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Short communication

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

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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.

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

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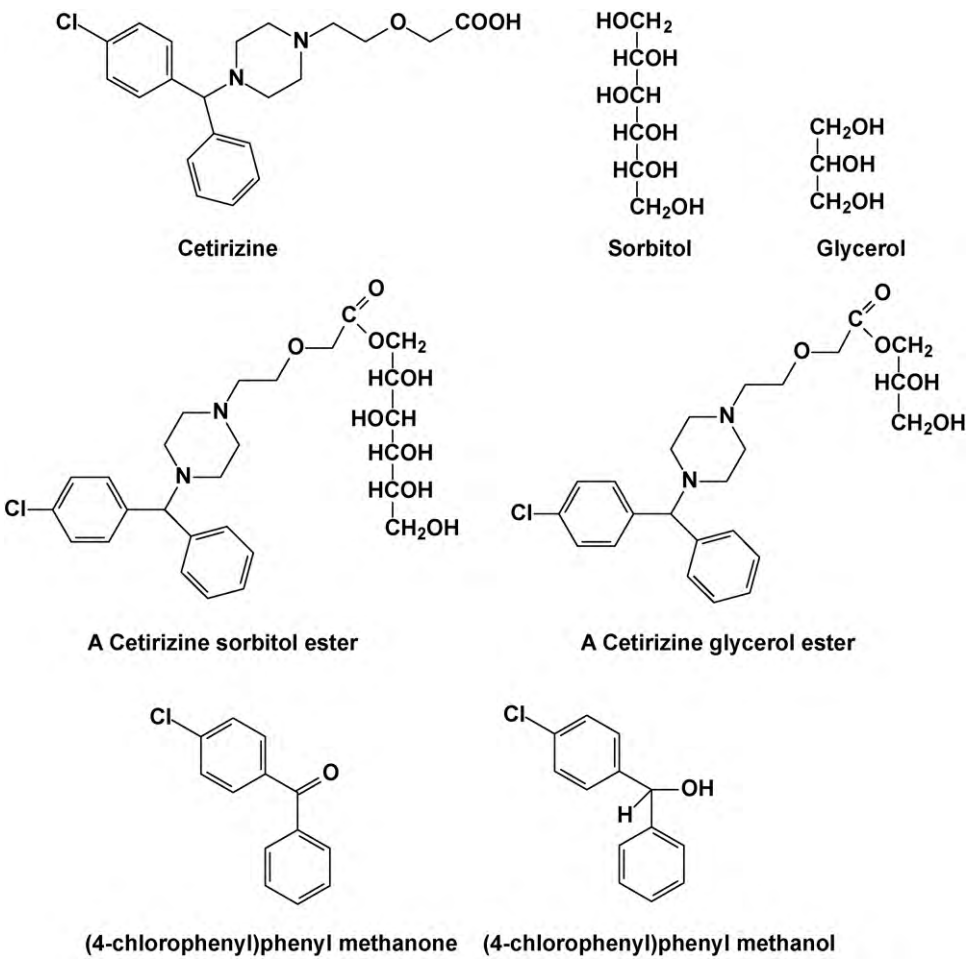

Fig. 1. Structures of cetirizine, sorbitol and glycerol as well as examples of the cetirizine esters and two of the degradation products.

