Quantitative Phase Analysis of Tibolone Polymorphs Using High-throughput Synchrotron X-Ray Diffraction

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INTRODUCTION

Tibolone is a hormone used by postmenopausal women for replacement therapy. The Cambridge Structure Database (CSD) presents two polymorphs for this drug: monoclinic $P2_1$ (Form I) and triclinic P1 (Form II). The Rietveld method (RM)[1] is an excellent tool for the refinement of crystal structures using X-ray powder diffraction data (XRPD) and was applied to unambiguously identify and quantify the active pharmaceutical ingredient (API) in tibolone raw materials acquired in manipulation pharmacy and synthesized in the Laboratories of the University of Sao Paulo, Brazil.

EXPERIMENT

For this purpose the data were collected in high-throughput transmission geometry in the D10B-XPD beamline and D12A-XRD1 of the Brazilian Synchrotron Light Laboratory (LNLS, Campinas, SP, Brazil) [2]. The refinements were performed using the TOPAS Academic v4.1 [3] software. The silicon NIST SRM640c was used to get the instrumental broadening using the modified TCH-pseudo-Voigt. Anisotropic size model were used for the physical broadening. The three samples analyzed are identified here by sample 1, sample 2 (prepared by some of the authors) and sample mp for the one of the manipulation pharmacy.

RESULTS AND DISCUSSION

In these samples, one could clearly identify the phase monoclinic (sample 1), monoclinic and triclinic (for sample 2 and mp).The percentage of triclinic polymorph was about 6 and 57 mass% in samples 1 and mp respectively. For all samples, the R-factors and goodness-of-fit indicators were around 12% and 1.5% respectively. A comparison between the 2 indexes as well as a visual inspection of the Rietveld plots clearly show that data obtained in the transmission geometry using a synchrotron source provided better accuracy. Figure 1 shows the Rietveld plot for the case of manipulation pharmacy. Figure 2 shows a magnification of the region where the peaks for the two phases could be clearly identified.

CONCLUSION

The conclusion of this work is that low resolution data and reflection geometry are not adequate for quantitative phase analysis of pharmaceuticals polymorphs (tibolone) due to the high superposition of peaks and high preferred orientation that occur in flat-plate sample-holders.

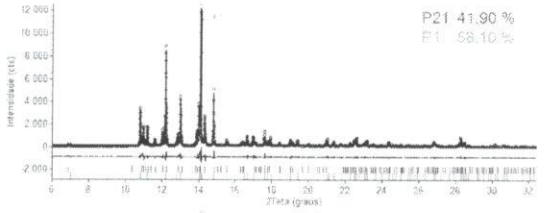

FIG. 1: Rietveld plot for the tibolone polymorph of the manipulation pharmacy.

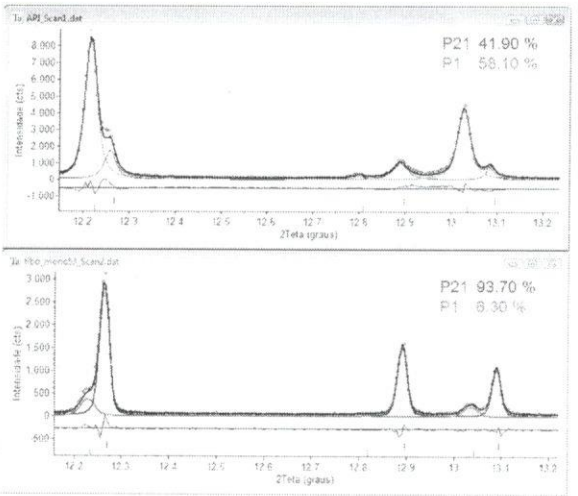

FIG. 2: Magnification of the Rietveld plot for the samples 2 and mp.

ACKNOWLEDGEMENTS

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