Process for Reducing Amorphous Content on Micronized Indacaterol Maleate for Dry Powder Inhaler Formulations

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INTRODUCTION

Indacaterol maleate (IM) is a beta-2 adrenergic receptor agonist, currently used as inhaled treatment for chronic obstructive pulmonary disease (COPD). IM has only been reported as a single crystalline polymorphic form [1]. As IM is intended for inhaled dosage, it requires a small particle size that cannot be achieved by crystallization. To achieve the desired particle size required, a milling process such as air jet micronization is required [2]. As a side-effect, a part of crystalline IM becomes amorphous. Preliminary experimental studies show that IM amorphous form is very stable and can stay stable for months. However, the amorphous form, thermodynamically unstable, will end up re-crystallizing with time. In addition, amorphous IM is less stable, potentially leading to hydrolysis and racemization [3]. This paper summarizes different strategies to minimize the amount of amorphous content in micronized IM.

METHODS

Micronized IM was obtained by using an air jet mill (Hosokawa AS100). Annealing in water vapor was performed in a constant climate chamber (Binder KMF 115), setting temperature and relative humidity (RH) to the desired target. Annealing in organic solvent was performed in a drying chamber (Binder VD 23), placing a capsule with organic solvent inside. Amorphous content was measured by Solution Calorimetry (TAM IV, Waters) in dimethylformamide with a limit of detection of 0.5 %. Quantification of amorphous content was calculated from a calibration curve generated from mixtures of crystalline and amorphous material at different ratios. Particle size distribution (PSD) measurements were performed by laser diffraction using a dry dispersion method (Sympatec HELOS/BR) and by scanning electron microscopy (SEM) (Phenom-World, Phenom Pro). Purity monitoring was performed using an in-house HPLC method (Agilent). Polymorphism was evaluated by XRPD (Bruker D8 Advance).

RESULTS AND DISCUSSIONS

Micronized IM generates variable amounts of amorphous material (typically ranging between 10 and 30%). Amorphous content was found to be stable at 25ºC and 60% RH for periods over six months. Amorphous content readily crystallised at 25ºC when exposed to methanol or ethanol vapour. This did not occur in water vapour, unless high temperature or a long period of time at high vapor humidity of at least 70% RH were employed.

Micronized material containing 25% amorphous content was placed under different conditions for annealing to reduce the amount of amorphous content. Annealing conditions and results are summarized in Table 1.

Annealing conditions	HPLC	D (0.9) µm	Amorphous content %
Micronized material	99.8%	3.8	25
70ºC in ethanol 12 hours	99.6% (0.2% ethoxy impurity)	4.1	< 0.5
70ºC and 70 % RH 3 days	99.8%	4.1	1.5
25ºC and 75 % RH 16 days	99.8%	3.9	2.5

Table 1 - Annealing conditions, chemical stability, PSD and amorphous content for the micronized sample and the annealed fractions.

Initial sample and annealed fractions were analysed by HPLC. Figure 1 shows the overlaid HPLC chromatograms. It can be observed that although annealing under an ethanolic atmosphere reduces amorphous content in a very fast way, it forms an impurity due to the interaction between IM and ethanol (Figure 2) that does not take place under humidity. There is no significant degradation of IM for the two other conditions tested under humidity. In none of the three tested annealing conditions there was significant particle growth nor aggregation (Table 1 and Figure 3). In all tested conditions no detectable polymorphic change took place.

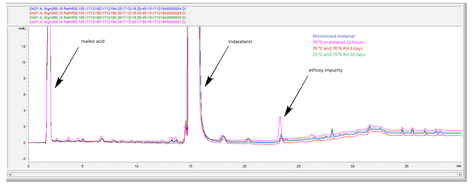

Figure 1 - HPLC chromatograms of micronized IM before and after annealing at different conditions.

Figure 2 - IM degradation pathway under ethanolic vapour.

REFERENCES

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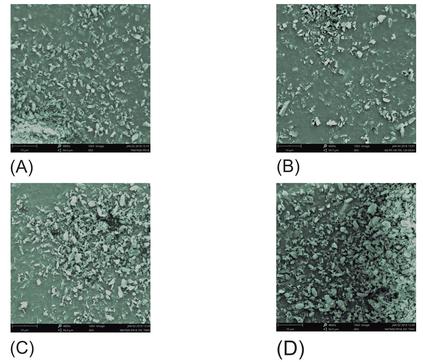

Figure 3 - SEM image of (A) freshly micronized IM, (B) annealed IM at 70ºC in ethanol (C) annealed IM at 70ºC and 70% RH and (D) annealed IM at 25ºC and 75% RH.

CONCLUSIONS

- **Amorphous IM generated during air-jet micronization is stable at ambient conditions and can be in that form for months. However, a way to remove amorphous content prior to formulation is required, due to its potential thermodynamical and chemical instability. The faster way to remove it is by using ethanol. However, this generates an undesired impurity.**
- **Amorphous content can be significantly reduced by using high humidity (70% RH or above). This does not increase crystal growth nor causes chemical degradation. The use of temperature (up to 70°C) speeds the crystallization process up without causing any degradation impurity.**