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

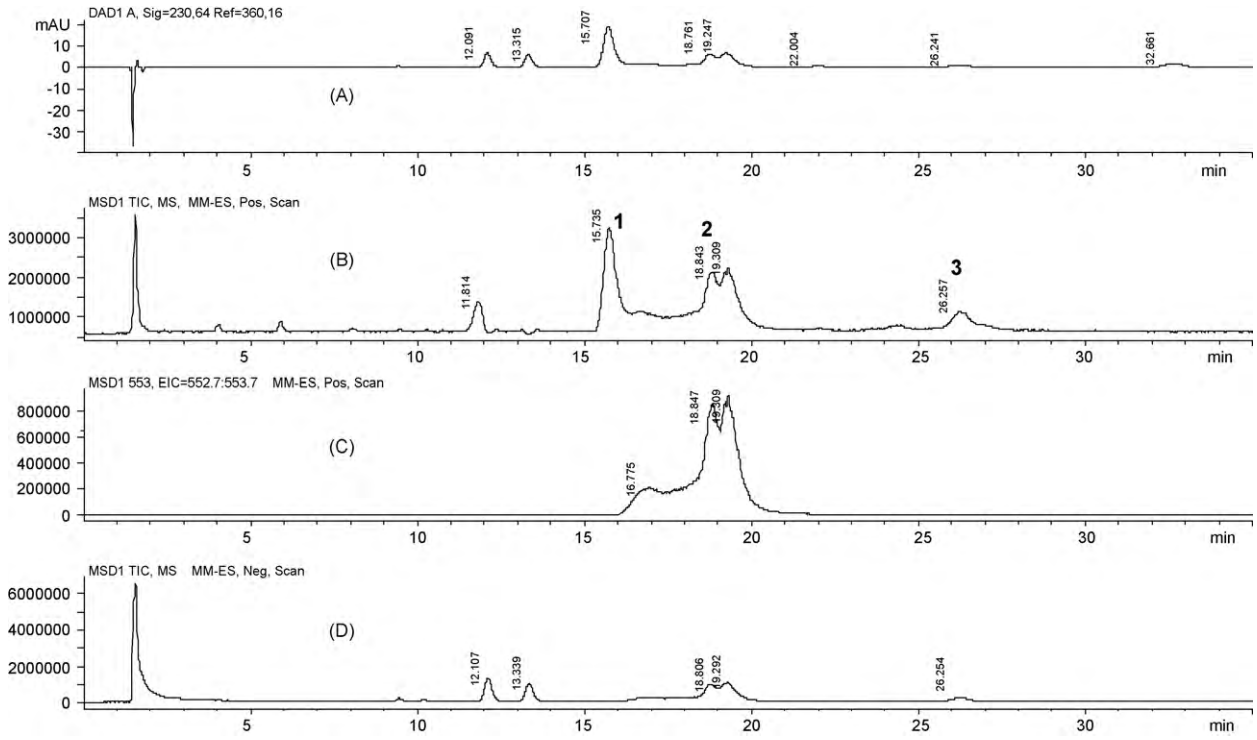

Fig. 2. Chromatograms of the reaction products of cetirizine with sorbitol heated at 100 °C for 48 h. Chromatographic conditions: Column: Phenomenex® Hypersil C18 ODS column (150 mm × 4.6 mm, 3 μm); mobile phase: acetonitrile, methanol, 0.2 M ammonium formate pH 5.5 and water (25:10:15:50, v/v/v/v); flow rate: 1 mL/min; detection: UV at 230 nm and MS (please see details in Section 2); column temperature: 40 °C. (A) UV trace at 230 nm; (B) total ion chromatogram in the positive mode; (C) extracted ion chromatogram (*m*/*z* 553) in the positive mode; (D) total ion chromatogram in the negative mode. (1) cetirizine; (2) sorbitol monoester of cetirizine; (3) dehydrated ester from cetirizine and sorbitol.

raised to 210 °C at 25 °C/min. Ionisation was performed at 70 eV and the scan range was 50–400 amu. Data treatment and library search was performed using ChemStation Agilent G 1701A software version D.01.02.

