Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Pharmaceutical and Biomedical Analysis 39 (2005) 543–551
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Development and validation of a dissolution test for a once-a-day combination tablet of immediate-release cetirizine dihydrochloride and extended-release pseudoephedrine hydrochloride

Michael D. Likar*, Hany L. Mansour, Jeffrey W. Harwood

Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA

Received 7 March 2005; received in revised form 28 April 2005; accepted 30 April 2005
Available online 21 June 2005

Abstract

A dissolution test for a once daily combination tablet containing 10 mg of cetirizine dihydrochloride (cetirizine HCl) for immediate release and 240 mg of pseudoephedrine hydrochloride (pseudoephedrine HCl) for extended release was developed and validated according to current ICH and FDA guidelines. The cetirizine HCl is contained within an outer layer of the tablet while a semipermeable membrane of cellulose acetate and polyethylene glycol controls the rate at which pseudoephedrine HCl is released from the tablet core. The dissolution method, which uses USP apparatus 2 with paddles rotating at 50 rpm, 1000 ml of deaerated water as the dissolution medium, and reversed-phased HPLC for quantitation, was demonstrated to be robust, discriminating, and transferable. These test conditions were selected after it was demonstrated that the cetirizine HCl portion of the tablet rapidly dissolved in aqueous media over the physiologically relevant pH range of 1.1–7.5, and that the extended-release profile of pseudoephedrine HCl was independent of dissolution conditions (i.e., apparatus, pH, and agitation).

Keywords: Asymmetric membrane film-coated tablets; Cetirizine; Dissolution; Method development and validation; Osmotic drug delivery; Pseudoephedrine; Reversed-phase high-performance liquid chromatography

1. Introduction

Cetirizine dihydrochloride (cetirizine HCl) is a selective histamine (H_1)-receptor antagonist that is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis [1]. Pseudoephedrine hydrochloride (pseudoephedrine HCl) is an α-adrenoreceptor agonist that is used for the symptomatic relief of nasal congestion in patients with allergic rhinitis [2]. The chemical structures of these active pharmaceutical ingredients (APIs) are shown in Figs. 1 and 2. Both of these drugs are well absorbed after oral administration [3,4], and they may be co-administered. For example, ZYRTEC-D 12 HOUR® Extended Release Tablets are available that contain 5 mg of cetirizine HCl and 120 mg of pseudoephedrine HCl [5].

This paper describes the development and validation of a dissolution test for a once-a-day combination tablet that contains 10 mg of cetirizine HCl for immediate release and 240 mg of pseudoephedrine HCl for extended release. The combination tablet, which is shown schematically in Fig. 3, uses an osmotically controlled drug delivery system based on asymmetric membrane (AM) technology to deliver the pseudoephedrine HCl [6]. The dissolution method was developed and validated according to current ICH [7,8] and FDA [9] guidelines.

2. Experimental

2.1. Materials

The AM-coated tablets of pseudoephedrine HCl were manufactured as previously described [10]. The target AM

* Corresponding author. Tel.: +1 860 441 6368; fax: +1 860 715 9517.
E-mail address: michael.d.likar@pfizer.com (M.D. Likar).

0731-7085/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2005.04.047

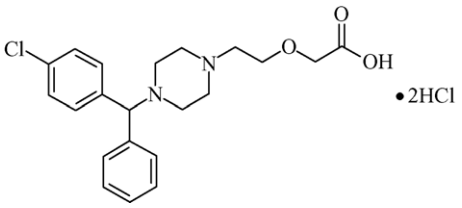

Fig. 1. The chemical structure of cetirizine dihydrochloride (CAS No. 83881-52-1).

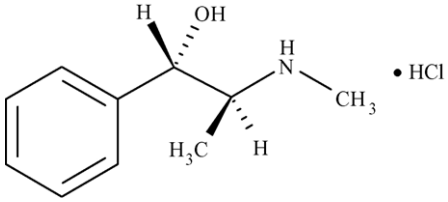

Fig. 2. The chemical structure of pseudoephedrine hydrochloride (CAS No. 345-78-8).

coating weight was 88.0 mg. The immediate-release layer of cetirizine HCl, followed by a taste-masking layer, was sprayed onto the AM-coated tablets [11]. The total weight of the tablet was approximately 673.0 mg. The AM-coated tablets described in Section 3.3.2, however, were not coated with the cetirizine HCl or taste mask layers.

