Influence of micronization method on the performance of gentamicin sulfate dry powder formulation

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ABSTRACT

Two micronization techniques are used in pharmaceutical technology: ball milling and fluid – energy milling (jet-milling). Both techniques can produce final particles less than 5 µm in diameter, but the energy input for each of the techniques is different. As a result, the properties of powders will be influenced differently depending on the milling technique employed. The objective of this study was to investigate and compare the influence of the ball-milling and air-jet-milling processes on the dose delivery of gentamicin sulfate from dry powder inhalers (DPI). De-agglomeration behavior of these powders in an air stream was quite different. Jet-milled powder shows better de-agglomeration behavior, and it's clear that for the elaboration of inhalation formulations of gentamicin sulfate powder, the use of jet-milling techniques is expedient.

KEYWORDS: gentamicin sulfate, micronization, de-agglomeration,dry powder inhalers

Aerosol inhalation as a method of drug delivery to respiratory tract has become well established in the treatment of lung disease. This route has several distinct advantages, one of the most important is that lower dosage than by the oral route can be administered with similar efficacy which will minimize unwanted side effects. This way of drug administration presents great interest for the antibiotic delivery directly to the target area in the treatment of lung diseases. Evaluating disadvantages and advantages of different delivery systems, such as metered dose inhalers (MDI), nebulizers, and dry powder inhalers (DPI) [1,2], it has become clear, that for the antibiotic delivery DPI is the most suitable device.

Because the respirable fraction of the emitted inhalation powder is largely dependent on the geometric size of the bulk drug particles [3], the active drug usually requires significant size reduction to the range of 2-5 µm by micronization. Two micronization techniques are used in pharmaceutical technology: ball milling and fluid-energy milling (jet-milling).

The tumbling ball mill is widely used for fine grinding of materials. It operates by retaining a bed of powder in a chamber in which the powder is comminuted by tumbling balls for an extended period of time. The residence time in the ball-mill chamber depends on the degree of size reduction desired. In a fluid-energy mill, the particles are suspended in high-velocity jet streams of air, and the size reduction is caused by the high-speed impact of particle-on-particle or particle-on-surface and the consequent abrasion in the grinding chamber [4].

Both techniques can produce final particles less than 5 µm in diameter, but the energy input for each of the techniques is different. As a result, the properties of powders will be influenced differently depending on the milling technique employed.

The changes in the physical properties of powders after the milling process can have a significant impact on inhalation formulation.The objective of this study was to investigate and compare the influence of the ball-milling and air-jet-milling processes on the dose delivery of gentamicin sulfate from DPI.

MATERIALS AND METHODS

Unmicronized gentamicin sulfate (lot no. 0210320; Intsel Chimos (man. by MARSING & Co. LTD. A/S)) was used as received.

Delivery system – medium resistance device- Cyclohaler® (a marketed capsule inhaler), operates at a flow-rate of 60 l/min, employs hard gelatin capsules, size 3.

Quantitative analysis of gentamicin sulfate: The samples were analysed by homogeneous immunoassay based on particle-enhanced turbidimetric inhibition immunoassay technology using the Dimension® clinical chemistry system [5].

Ball-milling: Planetary Grinder, type PM100 (Pr. Company – Retsch); nominal volume of the bowl - 125 ml; optimal padding volume 15-80 ml; maximal size of the initial particles <4 mm; quantity of the metal grinding balls - 25; diameter of the grinding balls - 10 mm.

Jet-milling: Apparatus "Alpine 200". Process conditions: ambient temperature; grinding pressure – 6 bar; capacity – 25 kg/h.

Scanning electron microscopy: Scanning electron microscopy (SEM; FEI, Quanta 200, Eindhoven, the Netherlands) was used to visualise the powders.

Laser diffraction - geometric particle size distribution: Laser diffraction Malvern® Mastersizer S was also used to measure the size of the particles. The parameters, which allow describing the particle size distribution, are the D(v,0.5) and D(v,0.9). The D(v,0.5) is a diameter of the measured particles, on a volume basis, 50 % of which are inferior and another 50 % are superior; whereas the D(v,0.9) is the diameter of the measured particles, on a volume basis, 90 % of which are inferior [6;7].