2.4. Sample preparation

Reaction mixtures or commercial drug preparations were diluted with water/acetonitrile (75:25, v/v) to a proper concen-

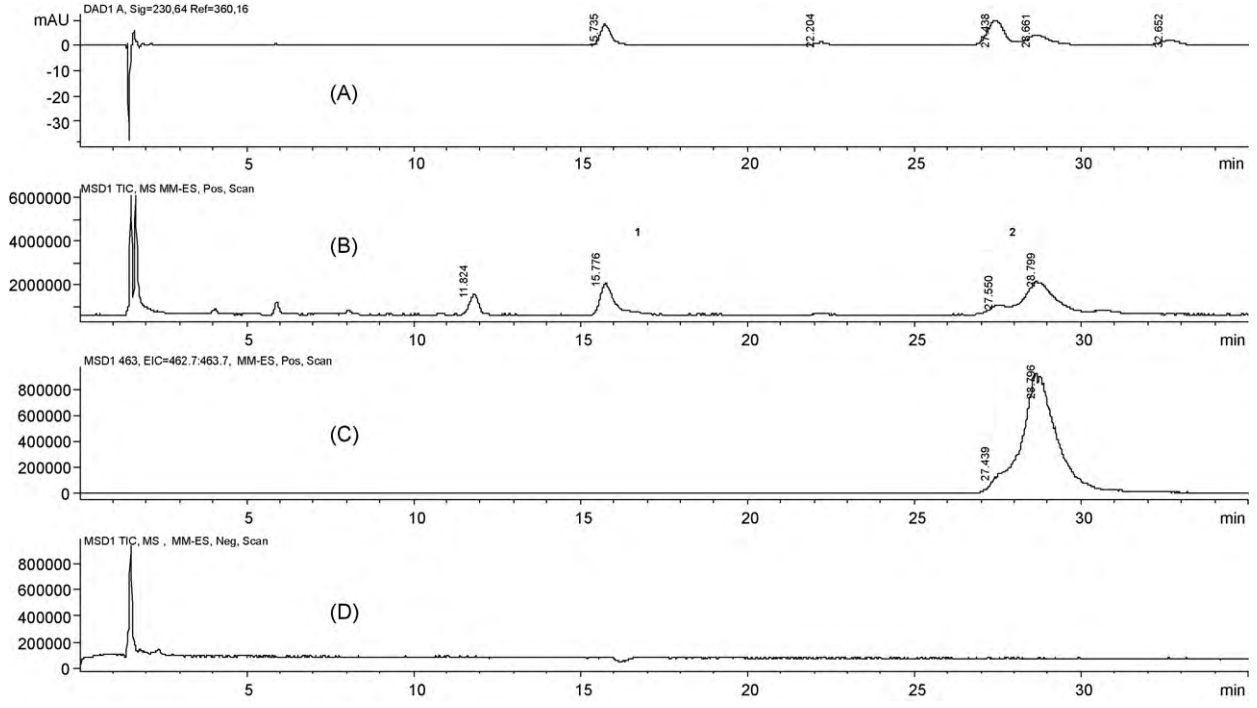

Fig. 3. Chromatograms of the reaction products of cetirizine with glycerol heated at 100 °C for 48 h. Chromatographic conditions as in Fig. 2. (A) UV trace at 230 nm; (B) total ion chromatogram in the positive mode; (C) extracted ion chromatogram (*m*/*z* 463) in the positive mode. (1) cetirizine; (2) glycerol monoester of cetirizine.

tration and filtered through 0.45 μm syringe filter (Millex®-HV Syringe Driven Filter Unit, Millipore, Ireland).

2.5. Generation of reaction products

In order to obtain an overview of possible reaction products of cetirizine and the excipients in question approximately 10 mg of cetirizine dihydrochloride was mixed with 100 mg sorbitol or 100 mg glycerol, respectively. After being added 20 μL of water, both mixtures were placed in glass vials which were sealed with Teflon-lined caps and then heated at 100 °C for 48 h.

2.6. Reaction kinetics

For the study of the reaction kinetics two solutions were prepared: (1) 500 mg cetirizine dihydrochloride and 10 g sorbitol were dissolved in 50.0 mL of water. (2) 500 mg cetirizine dihydrochloride and 5 mL glycerol were dissolved in 50.0 mL of water. Each 15 mL of the two solutions was stored at 40, 60 and 80 °C and samples were taken at 0, 1, 2, 3, 4 weeks, respectively.

