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Kinetics of degradation of quinapril hydrochloride in tablets

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Received October 17, 2002, accepted October 28, 2002

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Pharmazie 58: 249–251 (2003)

The effect of temperature and of humidity on the stability of quinapril hydrochloride (QHCl) in tablets as well as on the durability of the degradation process was investigated. The investigation has been performed by means of the "enhanced ageing" test (in the temperature range from 383 to 333 K, at a relative humidity between and 76%). From the results of the study it follows that QHCl in tablets undergoes decomposition according to a first order reaction model. The activation energies as well as enthalpy and entropy (for temperature 298 K) have also been determined. It is concluded that the decomposition of QHCl in tablets proceeds by way of hydrolysis of the ester group and an intramolecular cyclization.

1. Introduction

Quinapril hydrochloride (QHCl) is a synthethic inhibitor of the angiotensine converting enzyme (I-ACE). In therapy, it is used in the form of ethyl quinaprilate. The range of indications for QHCl includes chronic circulatory insufficiency, idiopathic and renal arterial hypertension, ischemic heart disease (particularly following myocardial infarction), prevention of arteriosclerosis, diabetic nephropathy. The use of QHCl may be particularly indicated in cases, in which other I-ACE have failed to exert a therapeutic effect, which may be due to a lesser tissue affinity [1–4].

Earlier kinetic studies have shown, that on storage, QHCl undergoes intramolecular cyclization with release of a water molecule. Its ester bond is readily hydrolyzed [5]. One of the most useful analytical methods for determination of QHCl in pharmaceutical preparations is HPLC [6–9], but other methods such as capillary electrophoresis CE [10], derivative UV spectroscopy method [7] have been used as an alternative. The available literature lacks any data on the kinetics and mechanism of degradation processes occurring in pharmaceutical preparations of QHCl (tablets).

The main purpose of this study was to establish the effect of temperature and humidity on the stability of QHCl in the presence of adjuvant substances typically used in the preparation of tablets, to determine the kinetic equations describing the concentration changes of QHCl in tablets as a function of time, to determine the velocity constants of decomposition of QHCl in tablets and the thermodynamic parameters of the reaction. The study was performed by means of a "stress" test (in the temperature range from 383 to 333 K, at a relative humidity between 0 and 76%). It was necessary to develop a selective analytical method to determine concentration changes of QHCl in the presence of its decomposition products and excipients.

2. Investigations and results

Chromatography was carried out on Hypersil MOS (250 $\times$ 4 mm; 5 μm particle size). The mobile phase consisted of phosphate buffer pH 2.0 (0.001 mol/l) and acetonitrile (1 : 1 v/v). The flow rate was 1 ml/min. The column effluent was monitored at 220 nm. All assays were performed at ambient temperature.

Linearity was determined as the ratio of the peak height and concentration of QHCl ranging from 0.04 mg/ml to 0.40 mg/ml. The parameters of regression were: $y = (17.46 \pm 0.33) \cdot x$; standard deviation 0.15; they were all statistically nonsignificant, the coefficient of linear correlation was equal to 0.999. The values of $\pm\Delta a$ were computed for $f = n - 1$ degrees of freedom, with $\alpha = 0.05$.

The developed method was selective towards the degradation products and internal standard (lovastatine). The following retention times for the tested substances were established: approx. 5 min for QHCl, approx. 6 min for the internal standard and approx. 3 and 4 min respectively for the degradation products: quinaprilate and derivative of QHCl – diketopiperazine (Fig. 1).

Precision was determined for 8 independent samples (variation coefficient 1.13%, standard deviation 0.0062).

During the degradation of QHCl in tablets occurring in an atmosphere of dry air over a time period from $t_0 \rightarrow t_\infty$, the value of $P_{QHCl}/P_{i.s.}$ decreased from P_0 to 0. Straight-line semilogarithmic diagrams were obtained:

$$\ln c_t = \ln c_0 - kt$$

where: c_t and c_0 = content of QHCl in the tablet (mg/tablet), at the respective times $t = 0$ and t; k = the observed rate constant for the first order reaction (s^{-1}). Parameters for this equation were computed by means of a method using minimal squares, to be found in the Microsoft Excel computer program. The slopes of the above diagrams correspond to the velocity constants of the first order reaction with a minus sign (Table).