Single – stage Glass Impinger - Aerodynamic assessment of fine particles: The two stages of the apparatus are designed such that at an airflow of 60 l/min through the system, the effective aerodynamic particle cut-off size of the lower impinger is 6,4 microns [8].

RESULTS AND CONCLUSIONS

The initial particle size distribution of gentamicin sulfate was determined using laser granulometry - wet way (sample of gentamicin sulfate was suspended in methanol, after 5 min of sonication - to achieve desaggregation of the strongly agglomerated powders - it was placed into the Small Volume Sample Dispersion Unit, rotation speed was 1900 rpm): D(v,0.5)=23,65 µm; D(v,0.9)=45,06 µm.

Rotation speed **rpm**	Time **min**	D(v,0.5) **µm**	D(v,0.9) **µm**	Powder compaction
100	30	20,04	44.56	-
100	120	19,03	45.79	+
150	60	15,78	40. 79	-
150	120	10,16	32.39	+
200	15	9,17	32.65	+
300	5	8,25	30.36	+

Tab.1 *Particle size reduction of gentamicin sulfate powder micronized by ball milling techniques.*

Ball milling process was extremely inefficient. To choose the manipulation time and optimal rotation speed of the bowl, several experiments were realized; data can be observed in the *Tab.1*.

Bowl rotation speed of 100 rpm was not sufficient for significant particle size reduction, both in the case of short time and relatively long time manipulations. Manipulation time increase (up to 120 min) leads to the powder compaction, without particle size reduction. Increase of rotation speed causes more effective particle size reduction, but powder compaction is very strong. For the higher rotation speeds (200 and 300 µm), even in the case of short time manipulations, the powder compaction is so strong, that it is very difficult to remove powder from the bowl's walls; and as a powder compaction does not allow further particle size reduction, therefore it is not possible to obtain through this technique particle size distribution required for inhalation powders.

Rotation speed **rpm**	Time **min**	D(v,0.5) **µm**	D(v,0.9) **µm**
300	60	6,18	20,50
	120	5,03	15,51
	180	4,27	15,01
	240	3,47	13,49
	300	3,05	11,50

Tab.2 *Gentamicin sulfate powder particle size distribution after micronization with ethanol.*

To avoid powder compaction, which is the main problem for effective micronization, as it does not allow downsizing of the particles, the small amounts of ethanol were being added to the bowl content (3-5 ml/70 cm^3 of powder) within 15 min intervals; the rotation speed was 300 rpm. After one hour of micronization particle size distribution was determined: D(v,0.5) - 6,18 µm; D(v,0.9) - 20,50 µm; as a powder compaction was avoided - micronization process was continued to obtain required particle size distribution of powder particles. Results are given in the *Tab.2*.

After 3-5 hours of micronization geometric particle size distribution of gentamicin sulfate measured immediately after grinding was in the range of 3-5 µm.

Jet-milling process in two passages were realized using apparatus "Alpine200" without selecting special conditions. The *Tab.3* presents gentamicin sulfate powder's geometric particle size distribution after first and second passages. Particle size distribution of jet-milled powder is suitable for inhalation formulations.

Scanning electron microscopy allowed powder visualization. In the case of grinded gentamicin, although laser granulometry techniques after sonication of the powder suspension showed that micronized powder's particles are in the respiration range, a strong agglomeration is observed on the SEM images (*Fig.1*). In contrary, jet-milled gentamicin powder is not agglomerated.

Besides the particle size of a drug, the de-agglomeration behavior in an air stream is important for the evaluation and comparison of inhalation powders obtained by different techniques. Single-stage glass impinger operates on the principle of liquid impingement to divide the dose emitted from the inhaler into the non-respirable dose impacting on the mouth and oropharynx which is swallowed and the remaining respirable dose (RD) [8].

