Journal of Pharmaceutical and Biomedical Analysis 53 (2010) 745–750

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Reaction between drug substances and pharmaceutical excipients: Formation of esters between cetirizine and polyols

He Yu[a], Claus Cornett[b], Jesper Larsen[b], Steen Honoré Hansen[b,*]

[a] College of Pharmaceutical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, People's Republic of China
[b] Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 4 December 2009
Received in revised form 30 April 2010
Accepted 4 May 2010
Available online 9 May 2010

Keywords:
Cetirizine
Glycerine
Sorbitol
Drug–excipient interaction

ABSTRACT

Reactions between active drug substances and excipients are of interest in the drug formulation process and should also be considered in the following storage of final preparations.

Some excipients react more readily with certain chemical groups in drug substances and in the present paper the ester formation between a drug substance having a carboxylic acid moiety and some polyols are described. The drug substance cetirizine was chosen as the model substance as it is already marketed and used as a common drug for treatment of allergic reactions. Among the marketed products are oral solutions and oral drops containing excipients like sorbitol and glycerol.

It was found that the carboxylic acid cetirizine readily reacts with sorbitol and glycerol to form monoesters. At a temperature as low as 40 °C, more than 1% of the cetirizine content was transformed into a monoester within 1 week using concentrations similar to those used in marketed preparations. The kinetic studies of the reaction performed at 40, 60 and 80 °C also revealed that the esters were unstable and they degraded especially at higher temperatures.

Analysis of two marketed preparations having expiry dates in 2011 showed content of the cetirizine esters corresponding to a range from 0.1 to 0.3% of the declared cetirizine content.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Excipients are additives used for the production and dispensing of pharmaceuticals. Preferably, they should have no therapeutic value and also no chemical reactivity. But since many popular excipients such as sugar alcohols, organic acids like citric acid and the parabens have chemical functional groups, the reactions between various drug substances and such excipients, and even reactions between different excipients in the drug formulation, are possible. The reactions may take place in the solid state as well as in solution [1–3]. The results of reactions between the active drug substance and excipients may be a reduction in the concentration of the active component of the drug, but at the same time new impurities of unknown structure and biological activity will appear and in worst case this may lead to adverse effects [4]. It is, therefore, important to be aware of such possible reaction during the drug formulation process as well as during drug storage. Some reviews on the topic drug substance–excipient interactions may be consulted [5–8].

Cetirizine, a non-sedating long-term antiallergic agent acting through histamine H_1 receptor antagonism, is clinically used for the treatment of allergic rhinitis, urticaria and hay fever. It is marketed as a dihydrochloride salt as it contains a piperazine ring, but the carboxylate group in the molecular structure is also an active center [9]. Cetirizine is marketed as a racemate in tablets as well as in oral drops and in oral solutions. In the formulation of cetirizine oral liquid preparations, sugar alcohols such as sorbitol and glycerol are commonly used excipients with relatively high concentrations. Therefore, cetirizine has been chosen as a model substance for the study of a possible ester formation with polyols.

A test for related substances in cetirizine dihydrochloride can be found in the European Pharmacopoeia [10] and the analysis of the known impurities is also described in the literature [11]. In the latter paper marketed liquid preparations of cetirizine were analysed for well-known impurities, but also some unidentified peaks were found to be present in the HPLC chromatograms.

In the present paper the reactivity between cetirizine and sorbitol or glycerol has been studied in order to verify whether this acylation reaction between a carboxylic acid and a polyalcohol takes place. The reaction products between cetirizine and the polyols have been identified by mass spectrometry and the kinetics of the acylation reaction has also been studied by liquid chromatography–mass

* Corresponding author at: Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark. Tel.: +45 35336256; fax: +45 35336030.
E-mail address: shh@farma.ku.dk (S.H. Hansen).