2.7. Quantitative analysis

No reference compounds of the cetirizine esters were available. The quantitative measurements of the esters formed in the reaction kinetic studies were therefore performed using the reaction mixtures obtained as described under Section 2.5 as calibration standards. Assuming that the molar absorbance is the same for the esters as for the cetirizine the amount of esters in the reaction mixtures was determined. With the knowledge of the concentration of the esters in the reaction mixtures, these mixtures were then used as calibration standards for the analysis of samples in the reaction kinetic study as well as for the commercial liquid preparations.

3. Results and discussion

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. Such reaction may take place in solution as well as in the solid state.

The reaction rate is most often much higher in solution and therefore it is of special interest to look for possible interactions in liquid drug formulation of the type oral solutions and oral drops.

In the United States Pharmacopoeia-National Formulary (USP-NF 32-27) [12] a standard mixture of excipients is given for the formulation of oral solutions. This standard mixture contains the polyols sorbitol and glycerol as well as citric acid. The reactivity of citric acid towards 5-aminosalicylic acid and the beta-blocker carvedilol has earlier been shown [1,2] and in the present paper the reaction of the polyols toward cetirizine, a drug substance having a carboxylic acid group, is described.

3.1. Identification of reaction products

LC/MS was used to identify reaction products between cetirizine and the polyalcohols. As illustrated in Figs. 2 and 3 monoesters were formed between cetirizine and sorbitol or glycerol in the reaction mixtures stored at 100 °C for 48 h, but also other reaction or degradation products of cetirizine can be observed. The *m*/*z* ratio 553 corresponds to the pseudo molecular ion (the protonated molecule, $[M+H]^+$) of the sorbitol monoester of cetirizine and a complex, broad signal was observed between 16 and 20 min. This is probably due to the possible formation of a number of isomers of this ester. The number of possible isomers is high as a number of positional isomers all present as diastereomers are formed when the racemic cetirizine reacts with the sorbitol having 4 asymmetric carbon atoms. The extracted pseudo molecular ion with *m*/*z* ratio 463 shown in Fig. 3 corresponds to the glycerol monoester of cetirizine. Although glycerol itself does not have a chiral center diastereomers are formed when the racemic cetirizine reacts with the terminal hydroxyl group of glycerol which again gives rise to more than one peak in the chromatogram.

Besides the monoester generated from cetirizine and sorbitol ($[M+H]^+ = 553$), a degradation product of the ester where water has been eliminated ($[M+H]^+ = 535$) was also observed ($t_R = 26$ min, Fig. 2B). The elimination of water has to take place in the sorbitol part of the molecule, but the structure of this degradation product was not further investigated. A corresponding dehydration product of the ester formed between cetirizine and glycerol was not observed. A number of other reaction/degradation products were observed in the reaction mixtures between cetirizine and the polyols. A product with $[M+H]^+ = 569$ corresponds to an oxidation product of the sorbitol ester and two products with $[M+H]^+ = 405$ and $[M+H]^+ = 421$ correspond to mono and dioxidation of cetirizine, respectively. The oxidation may take place either on the nitrogen atoms in cetirizine forming N-oxides or more likely at the doubly benzylic carbon in the cetirizine molecule. The latter theory is consistent with the degradation products identified below. The oxidation products were not further investigated as the primary focus of the present paper is the formation of esters of cetirizine. Besides the ester formation it was observed that the aqueous solutions of cetirizine mixed with sorbitol or glycerol became opaque after being stored at 60 and 80 °C for 1 week, and with time a brownish oily matter precipitated. This coloured precipitate from the reaction mixtures did not ionize using electro spray ionisation – neither in the positive ionisation mode nor in the negative. The precipitate was therefore analysed by GC–MS where it showed the presence of two peaks. The peaks were identified by library search to be (4-chlorophenyl)phenyl methanone and (4-chlorophenyl)phenyl methanol (Fig. 1).