Table: Thermodynamic parameters of the degradation of QHCl in tablets

Eq.	T (K)	$(k \pm \Delta k)\ 10^7\ s^{-1}$	n	Parameters	
				equations ln k = (1/T)	thermodynamic
RH = 76%					
Initial concentration of CHQ in the tablet = 6.128 mg					
				$a = -10530 \pm 2757$	$E_a = (87.6 \pm 15)$ [kJ/mol]
1.	343	$20.3 \pm .2.6$	9	$S_a = 641$	$\Delta H^{\neq} = (90.0 \pm 25)$ [kJ/mol]
2.	353	43.3 ± 5.0	10	$b = 17.56 \pm 7.8$	$\Delta S^{\neq} = (-98.9 \pm 180)$ [J/(Kmol)]
3.	358	76.0 ± 1.6	8	$S_b = 1.84$	
4.	363	107.1 ± 11.2	11	$r = -0.996$	
	298	$1.898 \cdot 10^{-8}$ *			
Initial concentration of CHQ in the tablet = 10.72 mg					
				$a = -10553 \pm 3213$	$E_a = (87.7 \pm 26)$ [kJ/mol]
1.	343	20.8 ± 2.1	8	$S_a = 746$	$\Delta H^{\neq} = (85.3 \pm 29)$ [kJ/mol]
2.	353	42.8 ± 3.5	9	$b = 17.64 \pm 9.1$	$\Delta S^{\neq} = (-98.3 \pm 169)$ [J/(Kmol)]
3.	358	75.6 ± 1.8	11	$S_b = 2{,}06$	
4.	363	111.1 ± 12.0	9	$r = -0.995$	
	298	$1.900 \cdot 10^{-8}$ *			
Initial concentration of CHQ in the tablet = 20.77 mg					
				$a = -10518 \pm 1986$	$E_a = (87.5 \pm 11)$ [kJ/mol]
1.	343	19.8 ± 6.1	10	$S_a = 461$	$\Delta H^{\neq} = (85.0 \pm 13)$ [kJ/mol]
2.	353	42.9 ± 4.3	9	$b = 17.50 \pm 5.6$	$\Delta S^{\neq} = (-99.4 \pm 198)$ [J/(Kmol)]
3.	358	70.0 ± 10.9	12	$S_b = 1.30$	
4.	363	107.0 ± 12.2	8	$r = -0.998$	
5.	298	$1.861 \cdot 10^{-8}$ *			
RH ~ 0%					
Initial concentration of CHQ in the tablet = 6.128 mg					
				$a = -16184 \pm 5667$	$E_a = (134 \pm 47)$ [kJ/mol]
1.	363	0.701 ± 0.11	11	$S_a = 1317$	$\Delta H^{\neq} = (132 \pm 50)$ [kJ/mol]
2.	373	2.60 ± 0.15	9	$b = 28.89 \pm 15.2$	$\Delta S^{\neq} = (-4.7 \pm 118)$ [J/(Kmol)]
3.	378	4.96 ± 0.33	11	$S_b = 3.52$	
4.	383	6.72 ± 0.44	7	$r = -0.993$	
5.	298	$4.576 \cdot 10^{-12}$ *			
Initial concentration of CHQ in the tablet = 10.72 mg					
				$a = -16178 \pm 5888$	$E_a = (135 \pm 48)$ [kJ/mol]
1.	363	0.700 ± 0.12	12	$S_a = 1368$	$\Delta H^{\neq} = (132 \pm 51)$ [kJ/mol]
2.	373	2.66 ± 0.23	8	$b = 28.16 \pm 15.7$	$\Delta S^{\neq} = (-10.8 \pm 114)$ [J/(Kmol)]
3.	378	4.96 ± 0.28	12	$S_b = 3.65$	
4.	383	6.72 ± 0.40	8	$r = -0.994$	
5.	298	$4.619 \cdot 10^{-12}$ *			
Initial concentration of CHQ in the tablet = 20.77 mg					
				$a = -16196 \pm 5765$	$E_a = (135 \pm 48)$ [kJ/mol]
1.	363	0.702 ± 0.44	11	$S_a = 1339$	$\Delta H^{\neq} = (132 \pm 40)$ [kJ/mol]
2.	373	2.67 ± 0.19	10	$b = 28.21 \pm 5.4$	$\Delta S^{\neq} = (-10.4 \pm 116)$ [J/(Kmol)]
3.	378	4.96 ± 0.29	8	$S_b = 3.58$	
4.	383	6.77 ± 0.38	9	$r = -0.993$	
5.	298	$4.582 \cdot 10^{-12}$ *			