0731-7085/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2010.05.001

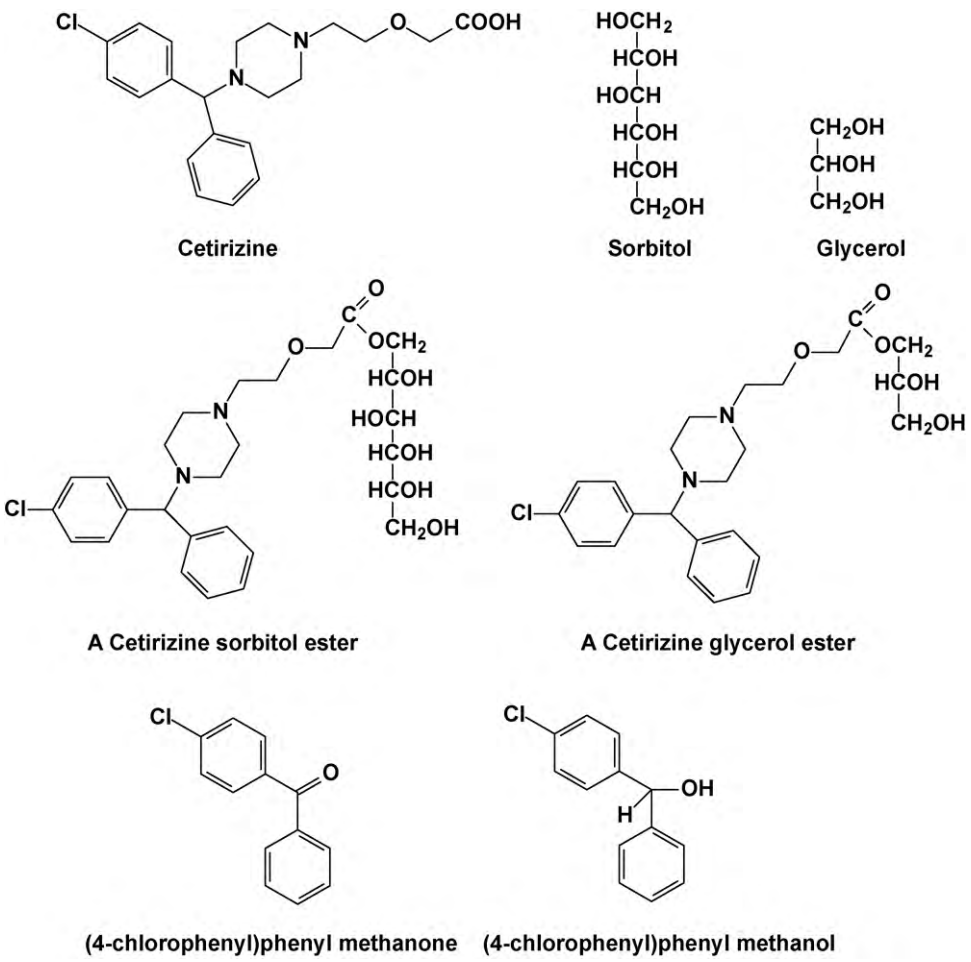

Fig. 1. Structures of cetirizine, sorbitol and glycerol as well as examples of the cetirizine esters and two of the degradation products.

spectrometry (HPLC–MS). Furthermore, two commercial liquid preparations of cetirizine have been analysed for possible content of the reaction products.

Chemical structures of compounds discussed in this paper are shown in Fig. 1.

2. Experimental

2.1. Chemicals and solvents

Cetirizine dihydrochloride and ammonium formate were from Sigma–Aldrich Chemie (Steinhem, Germany). Sorbitol was from Unikem (Copenhagen, Denmark). Glycerol and formic acid were from Merck (Darmstadt, Germany). Methanol (HPLC-grade) and acetonitrile (HPLC gradient-grade) were from VWR (Copenhagen, Denmark). Water was purified by using a Milli Q-water system (Millipore, Billerica, MA, USA).

2.2. Commercial liquid preparations of cetirizine

Two kinds of cetirizine liquid preparations were purchased from a local pharmacy in August 2009. One preparation was 1 mg/mL cetirizine oral solution which contains cetirizine dihydrochloride, 70% sorbitol, glycerol, propylene glycol, saccharin sodium, methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, banana aroma, sodium acetate and water. The expiry date was November 2011. The other preparation was 10 mg/mL cetirizine oral drops, which contains cetirizine dihydrochloride, glycerol, saccharin sodium, methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate, acetic acid, and water. The expiry date of this preparation was January 2011.

2.3. Instrumentation and chromatographic conditions

HPLC–MS. An Agilent Technology (Walbronn, Germany) G 1978A 1100/MSD LC/MS instrument equipped with a G1379A on-line degasser, a G1312A binary pump, a G1316A column oven, a G1367A WPALS autosampler and a G1315C photodiode array detector was used. A Phenomenex® Hypersil C18 ODS column (150 mm × 4.6 mm, 3 μm) was used in the isocratic mode with a mobile phase consisting of acetonitrile, methanol, 0.2 M ammonium formate pH 5.5 and water (25:10:15:50, v/v/v/v). The UV detection wavelength was set at 230 nm, the flow rate was 1 mL/min, and the column temperature was kept at 40 °C. The quadrupole mass spectrometer was operated with electrospray ionisation both in the positive mode and in the negative mode using the following parameters: capillary voltage 4000 V, nebulizer pressure 60 psig, drying gas flow 12 L/min, drying gas temperature 350 °C, vaporize temperature 150 °C, scan range from 180 to 800 amu.

GC/MS. An Agilent Technology GC/MS instrument consisting of a 6890N gas chromatograph and a 5973 MSD mass selective detector was used. Injection volume was 0.2 μL and a split ratio of 1:400 was used. Separation was achieved on an Agilent HP-5MS column with the dimensions 0.25 mm × 30 m and having a film thickness of 0.25 μm. Helium was used as the mobile phase at a flow rate of 1 mL/min. The inlet temperature was kept at 250 °C. An initial oven temperature of 100 °C was kept for 1 min and the temperature was

Download English Version:

https://daneshyari.com/en/article/1223347

Download Persian Version:

https://daneshyari.com/article/1223347

Daneshyari.com