TECNOLOGIA MECCANICA micronizers

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Benefits from the high-tech micronization process

for J series micronization lines

Many decades of experience in the field of plant construction added to our know-how in the field of the powder micronization and related apparatus make us the right partner in the supply of integrated and up to date solutions.

Individual solutions for plants are our daily job.

We engineer systems in our workshop and provide consulting on location. High technical knowledge and competence of our team – comprising experienced engineers, technicians, fitters, and commissioning personnel form the basis of successful cooperation.

Our engineering team has prepared in the following pages an overview of the most important daily themes, such as, the growing importance of bioavailability and bioequivalence, the new forms and means of drug administration, the increasing pressure of health authorities concerning drug activity and safety, the working of highly potent active pharmaceutical ingredients, the R&D products with unknown effects, the protection of the product from external contaminants.

For presentation of the newest technology, the complete range of our products and engineering performances and last but not least to go in more detailed discussion concerning the project and in particular your requirements, we would be pleased to get the possibility to introduce ourselves in our workshop.

Please do not hesitate to contact us, if you have any further questions or you need more information.

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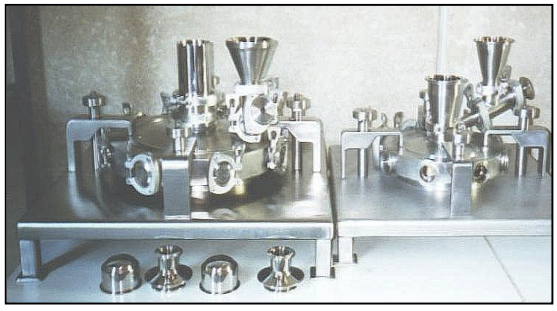

1.0 Purpose and scope

This technical paper has been issued with the purpose of clearing up some of the confusion which surrounds the micronization world. In fact often we find a lot of misunderstanding and mistakes around the micronization process in our daily job with new or prospective customers.

This situation has to be laid to the fact that the application of this technology to pharmaceutical process is extremely new and different from the past micronization of chemicals powder bulks. The common mistake is to confuse a chemical micronizer with a pharmaceutical one, these two equipments are completely different because the processes, that they will carry out, are completely different, so the process work of a chemical micronizer isn't suitable for a pharmaceutical product or where extremely fine and narrow particle size distribution are required.

For this reason we tried in the section number 2.0 of this document to outline the main principles which distinguish a high-tech pharmaceutical jet mill (the name with which are commonly known the pharmaceutical micronizers).

Afterwards, in the 3.0 section, we deal with the main pharmaceutical drugs requirements that makes the micronization process the right and the only solution, these new frontiers are the basic principles which push the jet mill technology to continue renewal and development.

Last, again we recommend not to confuse a chemical micronizer with a pharmaceutical one, we have experimented that all your process problems comes from the use of a chemical micronizer mirror polished used in a pharma environment, a pharmaceutical micronizer isn't a chemical micronizer with mirror polishing, it is really another kind of technology, extremely sophisticated and with working in progress day by day.

2.0 The operating principle of Jetmill

[Introduction]

MICRONIZERS or jet mills that were designed in the early 60's were huge in size. The Production models of today say, of 200mm chamber was considered a lab version then.

These old MICRONIZERS were capable of achieving sizes up to around 20 microns with extremely wide particle size distribution Gauss curve.

When the pharmaceutical industries started putting attention on 'increased active surface area' for the pharmaceutical actives, it became necessary to improve the performance of jet mills which necessarily involved re-defining the internal geometry to achieve a perfect spiral that will induce more collisions

[Areas that were re-defined]

- The chamber design
- Pressures for process gas
- Product feed
- Product collection to suit pharma execution
- Different material of construction to satisfy market requirements
- CIP/SIP systems to be provided if necessary
- Possibility to include explosion proof options
- Total automation of the control system

Our spiral jet milling uses process GAS to induce collisions. Thus our Jet Milling Technique can be called as “GAS JET MILLING”

[Gas jet milling technology]

Powder has to be feed into a flat cylindrical working chamber, it is injected through a venturi system in tangential pressurized air or nitrogen vector. Particles are boosted up inside the working chamber by a number of nozzles set in the periphery of milling chamber.
In this way the collision of the particles generates smaller size particles and the centrifugal force inside the mill combined with the different particles sizes makes the classification of the product into the required granulometry.