* the respective values of reaction velocity constants extrapolated from the Arrhenius equation for a temp. 293 K

Under humid conditions the degradation of QHCl proceeds as a two-stage reaction (Fig. 2). Velocity constants of reactions proceeding under these conditions were calculated from the following equations:

$$\ln c_t' = \ln c_0' - k't_2 \quad \text{and} \quad \ln (c - c')_t = \ln (c - c')_0 - kt_1$$

where: c_0', $(c - c')_0$ – initial concentration of QHCl in the tablet at time t_0; c'_t, concentration of QHCl in the tablet at time t_2, $(c - c')_t$ concentration of QHCl in the tablet at time t_1.

Parameters for this equation were computed by means of a method using minimal squares, to be found in the Microsoft Excel computer program.

The sloes of the above diagrams correspond to the velocity constants of the first order reaction with a minus sign (Table).

Activation energies as well as enthalpy and entropy (for 298 K) values for the degradation of QHCl occurring in an anhydrous atmosphere (RH = 0%) and humid air conditions (RH = 76%) were calculated (Table).

3. Discussion

The comparison of chromatograms of standard samples of quinapril, quinaprilate and of a diketopiperazine derative with chromatograms of degradation products of QHCl (in tablet form) has shown that QHCl is degraded by hydrolysis of the ester group in a dry atmosphere or in a humid environment (RH = 76%) (Fig. 1). QHCl in raw material in an anhydrous atmosphere decomposes only by way of intermolecular cyclization [5]. Hydrolysis of the ester group of QHCl in tablets occurring in dry air may be ren-

