Process for Obtaining Stable Micronized Glycopyrronium Bromide for Inhaled Treatment of Respiratory Diseases

David Gómez-Lamarca[1], Sílvia Donnici[1], Josep Terradas[2], José María Carulla[2] and Francesc Cabré[1]
Invent Farma Research and Development ([1]Laboratorios Lesvi S.L., [2]Inke S.A.) Barcelona, Spain

INTRODUCTION

Glycopyrronium bromide (GB), also referred to as glycopyrrolate, is an anticholinergic agent antagonist of M_3 receptors, currently used as inhaled treatment for chronic obstructive pulmonary disease (COPD) due its long-acting bronchodilator activity. GB is obtained as a single stable crystalline form (no other polymorphic forms have been reported). However, amorphous form can be generated during micronization, which has been reported as unstable and highly hygroscopic, leading to crystal growth and aggregate formation [1].

It has also been reported that micronization can lead not only to amorphous formation but also to crystal defects associated with the particle surface [2-4].

Several strategies have been disclosed to overcome aggregate and/or agglomerate formation, including among others suspension of GB in a hydrophobic anti-solvent [5] or the addition of a post-micronization conditioning step either in the presence of excipients [1] or on its own at moderate temperatures and long times [6].

This paper summarizes the work developed to find a way of stabilizing micronized GB suitable for treatment of COPD using post-micronization conditioning.

METHODS

GB was micronized by using a jet mill at room temperature and it was immediately conditioned according to flow chart from Figure 1 and by using the conditioning parameters described in *Table 1*.

Table 1 – *Conditioning parameters.*

GB Starting Material	Conditioning Temperature	Conditioning Duration
Micronized	130ºC	2 h
Micronized	130ºC	4 h
Micronized	130ºC	8 h
Micronized	70ºC	6 h

HPLC stability data was performed using the related substances method described in the GB monograph of the 8.0 Eur. Ph. [7]. Particle size distribution (PSD) measurements were performed by laser diffraction using a Sympatec method with dry dispersion of analysis with the R1 lens. Aggregate formation was monitored by laser diffraction using a Malvern 2000 method using wet dispersion and by scanning electron microscopy at a magnification level of 1000 (SEM, Zeiss Evo).DSC was performed using a Mettler Toledo DSC from 30 to 300ºC at 10ºC/min.

RESULTS AND DISCUSSIONS

GB shows an endotherm at about 180-190ºC by DSC. Stability tests were performed at temperatures up to 160ºC, where no significant degradation of the product was found *(Figure 2)*. Based on this, higher temperatures than the current state-of-the-art, were used to significantly decrease post-micronization conditioning time by at least over two thirds.

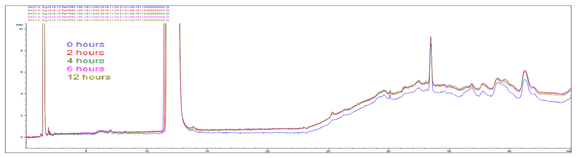


Figure 2 – *HPLC chromatograms of a micronized GB sample placed at 150ºC for two, four, six and twelve hours.*

Freshly micronized GB was conditioned as described in *Table 1*. Initial particle size distribution was suitable for its use as dry powder (*Figure 3* at time 0).

PSD evolution was monitored for post-micronization conditioned GB. *Figure 3* shows that when using a high temperature (130ºC) conditioning step after micronization, the particle size is stable for over three months. If GB is conditioned at lower temperatures (70ºC), 6 hours is not enough for particle size stabilization and after 9 days the particle size has dramatically increased.

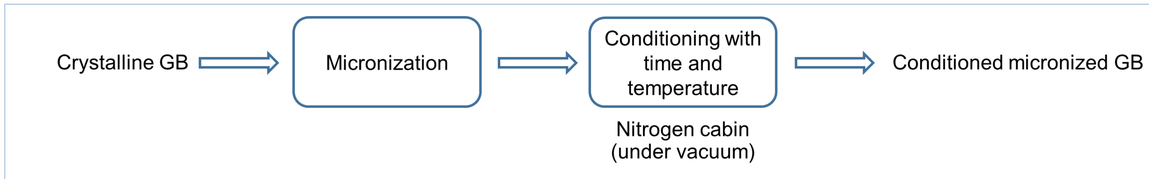


Figure 1 – *Flow chart of the process employed to condition micronized GB. A nitrogen cabin was used in the second step to reduce exposure to moisture.*