ACS reagent grade chemicals were used unless otherwise indicated. Hydrochloric acid was obtained from EM Science (Gibbstown, NJ). Potassium biphthalate, monobasic potassium phosphate, and sodium dihydrogen phosphate monohydrate were obtained from J.T. Baker (Phillipsburg, NJ). HPLC grade methanol and sodium 1-octanesulfonate (OSA) were obtained from Burdick & Jackson (Muskegon, MI) and J.T. Baker, respectively. The 0.1 M hydrochloric acid solution (pH 1.1), potassium biphthalate USP buffer (pH 4.5; 5 mM), monobasic potassium phosphate USP buffer (pH 6.8; 50 mM), and simulated intestinal fluid (SIF; pH 7.5) were prepared according to the directions in USP 23 [12], except that the potassium biphthalate buffer concentration was decreased

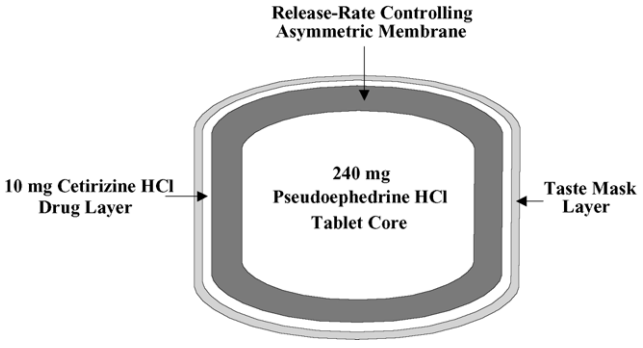

Fig. 3. Cross-section of the cetirizine HCl/pseudoephedrine HCl 10 mg/240 mg tablet.

to minimize chromatographic interferences and the SIF was prepared without pancreatin. These media were deaerated prior to use by sparging with helium for 15 min. The cetirizine HCl and pseudoephedrine HCl reference standards, which were characterized by tests including appearance, IR spectroscopy, acid–base titration, chromatographic purity by HPLC, loss on drying, and residue on ignition, were assigned purity values of 99.6 and 100.0%, respectively, when dried prior to use.

2.2. Dissolution test conditions

Dissolution testing was performed in compliance with USP ⟨7 1 1⟩ using apparatus 2 (e.g., Hanson SR8—Plus™ Dissolution Test Station) with paddles rotating at 50 rpm. The dissolution medium was 1000 ml of deionized water having a resistivity of about 18 MΩ cm. The medium, which was deaerated using a "Dissofill" Media Preparation System from Copley Scientific (Nottingham, UK), was maintained at 37 ± 0.5 °C. The 1-liter glass dissolution vessels were covered to minimize evaporation. The tablets were inserted into capsule weights to keep them from sticking to the walls of the dissolution vessel. Twelve tablets were tested unless otherwise indicated. Sample aliquots were withdrawn at 15, 30, 45, and 60 min, and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h. When manual sampling was used, aliquots of 5 ml were withdrawn from the dissolution vessel using a glass hypodermic syringe equipped with a stainless steel needle. These solutions were immediately filtered using a 0.45-μm Millex®-HV PVDF filter from Millipore (Billerica, MA). The first 3–4 ml of filtrate was discarded prior to collecting the sample for analysis. For automated sampling, a Dissoette II autosampler from Hanson Research (Chatsworth, CA) was used to withdraw 5 ml aliquots through a 10-μm HDPE filter from SEAL Analytical (Mequon, WI).

2.3. HPLC method

An HPLC method with UV detection was selected because of its ability to separate cetirizine and pseudoephedrine from each other and from the tablet excipients. The reversed-phase HPLC procedure utilized a Zorbax® StableBond SB-CN column (5 μm; 15 cm × 4.6 mm i.d.) from Agilent Technologies (Palo Alto, CA) and UV detection at 214 nm. The column temperature was maintained at 30 °C. The mobile phase of sodium phosphate (pH 6.5; 0.1 M)–methanol (1:1, v/v) also contained OSA (5 mM) as an ion-pairing agent. The flow rate was 1.0 ml/min, the injection volume was 10 μl, and the run time was 10 min. A combined standard solution containing cetirizine HCl and pseudoephedrine HCl at concentrations of 10 μg/ml and 0.12 mg/ml, respectively, was prepared in deionized water and used for quantitation. This solution contains 100% of the final, or "nominal," assay concentration of cetirizine HCl (i.e., 10 mg into 1000 ml of the dissolution medium) and 50% of the nomi-