[Our micronization technology]

Our spiral fluid jet MICRONIZER comprises of a flat cylindrical grinding chamber, an injector and connections for a product feed chute and an air injector. The air injector accelerates the product through the main injector nozzle and into the cylindrical grinding chamber.
Once inside the grinding chamber the particles are then subjected to a combination of forces. The free vortex created by the nozzle angle and the jet stream exerts a centrifugal force on the particles and the gas flow through the MICRONIZER creates an opposing drag force. Larger particles of greater mass are forced towards the outside of the grinding chamber, whilst the finer particles migrate towards the outlet port and eventually into the product collector. It is the particle to particle collisions created within the MICRONIZER that cause the majority of the size reduction.

Several factors affect the fineness of the product discharging from a Spiral Jet Mill. These are:

- Product throughput
- Nozzle pressure
- Nozzle size
- Nozzle angle
- Air Flow
- Feed Particle Size
- Chamber diameter and width
- Product outlet diameter

Although there is potential for adjustment of all of these variables it is more usual, once the main parameters have been set to use the feed rate to achieve the required end product fineness.

[Comparative advantages of our jet mill]

MOST JET MILLS USE A DYNAMIC CLASSIFIER IN THEIR JET MILLS

As you are aware, the very reasoning of jet milling next to the MICRONIZATION needs was to minimize material to metal contact.

A DYNAMIC CLASSIFIER HAS THE NEED TO HAVE CONTACT WITH THE MATERIAL BEFORE CLASSIFYING. FURTHER VERY FINE LINES IN CUTTING ON PARTICLE SIZE IS NOT POSSIBLE.

THUS THERE IS A NEED OF BETTER TECHNOLOGY HERE. WE BETTERED THIS CLASSIFICATION TECHNOLOGY BY RESORTING TO USE A STATIC CLASSIFIER COMBINED WITH A MILLING CHAMBER BASED ON A STATISTICAL MATRIX MODEL. A STATIC CLASSIFIER DOES ADDRESS THE MATERIAL CONTACT BY LARGELY MINIMIZING IT.

BUT THE QUESTION OF FINE CUTTING WAS YET TO BE ADDRESSED. WE WILL SEE HOW WE HAVE ADDRESSED THIS PROBLEM.

[Placement of static classifier]

To decide on fine cutting and also minimizing material to metal contact the classifier must not be a wheel. For it will have too many fins and this will increase material to metal contact. Hence the static classifier is of a special geometry and is placed in the center of the jet mill chamber.

[Principle of operation]

The drag forces generated in the spiral jet mill move the particles towards the center exit.

The static classifier by virtue of its positioning classifies the material to exit based on the energy carried by the particles.

[Theory of operation]

You will agree that the Jet Milling chamber is the energizing area in the jet mill. Also it is a Hermetically closed chamber as well.

The energy gain to all particles in the chamber is equal being a closed chamber. But by virtue of collisions generated, every particle in the energizing chamber has a different size.

Now it is well known theory in dynamics that particle energy is the product of size and the force. Thus the bigger particles carry more energy and smaller particles carry smaller energy or lesser energy.

It is also known that in any spiral the heavier particle lay at the outer periphery while the smaller particles move inwards. Thus the particles nearing the central ring of the chamber are smaller and also carry the least energy.

THE STATIC CLASSIFIER BY VIRTUE OF POSITIONING EXITS THE PARTICLES CONTAINING THE LEAST ENERGY

[The statistical matrix]

All these extremely fast dynamics collisions are based on a sophisticated statistical matrix, so sophisticated that we are able to improve our equipments only with the aid

of more sophisticated computer hardware. By a suitable calculation of feed size and feed rate together with the process gas pressure it is possible to predict at what size the particles will carry least energy and consequently their falling angle.

These calculation are also based on the following variables:

1. PRODUCT THROUGHPUT
2. NOZZLE PRESSURE
3. NOZZLE SIZE
4. NOZZLE ANGLE
5. AIRFLOW
6. FEED PARTICLE SIZE (INPUT SIZE)

To make this adjustments simpler, once the main parameters are set, we manipulate the feed rate to achieve the required size and fineness, thus the particles exiting out of the mill have thus reached the final size.