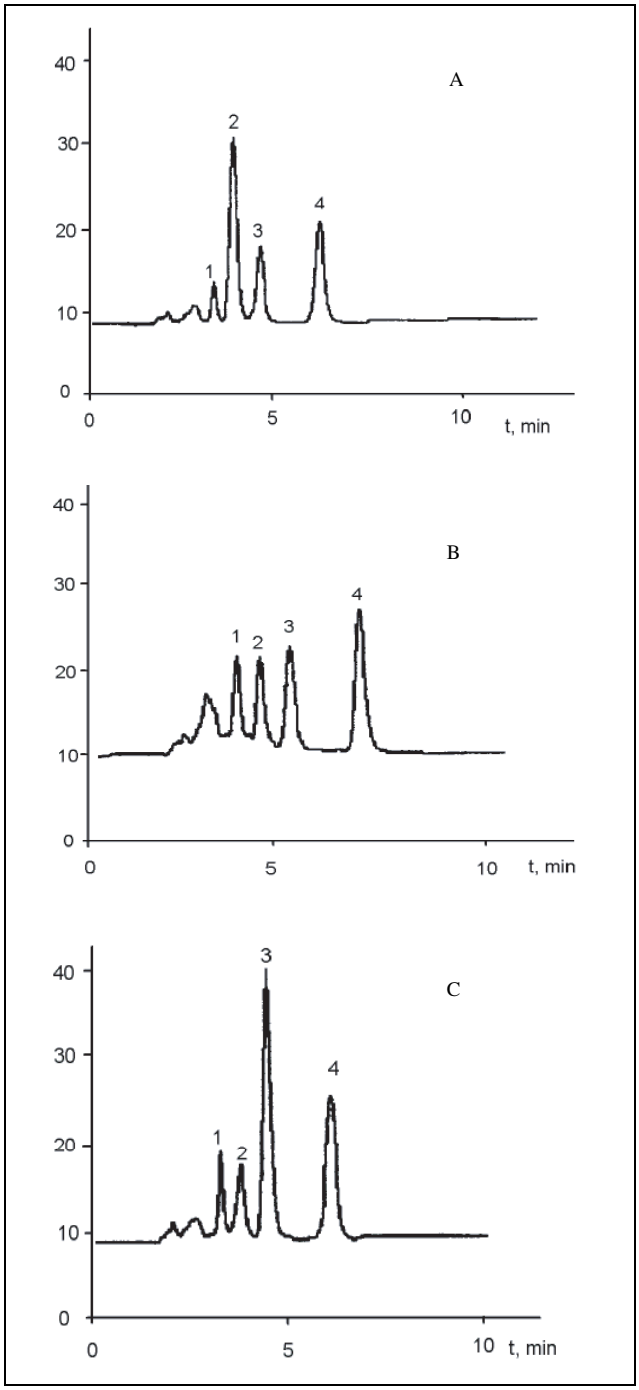

Fig. 1: HPLC-chromatogram: of standard solutions [A], of an extract of a 10 mg QHCl tablet subjected prior to extraction to the degradation process in solid phase at 353 K and RH = 76% for 100 h [B] and of an extract of tablets subjected to degradation in solid state at 373 K and RH = 0% for 60 h [C]. 1: Quinaprilate, 2: Diketopiperazine derivative, 3: Quinapril hydrochloride, 4: Lovastatine (internal standard)

dered possible by the release of a water molecule during cyclization of QHCl, which, when retained by the tablets mass, can create conditions for a hydrolytic esterolysis.

The decomposition of QHCl in tablets proceeds according to a first order reaction model, but in the presence of humidity the degradation is brought about by a two-stage reaction. The reaction velocity constants are independent of the dose of QHCl in the tablet.

The thermodynamic parameters of QHCl degradation in tablets in dry air are higher than those observed in a humid atmosphere.

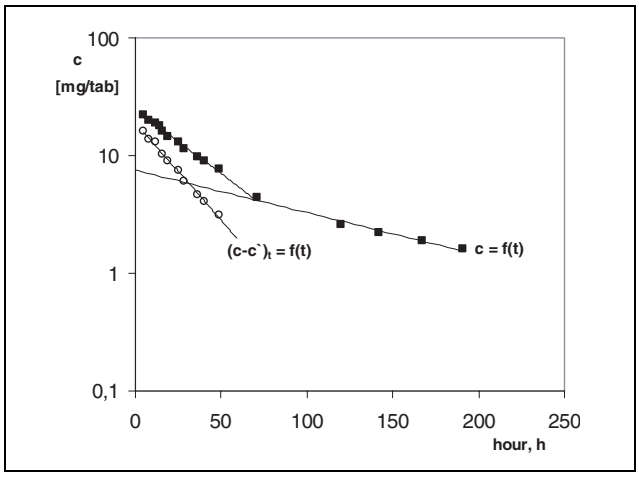

Fig. 2: Semilogarithmic plot c = f(t) for decomposition of QHCl in solid phase in relative humidity RH = 76,4%

4. Experimental

4.1. Material and reagents

Quinapril hydrochloride (QHCl), quinaprilate, diketopiperazine derivative and lovastatine were derived from P.P.H.U. Biofarm Ltd. Each tablet was claimed to contain 5 mg or 10 mg or 20 mg of quinapril hydrochloride and lactose, hydroxypropylcellulose, hydroxypropylmethylcellulose, macrogol 400, crospovidon, magnesium stearate, as excipients. All chemicals were analytical grade reagents.

4.2. Methods

Chromatography was carried out on Hypersil MOS (250 × 4 mm, 5 μm particle size). The mobile phase consisted of phosphate buffer (0.001 mol/l), pH 2.0 and acetonitrile (1 : 1 v/v). The flow rate was 1 ml/min. The column effluent was monitored at 220 nm. All assays were performed at ambient temperature.

4.3. Kinetic procedure

In order to establish the mechanism of degradation of CHQ – in tablet from, a test of "enhanced ageing" was applied.

Tablets containing 5, 10 and 20 mg of CHQ were placed into 5 ml glass vials. For determination of stability of the preparation in an atmosphere of dry air, the respective vials immersed in a sand both were transferred into heat chambers and kept there at the following temperatures: 383 K, 373 K, 363 K and 358 K. Vials containing tablets of CHQ designated for assessment of the following temperatures: 363 K, 358 K, 353 K and 343 K. The desiccators contained a saturated inorganic salt solution (NaCl) that capable of maintaining the required relative humidity (~76%).

At respective time intervals, depending on the degradation velocity, that tablets were withdraw from the chambers, and after cooling to room temperature – they were transferred into measuring flask (100 ml) and 3.0 ml of water added to the flasks, their contents were shaken until the tablet disintegrated. Then, 22.0 ml of methanol were added and the contents were extracted by means of shaking for 15 min. The extracts were then filtered, and the obtained filtrates were analyzed by HPLC. The evolving signals were recorded over a time span from 2 to 10 min.

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