OLMESARTAN MEDOXOMIL: ANALYTICAL METODOLOGY VALIDATION, BIOPHARMACEUTICAL EVALUATION AND POLYMORPHIC ANALYSIS

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Introduction: The prodrug olmesartan medoxomil (OLM) is a selective angiotensin II receptor blocker (ARB). In Brazil, it is available as coated tablets (Benicar®). It was approved by FDA in 2002. There is no monograph available for this drug in any official code.
Objective: According to this, the main purpose of this study consisted in develop a quality control analytical methodology for OLM in bulk material and pharmaceutical form, establish *in vitro* dissolution kinetic for OLM coated tablets, and at last investigate the possibility of polymorphic structures presence in OLM bulk product.
Materials and Methods: The investigation of melting range and application of techniques such as infrared spectrophotometry (IR), as well as the ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy were used to identify the OLM bulk material. Ultraviolet (UV) spectrophotometry, high-performance liquid chromatography (LC) and thin-layer chromatography (TLC) were utilized for qualitative analysis of the drug in coated tablets. The quantitative determination was carried out through the development and validation of stability-indicating LC method, evaluating the parameters described in the guidelines such as: specificity, robustness, linearity, detection and quantitation limits, precision, and accuracy. An isocratic LC separation was performed using a Phenomenex RP-18 column using a mobile phase consisting of water:triethylamine:acetonitrile (60:0.3:40 v/v/v, pH adjusted to 6.3 with phosphoric acid). The flow rate was 1.2 mL min^{-1}, and the detection was achieved with a photodiode array detector set at 257 nm. The dissolution test was developed and validated according to the guideline proposed by the USP Forum, using 900 ml of water + 0.5% sodium lauryl sulfate (w/v) pH 6.8, at 37 ± 0.5°C, such as dissolution medium, paddle at 50 rpm and quantitation by LC and UV spectrophotometry. The attenuated total reflectance Fourier transformed infrared (ATR-FTIR) spectroscopy, along with differential scanning calorimetry (DSC), thermogravimetry (TG), X-ray powder diffraction (XRPD), and scanning electron microscopy (SEM) were applied to investigate the presence of polymorphism in OLM bulk product.
Results and Discussion: The characterization of OLM through qualitative analysis demonstrated that both bulk material and coated tablets were considered adequate to be used in this study. The LC method developed and validated for quantitative determination of OLM in coated tablets was considered simple, sensitive, specific, precise, accurate and reproducible. Based on results of specificity procedure and forced degradation studies, undertaken according to the ICH guidelines, the method can be considered specific and stability-indicating, for the reason that there was no interference of the excipients and of the degradation product formed in the determination of OLM in bulk samples. Thus, the method can be applied in stability testing of the commercially available OLM coated tablets. The results about analysis of drug released percentage, by both methods, did not show statistical difference ($P = 0.05$). The dissolution profiles of Benicar® reference medicine, and Olmetec®, another commercial formulation available, were considered similar, using independent-model and dissolution efficiency methods. The dissolution kinetic of both formulations, evaluated through the application of dependent-model, reveals that Benicar® followed the *Hixson-Crowell* model, while the Olmetec® the *zero-order* model. The calculated values of $t_{50\%}$ and $t_{80\%}$, obtained from zero-order equation, were similar of experimental values found in the dissolution profile for both products. Upon the OLM bulk polymorphic behavior, the different cooling rate of recrystallization originated two different structures in methanol: pseudopolymorphic, by slow cooling under refrigeration (8±2°C), and polymorphic, by rapidly cooling under N2 gas atmosphere. The ATR-FTIR spectroscopy, XRPD, thermal analysis, and SEM enabled us to identify these two structures of OLM in solid-state, due to the differences in their unique vibrational peaks, 2θ values, melting points, and distinct crystal shape and size, respectively.
Conclusions: All proposed methods could be utilized in the quality control of OLM bulk material and coated tablets. In addition to this, the techniques utilized to investigate the OLM polymorphic behavior were considered enough to detect the presence of distinct polymorphic forms of this drug.
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