3.0 Benefits from micronization – Pharmaceuticals

The utilization of the high-tech fluid jet mill involves many benefits for the micronization process, below it is outlined a list of the main advantages, in order to go in more detailed discussion, we would be pleased to get the possibility to introduce ourselves in our workshop.

- Bioavailability

  One of the most important characteristics of a jet milled product is the huge increase in surface area. When reduced to 5 microns, a starting product of 600 micron has about 1.750.000 times more particles and the surface area is 120 times greater. This allows better pharmaceuticals thanks to their superior bioavailability, this quality factor measures the rate and the extent of therapeutically active drug that reaches the systemic circulation and is available at the site of action.

- Extremely wider available surface area

  The surface area of a micronized product (when reduced to 5 microns from a starting product of 600 micron) is 120 times greater. This allows faster reaction times for chemicals, faster burn rates in solid fuel rockets (air to air missiles) more powerful explosives, stronger plastics and adhesives.

- Bioequivalence

  Another important characteristic of a product prepared with micronized drugs is its bioequivalence thanks to the extremely narrow particle size distribution. In fact two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

- Dissolution

  A direct relationship between the surface area of the drug and its dissolution rate can be demonstrated, because the surface area increases with decreasing particle size, higher dissolution rate may be achieved through reduction of the particle size. This effect has been highlighted by the superior dissolution rate observed after micronization of certain sparingly soluble drugs as opposed to the regularly milled form. Micronization increases the surface area exposed to the dissolution medium and hence improves the rate of dissolution.

  Several investigations have demonstrated that formulations containing smaller particles were absorbed faster than formulations containing larger particles. It should be recognized, however, that the mere increase in the surface area of the drug does not always guarantee an equivalent increase in dissolution rate. Rather it is the increase in the effective surface area or the area exposed to the dissolution medium, and not the absolute surface area, that is directly proportional to the dissolution rate.

  Phisical properties of the drug particles other than size also effect indirectly the effective surface area by modifying the shear rate of the fresh solvent that comes in contact with the solid, these properties include the particle shape and the density.

- New forms and means of drug administration

  The powerful results succeeded with high-tech fluid jet mill make the drug producers able to propose new forms and means for drug administrations, plus the very easily process reproduction with the same results permits the validation of the new form for drug administration, some examples are:

  - pharmaceuticals for asthma patients need to pass deep into the lungs and medicines comprised of very fine particles travel deeper,
  - an increase in potency can be achieved with an increase in surface area so a lower dosage of the drug is required to do the same job.

- Ointment preparation

  Ointment preparation or manufacture depends on the type of vehicle and the quantity to be prepared, the objective is the same, to disperse uniformly throughout the vehicle a finely subdivided or dissolved drug substances. The drug materials finely micronized can be more effectively dispersed in the vehicle than a normal milled powder.

- Health authorities and drug activity and safety

  The endurance and the reliability demonstrated by the high-tech fluid jet mill facilitate the work with health authorities and drug activity and safety. In fact the equipment can process drugs with:

  - protection of the product from external contaminants
  - uniforming and omogenizing effect of the one single collecting point
  - rapid cleaning and easy validation with no cross contamination
  - no product contamination
  - no product agglomeration for the closest spherical geometry achieved
  - simplicity management of the whole micronizing unit

- Generally improved characteristics
  generally, all the characteristics of a micronized product are improved and lent to the top by a high tech fluid jet mill.
  - superior increase of powder's solubility
  - better limitation of caking in sticky product
  - extremely lowest consumption of process gas
  - production yields close to 100%
  - jet mills with cosmetic powders
    - greater dispersion and mixing effect of the powder particles
    - possibility to micronise to extremely fine and tight particle size distributions (Silky Touch)
    - optimisation of chromatic effect
    - quicker production saving classical steps and equipment
  - easy scale up maintaining the same particle size distribution
  - better and safe clearing of the powder from water and solvent process's residuals
  - milling of abrasive products without contamination

4.0 Benefits from micronization – Cosmetics

Micronization is the most modern technology that rapidly is becoming the standard in the industry of manufacturers of decorative cosmetics. Independent of product formulation, the micronisation provides the perfect dispersion of pigments and binders and offers unbeatable quality in terms of brilliant colours, silky touch, resistance of the maquillage and long shelf life of the products. Soft feeling and brilliant colours of micronized cosmetics are mainly related to the finer particle size, the traditional cosmetics, made with pin mills, have particle size between 80-150 microns, while micronized products never exceed 20 microns, below the lowest limit of touch perception that is 50 microns.

