A Discriminating Dissolution Method for Glimepiride Polymorphs

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ABSTRACT: Glimepiride, an oral antidiabetic drug, is practically insoluble in water and exists in two polymorphic forms, I and II, of which form II has higher solubility in water. Because the dissolution rate of drugs can depend on the crystal form, there is a need to develop discriminating dissolution methods that are sensitive to changes in polymorphic forms. In this work, a dissolution method for the assessment of 4 mg glimepiride tablets was developed and validated. The optimal dissolution conditions were 1000 mL of phosphate buffer (pH 6.8) containing 0.1% (w/v) of sodium dodecyl sulfate as the dissolution medium and a stirring speed of 50 rpm using a paddle apparatus. The results demonstrated that all the data meet the validation acceptance criteria. Subsequently, tablets containing forms I and II of glimepiride were prepared and subjected to dissolution testing. A significant influence of polymorphism on the dissolution properties of glimepiride tablets was observed. These results suggested that the raw material used to produce glimepiride tablets must be strictly controlled because they may produce undesirable and unpredictable effects. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:794–804, 2012

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INTRODUCTION

In vitro dissolution tests for immediate-release solid oral dosage tablets are extremely important, as these tests are crucial for assessing the quality of all drug product lots and can guide the development of new formulations.[1]

In vitro study of dissolution is an alternative to bioequivalence studies. Dissolution tests can, therefore, provide evidence for similarities and differences between medicinal formulations.[2] From a quality assurance point of view, a more discriminating dissolution method is preferred because the test will indicate possible changes in the quality of the product before *in vivo* performance is affected.[3]

For drugs with poor water solubility, there is some difficulty in selecting an appropriate dissolution medium with discriminating power. The choice of a medium capable of discriminating among critical manufacturing variables is crucial in such cases.[4] Among these critical variables, the possible presence of different polymorphic forms deserves to be investigated. Polymorphic forms have been shown to influence the solubility and, therefore, the dissolution rate of numerous drugs.[5]

Therefore, there is a real need to develop discriminating dissolution tests for drugs with poor water solubility, which can discriminate between critical manufacturing variables such as polymorphism in pharmaceutical solids.

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Glimepiride (CAS 93479-97-1), chemical name 1-[[4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamide) ethyl] phenyl]sulfonyl]-3-(*trans*-4-methylcycloheyil) urea,[6] is an oral antidiabetic drug in the sulfonylurea class, which is widely used in the treatment of type 2 diabetes.[7] It is a white to yellowish white, crystalline, odorless powder and its molecular formula is $C_{24}H_{34}N_4O_5S$. Glimepiride has a molecular weight of 490.62, is sparingly soluble in water, and is classified as a class II drug according to the Biopharmaceutics Classification System.[8] There are two polymorphs of this molecule reported in the literature, form I and form II, of which form II has about 3.5-fold higher solubility than that of form I.[9]

There is a growing number of studies describing the determination of glimepiride concentration in biological fluids[10–18] and pharmaceutical formulations[19–30] using a variety of methods. However, there is no dissolution method for glimepiride tablets in the literature.

In light of the considerations outlined above, this work aims to develop and validate a discriminating dissolution method for glimepiride polymorphs.

EXPERIMENTAL

Chemical and Reagents

All reagents used were of analytical grade. Sodium hydroxide, disodium hydrogen phosphate (Na_2HPO_4), sodium dihydrogen phosphate monohydrate ($NaH_2PO_4{\cdot}H_2O$), ethanol, chloroform, ammonium acetate, citric acid, glacial acetic acid, sodium dodecyl sulfate (SDS), and hydrochloride acid were purchased from Vetec. (Rio de Janeiro, Rio de Janeiro, Brazil). Methanol was of high-performance liquid chromatography (HPLC) grade and was acquired from Sigma–Aldrich (St. Louis, Missouri). HPLC-grade water, used as the mobile phase, was prepared by Milli-Q reverse osmosis and met the United States Pharmacopoeia (USP) requirements. Glimepiride reference substance (assigned purity of 100.12%) was supplied by Zhejiang Xianju Huakang Pharmaceutical & Chemical Company, Ltd. (Xianju, Zhejiang, China). A glimepiride reference product (Amaryl tablets; Sanofi-Aventis, Suzano, São Paulo, Brazil), which is claimed to contain 4 mg of the active component, was purchased from a local market. The placebo mixtures with the same composition as the pharmaceutical formulations were prepared in the laboratory using the following pharmaceutical grade excipients: lactose hydrous, SDS, sodium starch glycolate, povidone, microcrystalline cellulose, magnesium stearate, and lake indigo carmine.

Equipment

Dissolution tests were performed in an Electrolab TDT-08 L multi bath ($n = 8$) dissolution test system (Electrolab, Mumbai, Maharashtra, India) in accordance with the USP general method.[31]

The HPLC equipment used was a Shimadzu series LC-10A (Shimadzu, Kyoto, Quioto, Japan) consisting of an LC AVP pump, a CLASS-VP 5.02 integration system, a DGU-14 A degasser, a 7725i manual injector with a 20 μL loop, a SPD-10AVP integrated ultraviolet detector, a FCV-10ALVP valve, a CTO-10AVP column oven, and a SCL-10 AVP controller. The separation was performed on a Waters Symmetry C-18 column ($4.6 \times 250\ mm^2$, 5 μm; Waters, Milford, Massachusetts).

Powder X-ray diffraction (PXRD) of samples was performed on a Rigaku ultima IV X-ray diffractometer (Rigaku Company, Ltd., Tokyo, Honshu, Japan).

Infrared (IR) spectra were obtained using a Prestige-21 Fourier transform (FT) IR spectrophotometer (Shimadzu, Tokyo, Honshu, Japan).

Differential scanning calorimetry (DSC) was performed using a Mettler Toledo instrument model DSC 1 STARe system (Mettler–Toledo, Barueri, São Paulo, Brazil).

Scanning electron microscopy (SEM) photographs were taken with a Jeol scanning electron microscope model JSM 7500F (Jeol, São Paulo, São Paulo, Brazil).

The following equipments were also used: a single rotary tablet compression machine (Lemaq model LM08B; Lemaq, Diadema, São Paulo, Brazil), a digital pH meter (Marconi model PA 200; Marconi, Piracicaba, São Paulo, Brazil), an ultrasonic bath (Unique model USC2800A; Unique, Indaiatuba, São Paulo, Brazil), and an analytical balance (Kern model 410; Kern & Sohn GmbH, Balingen, Zollernalbkreis, Germany).

Solutions

All dissolution media used in this study were degassed at 41°C in an ultrasonic bath for 30 min prior to use.

A stock standard solution containing 200 mg L^{-1} of glimepiride was prepared by accurately weighing 10 mg of the glimepiride reference substance and then transferring it to a 50-mL volumetric flask and adding 40 mL of methanol. The flask was sonicated for 5 min and the remaining volume was filled with methanol. Working standard solutions were prepared immediately prior to use by appropriately diluting the corresponding stock solutions of glimepiride with the dissolution medium.

Sample solutions were prepared by placing one tablet in a vessel containing the dissolution medium (1000 mL) at a temperature of 37 ± 0.5°C. Samples were collected at the end of a specified time and filtered using a quantitative VETEC filter paper (Vetec). For the HPLC analysis, samples were injected directly into the HPLC system.