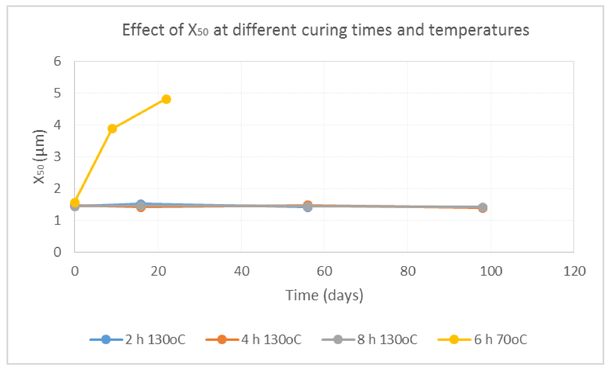


Figure 3 – *X_{50} evolution with time for GB sample conditioned at 70ºC for six hours and 130ºC for two, four and eight hours.*

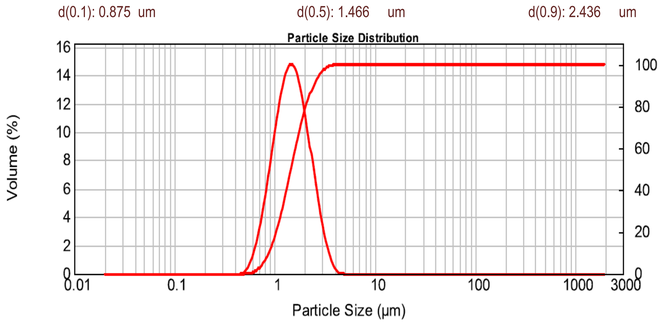


Figure 4 – *Histogram by wet dispersion for a micronized GB sample conditioned at 130ºC for two hours, where aggregates are not formed.*

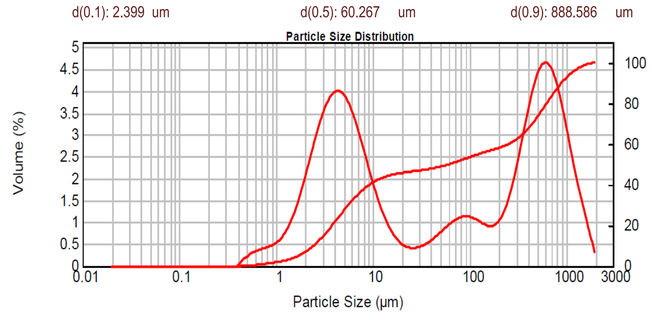
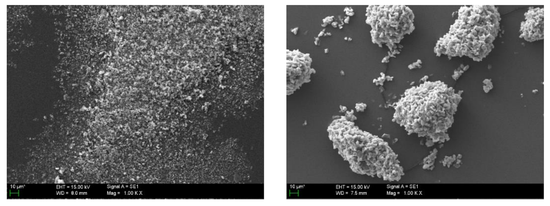


Figure 5 – *Histogram by wet dispersion for a micronized GB sample conditioned at 70ºC for six hours, where aggregates are formed.*

Even when the initial particle size of the freshly micronized GB is suitable for its use as dry powder, if the API is not properly conditioned, it shows a strong tendency to aggregate. Aggregate formation was monitored by laser diffraction *(Figures 4 and 5)* and by SEM *(Figures 6A and 6B).*



(A) (B)

Figure 6 – *SEM image of a micronized GB sample conditioned at (A) 130 ºC for two hours and (B) 70ºC for six hours.*

CONCLUSIONS

- **Micronized GB can be obtained with a particle size distribution suitable for its use as dry powder in inhaled treatment of COPD.**
- **An effective post-micronization conditioning step is required to avoid aggregate formation.**
- **This conditioning step takes place at considerably high temperatures between about 125ºC and 160ºC for short periods of time.**
- **Micronized GB using the procedure described above presented three months stability for its particle size distribution at the time of the poster submission. Stability studies are currently on-going.**

REFERENCES

[1]: Morton D, Shott M, Davies R: Methods for preparing dry powder compositions of Glycopyrrolate. E.P. Patent 1,755,555: 2012.
[2]: Forcino R, Brum J, Galop M, Sun Y: Using Thermally Stimulated Current (TSC) to Investigate Disorder in Micronized Drug Substance Produced at Different Milling Energies. *Pharm Res* 2010, 27(10): 2234-2241
[3]: Shah UV, Wang Z, Olusanmi D, Narang AS, Hussain MA, Tobyn MJ, Heng JYY: Effect of milling temperatures on surface area, surface energy and cohesion of pharmaceutical powders. *Int J Pharm* 2015, 495: 234-240
[4]: Chamarthy SP, Pinal R: The nature of crystal disorder in milled pharmaceutical materials. *Colloids and Surfaces A* 2008, 331: 68-75
[5]: Pasquali I, Casazza A, Losi E, Saunders M: Particle size reduction of an antimuscarinic compound. U.S. Patent 2014/0322142: 2014
[6]: Muhrer G, Rasenack N: Process for reducing the tendency of a glycopyrronium salt to aggregate during storage, EU Patent 2,235,595: 2012
[7]: European Pharmacopoeia 8.0: Chapter 15: Glycopyrronium bromide (4) 1783. EDQM Council of Europe, Strasbourg, France: 2011