The traditional process is more expensive, due to several colour corrections and sieving operations that cannot be avoided, the finished product requires at least 3 different machines and 4 operation phases, without considering the colour corrections, and a smooth touch can be achieved only with expensive binders and careful sieving. Moreover, the pigments do not develop their full coverage, partly because they are not micronized and presence of agglomerates of 50-150 microns and partly because the dispersion isn't perfect. The addition of pearls before milling reduce the brilliance that could be also jeopardized by further colour corrections.

Micronizers can simplify the process, using a similar technology but fewer machines (only blender, micronizer and mixer) and consequently few operational phases. The perfect mixing of components, at primary particle level, allows complete dispersion of pigments and binders, without agglomerates. Sieving operation is eliminated, pearls are added at final mixing stage, along with colour correction components.

Related to traditional compact powders, it should be also mentioned the re-crystallization effects that occur over time, due to ageing of binder and formation of hard agglomerates. This phenomenon does not appear in micronized powders since dispersion of binder is so perfect to avoid re-crystallization point. Therefore, the shelf life is much longer, and the product conserves the same original characteristics.

To take full advantage of micronization process, the technology should be up-dated for the use of micronised mono-chromatic bases that offer major flexibility of production and avoid colour corrections.

- Dry expanders process

Generally a monochromatic base "EXPANDER" is obtained from each pure pigment (or group of compatible pigments), mixed at certain percentage with the white base (talc) and micronized. This intermediary product is "dry since the binders are added upon final high-speed mixing. The final formula is composed from different micronized mono-chromatic bases, that have been stored independently with the addition of binders and pearls in special high-speed mixers.

Experience has shown that in majority of cases, colour corrections are not necessary since correctly set parameters give excellent reproducibility on a batch to batch basis. This fact is also due to complete grinding of pigment agglomerates in the micronizer, all its coverage capacity being developed during the preparation of monochromatic base.

- Wet expanders process

An alternative to the preparation of "dry" bases is used by several manufacturers who add a certain percentage of binder to the phase, before micronization, obtaining "wet" monochromatic bases. Passage of binder through the micronizer implies its perfect dispersion and better colour definition of the monochromatic base.

The finished product is composed in a mixer (or high speed mixer), with only addition of pearls. The balance of white base and binder to achieve the formula is prepared through quick micronization of these components, that requires very short time. This alternative allows the application of "just in time" manufacturing concept, since very different products can be quickly prepared from monochromatic bases that have been previously micronized and stored, with very few loss of time for cleaning and change of colour.

5.0 Support to micronization process

The high-tech micronization process allows high quality results such as:

- Particle size distribution D100 below 5 micron
- Particle size distribution D90-95 below 1 micron
- Control of the particle shape
- Very narrow product batches, (0.2 g)
- Extremely narrow PSD, (Gauss's curve)
- Very low product loss, (typical yields are 99.5% of batch size)

- Greater dispersion and mixing effect of the powder particles
- Safe work of highly potent active pharmaceutical ingredients
- Safe work of r&d products with unknown effects

but, when the process is extremely delicate, in order to reach or go beyond the micronization limits, you need always support for the correct micronization protocols, and our engineering team guarantees this support for the entire life of our/your micronization equipment.

6.0 Future innovations

Our company actually is working on the future of the micronization process, some of the main themes of development are listed below:

- new techniques for particle size distribution measurement
- extremely chemically delicate and potent drugs processing
- less process gas consumption
- nano particles for nano tech applications
- cryogenic applications, (not simple chilled process gas)
- …

some of these applications are far to come, and actually they have been developed only at laboratory stage, other are already practicable and they are subject of our most innovative proposals.

Our Workshop address:

Tecnologia Meccanica Srl

Via S. Cristina 37 - 24048 Albegno di Treviolo – Bergamo – Italy

Telephone +39 035 691320
Facsimile +39 035 201175

Electronic mail info@tecnologia.it
Website www.tecnologia.it