Comparative Stability Studies between Air Jet Micronized and Wet Milled Glycopyrronium Bromide towards Humidity

David Gómez-Lamarca, Sílvia Donnici, Ángel Esquinas, José María Carulla and Francesc Cabré
Inke S.A. (NuPharm Group) Barcelona, Spain

INTRODUCTION

Drug substances intended for inhaled dosage require a small aerodynamic particle size that can be achieved by different strategies. The most common way is by air jet micronization. However, other technologies, such as wet milling, are becoming popular alternatives to these traditional processes. These techniques are in general softer to the material, leading to less amorphous formation [1].

Glycopyrronium bromide (GB), also referred to as glycopyrrolate, is an anticholinergic agent, currently used as inhaled treatment for chronic obstructive pulmonary disease (COPD), with long-acting bronchodilator activity. GB is obtained as a single stable crystalline form. However, an amorphous form can be generated during air jet micronization, which has been reported as highly hygroscopic, leading to crystal growth and aggregate formation [2]. In addition, crystal defects can also appear during particle size reduction operations [3-5].

This paper summarizes the comparative work for material obtained by traditional air jet micronization (AJM) and by wet milling (WM) followed by spray drying.

METHODS

AJM GB was obtained by using an air jet mill (Hosokawa AS 100) at room temperature. After processing the material was immediately conditioned at 130ºC for two to four hours in a drying chamber (Binder VDL 115) [6]. WM GB was obtained using a circulating bead mill unit (Netzsch MiniCer), by suspending GB in ethyl acetate with 200 µm zirconium oxide balls. The grinded suspension was then spray dried (Buchi B-290) at 110 ºC inlet temperature to obtain a dry recovered form of the WM GB.

Particle size distribution (PSD) measurements were performed by laser diffraction using a dry dispersion method (Sympatec HELOS/BR) and a wet dispersion method (Malvern 2000). Crystals were also monitored by scanning electron microscopy (SEM) (Phenom-World, Phenom Pro) for initial samples and for samples stored for 24 hours at different relative humidity (RH) exposure.

Amorphous content was measured by Dynamic Vapour Sorption (DVS) (Mettler Toledo TGA/DSC 1LF coupled with a Modular Humidity Generator MHG 32) by measuring the weight difference between the first and third steps at 20% RH with a second step at 70% RH. Limit of quantification was established to below 1%.

RESULTS AND DISCUSSIONS

Both conditioned AJM and WM GB were devoid of any amorphous material and were exposed to controlled RH ranging between 40% and 80% RH at 25ºC for 24 hours. Surprisingly, while AJM GB only starts to aggregate above 70% RH, WM GB shows a crystal growth in particle size at humidity as low as 40%. This is evidenced by PSD measurements by dry dispersion (Figure 2) and by wet dispersion (Figure 3), where aggregates are only observed for AJM GB exposed to RH above 70%, while crystal growth is observed for WM GB exposed to RH as low as 40%.

Comparative SEM imaging between initial product (Figure 1 A and B) and exposed at 70% RH (Figure 1 C and D) evidence a high cohesion of WM GB, making it less favourable for formulation.

Although GB is devoid of amorphous content, its particle size instability is probably due to crystal fractures or crystallites caused during AJM and WM. The aging step for AJM probably helps heal these fractures, making its particles more stable against crystal growth than WM GB towards humidity [7].

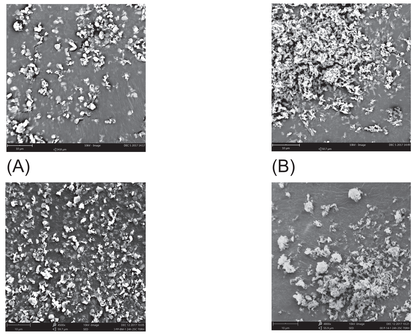

Figure 1 - *SEM image of (A) AJM GB, (B) WM GB, (C) AJM GB exposed to 70% RH and (D) WM GB exposed to 70% RH.*

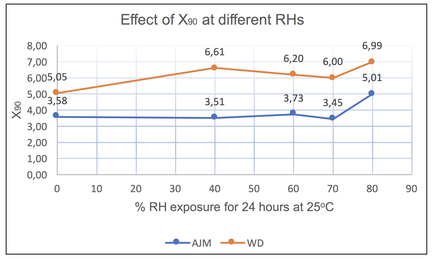

Figure 2 - *X^{90} by Sympatec (dry dispersion) for AJM and WD GB exposed at different humidity for 24 hours at 25ºC.*

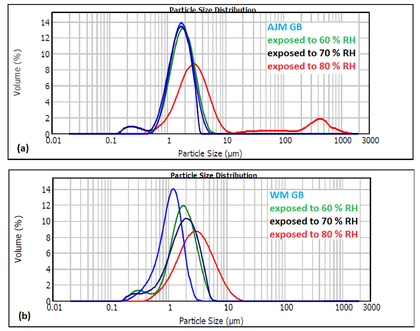

Figure 3 - *Overlaid histograms by Malvern (wet dispersion) for (A) AJM GB and (B) WM GB before exposure and exposed at 60, 70 and 80% for 24 hours at 25ºC.*

CONCLUSIONS

- **AJM GB shows a distinct advantage towards WM GB. Not only does the process for WM require the use of an organic solvent, making the process less environmentally friendly, but it also generates an API that is less stable than conditioned API obtained by AJM GB.**
- **Traditional micronized material is stable at up to 70% RH, while crystal growth occurs to humidity as low as 40% RH by WM followed by spray drying. This renders AJM more suitable for inhaled formulation purposes.**

REFERENCES

[1] Loh ZH, Samanta AK, Heng PWS: Overview of milling techniques for improving the solubility of poorly water-soluble drugs. *Asian J Pharm Sci 2015,* 10: 255-274.
[2] Morton D, Shott M, Davies R: Methods for preparing dry powder compositions of Glycopyrrolate. EU Patent 1,755,555: 2012.
[3] Forcino R, Brum J, Galop M, Sun Y: Using thermally stimulated current (TSC) to investigate disorder in micronized drug substance produced at different milling strategies. *Pharm Res* 2010, 27(10): 2234-2241.
[4] Shah UV, Wang Z, Olusanmi D, Narang AS, Hussain MA, Tobyn MJ, Heng JYY: Effects of milling temperatures on surface area, surface energy and cohesion of pharmaceutical powders. *Int J Pharm* 2015, 495: 234-240.
[5] Chamarthy SP, Pinal R: The nature of crystal disorder in milled pharmaceutical materials. *Colloids and Surfaces A* 2008, 331: 68-75
[6] Gomez-Lamarca D, Donnici S, Terradas J, Carulla JM, Cabre F: Process for obtaining stable micronized glycopyrronium bromide for inhaled treatment of respiratory diseases. RDD Europe 2017, 2: 243-248
[7] Forcino RG, Williams GR, Brum J, Vogt FG: The study of micronization induced disorder in active pharmaceutical ingredients. *Am Pharmaceut Rev 2013,* 16(6): 40-46