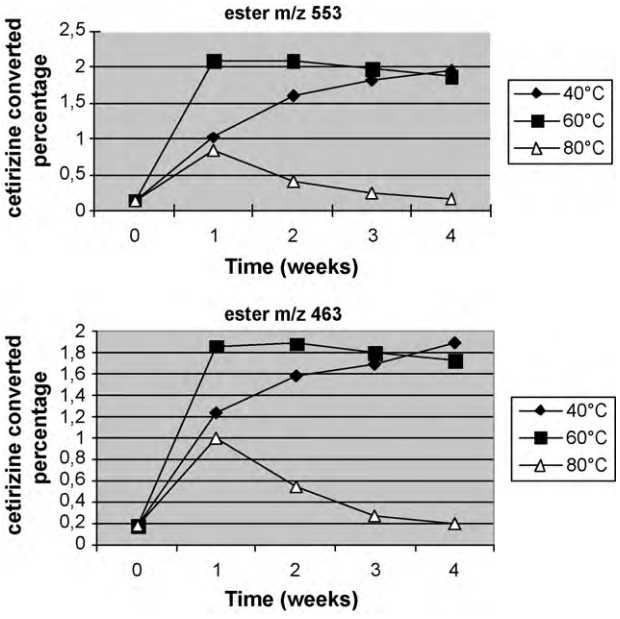

Fig. 4. Formation of the esters in aqueous solution. (A) The monoester formed between cetirizine and sorbitol (*m*/*z* 553); (B) the monoester formed between cetirizine and glycerol (*m*/*z* 463).

