product.

9. **Efavirenz:**

AIDS constitutes one of the most serious infectious diseases, representing a major public health priority. Efavirenz (EFV), one of the most widely used drugs for this pathology, belongs to the Class II of the Biopharmaceutics Classification System for drugs with very poor water solubility. To improve EFV's dissolution profile, changes can be made to the physical properties of the drug that do not lead to any accompanying molecular modifications. Therefore, the study objective was to develop and characterize systems with efavirenz able to improve its dissolution, which were co-processed with sodium lauryl sulfate (SLS) and polyvinylpyrrolidone (PVP). The technique used was co-micronization. Three different drug:excipient ratios were tested for each of the two carriers. The drug dispersion dissolution results showed significant improvement for all the co-processed samples in comparison to non-processed material and corresponding physical mixtures. The dissolution profiles obtained for dispersion with co-micronized SLS samples proved superior to those of co-micronized PVP, with the proportion (1:0.25) proving the optimal mixture. The improvements may be explained by the hypothesis that formation of a hydrophilic layer on the surface of the micronized drug increases the wettability of the system formed, corroborated by characterization results indicating no loss of crystallinity and an absence of interaction at the molecular level.

10. Norethindrone[20]:

Norethindrone (or norethisterone) is a molecule used in some combined oral contraceptive pills and in some progestogen only pills. In this study, Norethindrone Oral Tablet 0.35 mg is being developed for use in therapy of premenstrual syndrome, painful periods, abnormal heavy bleeding, irregular periods, or to postpone a period. Micronization is a process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by use of attrition methods (e.g. Fluid energy or Air Jet Mill). Micronization technique is a economic and effective technique for improving the dissolution of Norethindrone, a poorly soluble drug. Particle size reduction was achieved by Air Jet Milling. Micronization of Norethindrone enhanced its dissolution rate to a significant extent when compared with unmicronized material. Norethindrone Oral Tablets commercially available in Indian market dissolved similarly to tablets prepared with unmicronized Norethindrone, while those prepared with micronized Norethindrone showed higher dissolution rate. The experimental findings suggest that micronization technique can be used for the preparation of rapidly dissolving formulations of Norethindrone, and could potentially lead to improvement in the *in-vivo* bioavailability of oral Norethindrone Tablets.

11. Naproxen

Nanoparticles of Naproxen was obtained by using planetary mill.

12. Griseofulvin

Nanoparticles of Griseofulvin was obtained by wet stirred media mill technique.

13. Paclitaxel (Intraperitoneal)

Nanoparticles of Paclitaxel was obtained by using roller mill.

14. Indomethcin

Nanoparticles of Indomethcin was obtained by using planetary ball mill.

15. Phenytoin

Nanoparticles of Phenytoin was obtained by using oscillating beads milling apparatus.

16. Itraconazole, Azodicarbonamide, Sulphamethoxazole[21]:

Microparticles of Itraconazole, Azodicarbonamide, Sulphamethoxazole was obtained by using wet milling machine.

17. Miconazole

Nanoparticles of Miconazole was obtained by media mill technique for obtaining nanoparticles

18. Telmisartan

Nanoparticles of Telmisartan was obtained by High Pressure Homogenisation Technique for obtaining nanoparticles

19. Nitrendipine

Nanoparticles of Nitrendipine was obtained by High Pressure Homogenisation Technique.

20. Ketoprofen[22]

Microparticles of Ketoprofen was obtained by High pressure piston pump.

21. Quercetin

Nanoparticles of Quercetin was obtained by High Pressure Homogenisation Technique.

22. Curcumin

Nanoparticles of Curcumin was obtained by High Pressure Homogenisation Technique.

23. Itraconazole

Nanoparticles of Itraconazole was obtained by High Pressure Homogenisation Technique.

24. Emodin

Nanoparticles of Emodin was obtained by High Pressure Homogenisation Technique.

25. Beclomethasone Dipropionate

Nanoparticles of Beclomethasone Dipropionate was obtained by High Pressure Homogenisation Technique.

26. Baicalien

Nanoparticles of Baicalien was obtained by High Pressure Homogenisation Technique.

27. Atorvastatin

28. Pranlukast

29. Quercetin

30. Astaxanthin

31. Flurbiprofen

32. Puerarin

33. Lutein

34. Alkylpolyglycoside C8-10

35. Glibenclamide

36. Itraconazole

Excipients Used in Mechanical Micronization:

- Polyvinyl pyrrolidone (PVP)
- Polyvinyl acetate (PVA)
- Sodium lauryl sulphate (SLS)
- Caboxy methyl cellulose (CMC)
- Hydroxy propyl methyl cellulose (HPMC)
- Hydroxy propyl cellulose (HPC)
- Poly ethylene glycol (PEG)
- Sodium alginate
- Sodium docusate
- Poloxamer
- Tocopheryl Polyethylene Glycol Succinate (TPGS)
- Sodium deoxycholate
- Polymethyl-methacrylate (PMMA)
- Tween 80
- Gelatin
- Chitosan

Applications of Mechanical Micronization

1. Bioavailability Improvement
2. Solubility Enhancement
3. Dissolution Enhancement
4. Improvment of formulation Homogeneity and controlled particle size distribution
5. A wide range of drug types, including solid dosage, injectable, ocular, and inhaled products, can benefit from mechanical micronization

Conclusion

The detailed procedure and information has been collected in above review .As we know Micronization is a conventional technique for the particle size reduction and is a commonly used method for increasing solubility of BCS class II drugs . This review contains types of micronization , advantages , excipients Used in Mechanical Micronization , Drugs used in Mechanical Micronization, Applications of Mechanical Micronization .This compilation of knowledge will help the researcher,student, and reader .

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