The hard gelatin capsules were filled with the powder to approximately 50% of its volume and placed in Cyclohaler inhaler. The capsule was then pierced and the liberated powder was drawn through the impactor operating at a flow rate of 60 l/min for 10 sec. The amount of the powder deposited in the upper and lower chambers are washed out with physiological solution. Solution concentrations were determined by immunoassay method. Delivered dose (DD) was determined as a total mass of powder deposited in glass impinger; respirable dose (powder deposited in the lower chamber of the glass impinger) - as a percent of delivered dose.

Passage	D(v,0.5) **µm**	D(v,0.9) **µm**
1	4,596	9,487
2	4,107	7,817

Tab.3 *Particle size distribution of jet milled gentamicin.*

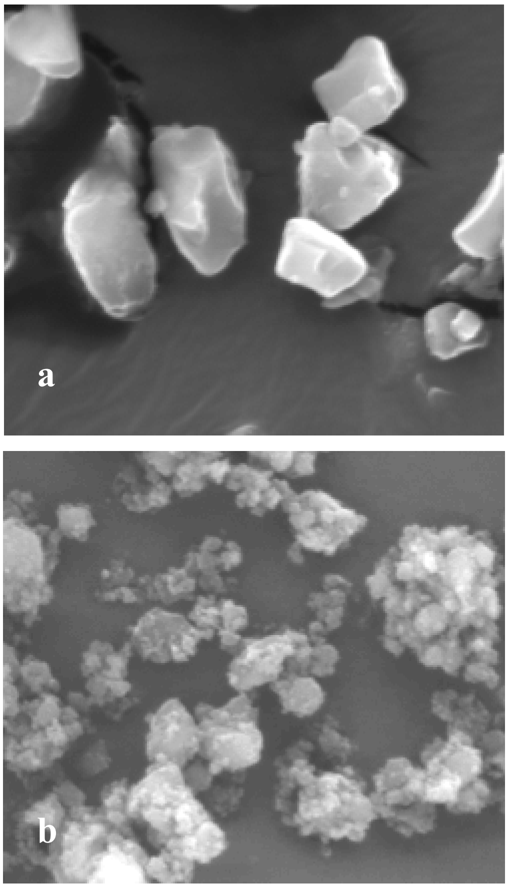

Fig.1 *SEM Images of the a) jet-milled and b) grinded gentamicin sulfate.*

Micronized powders	Delivered	Respirable dose	
		mg	%
Grinded gentamicin sulfate	38,36	3,21	8,34
Jet-milled gentamicin sulfate	35,89	6,74	18,77

Tab.4 *Aerodynamic assessment of gentamicin sulfate powders.*

Results presented in the *Tab.4*, shows that respirable dose generated by the jet-milled powder is twice greater than generated by grinded gentamicin sulfate. Despite of the data of laser granulometry, which shows that geometric particle size distribution of both powders are approximately the same (D(v,0.5):3-5μm), the de-agglomeration behavior of these powders in an air stream is quite different. Sonication, which has a place before the measuring of the particle sizes by laser diffraction method, is capable to de-agglomerate particles of grinded gentamicin, while the force of an air stream is not sufficient for that. Jet-milled powder shows better de-agglomeration behavior, and it's clear that for the elaboration of inhalation formulations of gentamicin sulfate powder, the use of jet-milling techniques is expedient.

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Влияние метода измельчения на поведение гентамицина сульфата в форме сухого ингаляционного порошка

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Р Е З Ю М Е

В фармацевтической технологии для измельчения порошков используют метод измельчения с помощью мельниц и метод измельчения в воздушном потоке. Оба метода позволяют получить порошки с конечным размером частиц менее 5 мкм, хотя затраченная энергия является различной. В результате, характеристики полученных порошков будут различными. Целью наших исследований являлась сравнение влияния обеих методов на дозу порошка гентамицина сульфата, доставляемую в легкие с помощью сухих порошковых ингаляторов. Способность дезагломерации в воздушном потоке для измельченных разными методами порошков была различной. Порошок, измельченный в воздушном потоке характеризовался лучшей дезаглмерацией, и для разработки ингаляционных порошков рекомендуется использование этого метода.

Ключевые слова: *гентамицина сульфат, микронизация, дезагломеризация, сухие порошковые ингаляторы*