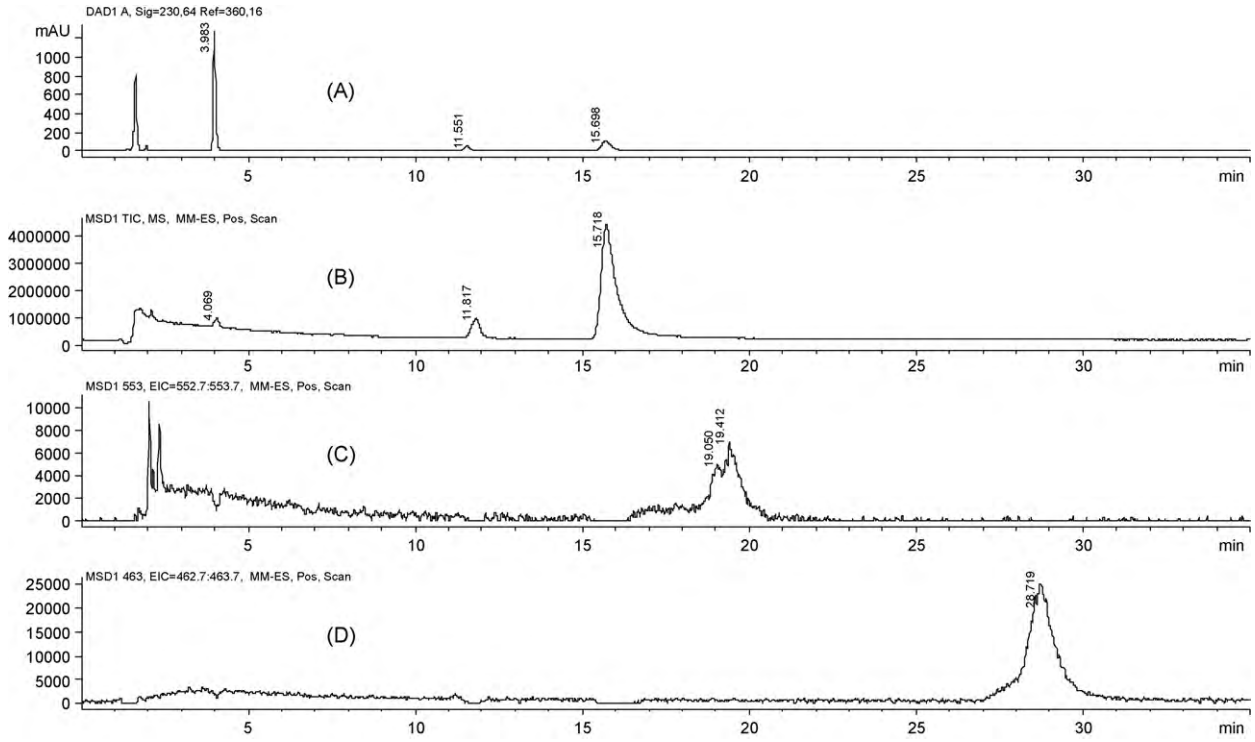

Fig. 5. Chromatograms of the commercial liquid preparations of cetirizine. Chromatographic conditions as in Fig. 2. (A) UV trace of 1 mg/mL cetirizine oral solution at 230 nm; (B) total ion chromatogram of 1 mg/mL cetirizine oral solution in the positive mode; (C) extracted ion chromatogram (*m*/*z* 553) of 1 mg/mL cetirizine oral solution in the positive mode; (D) extracted ion chromatogram (*m*/*z* 463) of 1 mg/mL cetirizine oral solution in the positive mode.

3.2. Study of the reaction kinetics

The samples prepared for the study of the reaction kinetics were stored at 40, 60 and 80 °C for a period of 4 weeks. All samples were analysed every week by LC/MS. Assuming that the molar absorptivity of the ester is the same as that of cetirizine, the conversion percentage of cetirizine into ester was calculated by the peak area of the UV chromatogram obtained with the reaction mixtures heated at 100 °C for 48 h (Figs. 2 and 3). These reaction mixtures were then used at different concentrations as calibration standards for cetirizine esters when analysing the samples from the reaction kinetic study. LC–MS was used for the quantification of the content of esters formed in the kinetic study in order to be able to make quantification at the low concentrations in the beginning of the study. The content of the esters were calculated (Fig. 4) using the extracted ion chromatograms.

Fig. 4 shows that the reaction rate increases with temperature but it is obvious that the formed esters are unstable and are degraded into other products especially at higher temperatures. It may be deduced from the figure that the temperature plays a key role in the formation and degradation of cetirizine esters as the formation of esters increased with time at 40 °C, and within 1 week about 1% of cetirizine was converted into polyol esters. But at 60 °C and particularly at 80 °C, ester content increased initially but was then reduced. The decrease coincided with the change in appearance of the solutions, so the decreasing content of the esters probably was related to the formation of the precipitate.

3.3. Analysis of the commercial liquid preparations

Two commercial liquid preparations of cetirizine were analysed (Fig. 5) for the possible content of sorbitol or glycerol esters of cetirizine. The glycerol ester of cetirizine was found in both formulations, while the sorbitol monoesters of cetirizine were only found in the oral solution. This is what could be expected from the knowledge of the ingredients of the preparations. The conversion percentage of cetirizine into the ester was estimated using the peak area of the extracted ion chromatogram as shown in Fig. 5 to be 0.07% of the sorbitol ester and 0.12% of the glycerol ester in the oral solution (1 mg/mL). In the oral drops (10 mg/mL) which did not contain sorbitol only the glycerol ester was found at a concentration level corresponding to 0.3% of cetirizine.

4. Conclusion

It has been shown that the drug substance cetirizine reacts with sorbitol and glycerol to form monoesters. The reaction readily takes place in solution and in a model experiment performed at 40 °C about 1% of cetirizine had reacted within a week.

The monoesters of cetirizine were also found to be present in marketed liquid drug preparations in concentrations corresponding to 0.1–0.3% of the cetirizine content.

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