Acta Poloniae Pharmaceutica – Drug Research, Vol. 67 No. 1 pp. 99–102, 2010 ISSN 0001-6837
Polish Pharmaceutical Society

INFLUENCE OF HUMIDITY AND HYDROXYPROPYL CELLULOSE, HYDROXYPROPYLMETHYL CELLULOSE, GLYCERYL BEHENATE OR MAGNESIUM STEARATE ON THE DEGRADATION KINETICS OF QUINAPRIL HYDROCHLORIDE IN SOLID PHASE

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Abstract: Catalytic effect of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, glyceryl behenate and magnesium stearate in the presence of 50.9% – 76.4% humidity at 318 K on stability of quinapril hydrochloride (QHCl) was examined by HPLC method. The differences in kinetic mechanism of degradation of QHCl were observed. The effect of humidity on QHCl stability in the presence of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, glyceryl behenate or magnesium stearate was linear and according to the equation $ln\ k_i = aRH\% + b$.

Keywords: quinapril hydrochloride, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, glyceryl behenate, magnesium stearate, stability, HPLC

Kinetic decomposition of a chemical compound can be influenced by external factors such as temperature, humidity, light, oxygen/air etc. Decomposition of biologically active substance in pharmaceutical formulation can be additionally affected by its reactivity with excipients used during pharmaceutical formulation production process (1-4).

Quinapril hydrochloride (QHCl; Fig. 1) belongs to the class of drugs called angiotensin converting enzyme inhibitors and is used as a first line treatment of hypertension. The drug is also used for treating coronary heart disease, arteriosclerosis, diabetic nephropathy and many other cardiovascular system diseases (5-7). The molecule of QHCl (Fig. 1) contains an ester group that easily undergoes hydrolysis in an alkaline medium, while in an acidic and neutral media QHCl undergoes intramolecular cyclization like lisinopril (8-11).

The literature gives no information about the effect of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, glyceryl behenate and magnesium stearate and the air humidity on the stability of QHCl, which is an important problem from the QHCl tablets technology point of view [12-14]. The aim of this work was to determine the influence of relative air humidity, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, glyceryl behenate and magnesium stearate on the chemical stability of QHCl in solid phase at 318 K. The measurements were performed in the humidity range from 50.9% to 76.4%, by a HPLC method.

EXPERIMENTAL

Materials and reagents

Quinapril hydrochloride and benazepril hydrochloride were supplied from the BIOFARM and NOVARTIS, respectively. Hydroxypropyl cel-

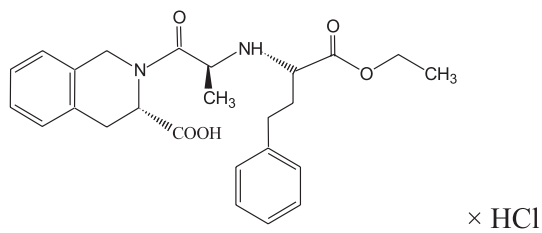

Figure 1. Chemical structure of quinapril hydrochloride.

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lulose (HPC), hydroxypropylmethyl celullose (HPMC), glyceryl behenate (GB) and magnesium stearate (ST) were purchased from BIOFARM. The other chemicals substances were purchased from Sigma-Aldrich. Acetonitrile and methanol (both, HPLC grade) were purchased from Merck.

HPLC methodology

The liquid chromatograph Shimadzu (pump LC-6A, UV-VIS detector set to 220 nm, SPO-6AV, integrator c – RGA) was used equipped with a Hypersil MOS column (250 × 4 mm; 5 μm particle size). Typical operation conditions were as follows: the flow rate 1.5 mL/min, the injection volume 100 μL and the wavelength 220 nm.

The mobile phase consisted of phosphate buffer pH 2.0 (0.001 mol/L) and acetonitrile (1:1, v/v). After mixing, the mobile phase was filtered through a sintered-glass filter and degassed according to the literature (10).

Solutions

Aqueous phosphate buffer was prepared by dissolving 0.0681 g of potassium dihydrogen phosphate (KH_2PO_4) in 450 mL of bidistilled water, adjusted to pH 2.0 with phosphoric acid (85%) and made up to 500.0 mL with water.

Stock solutions of QHCl (0.4 mg mL^{-1}) were prepared in methanol. The stability of the QHCl standard solutions were checked over 96 h at ambient conditions, and demonstrated no change in its concentrations (± 1%).

Synthetic model mixtures

The synthetic model mixtures were prepared in a mortar by slow addition of approximately 1.00 g QHCl to each 1.00 g of HPC, HPMC, GB or ST and blended until became homogeneous.

Symbols of drug – excipient mixtures: QHCl with hydroxypropyl cellulose – QHPMC, QHCl with hydroxypropylmethyl cellulose – QHMC, QHCl with magnesium stearate – QST and QHCl with glyceryl behenate – QBH.

Kinetic conditions

Portions of 20.00 mg of the synthetic model mixtures (QHPC, QHPMC, QST, QBH) were weighed and placed in glass vials introduced into dessicators, containing saturated aqueous solutions of appropriate inorganic salts, which ensured the desired relative humidity of the ambient air (sodium chloride RH = 76.4%; sodium nitrate RH = 66.6%, potassium iodide RH = 60.9%, sodium bromide RH = 50.9%) and inserted in heat chambers set at 318 K. Each series comprised of 15-20 samples. At suitable time intervals, the glass vials were withdrawn, cooled to the room temperature and its content dissolved in methanol. The obtained solutions were quantitatively transferred into measuring flasks, filled up to 25.0 mL with methanol and filtered (solution A). To 1.0 mL of the solution A 0.5 mL of internal standard solution (IS, benazepril hydrochloride) was added (solution A_i).

Next, the standard solution of QHCl in methanol (concentration 0.4 mg mL^{-1}) was prepared (solution B). The chromatograms were interpreted as the ratio: $P_{QHCl}/P_{IS} = f(t)$, where P_{QHCl} is the peak area of QHCl and P_{IS} represents the peak area of IS.

RESULTS AND DISCUSSION

Concentration changes of QHCl in the synthetic model mixtures under the above described conditions were analyzed by HPLC which was validated by the determination of:

selectivity – the applied method is selective towards the QHCl (t_R ~ 6 min), its degradation of products (t_R = 4 min), HPC, HPMC, ST, BH (no signal observed) and internal standard (t_R = 9 min);

linearity – the parameters of regression were as follows: ($y = ac = 17.50 \pm 0.33$) × c; b – was statistically insignificant, high values of the correlation coefficient (r) about 0.9998 indicated a good linearity of the HPLC method;

precision – low values of the relative standard deviation (about 1.0%) indicated a good precision of the HPLC method;

detection limit (LOD) and quantification limit (LOQ) – 0.005 mg/mL and 0.01 mg/mL, respectively, were calculated.

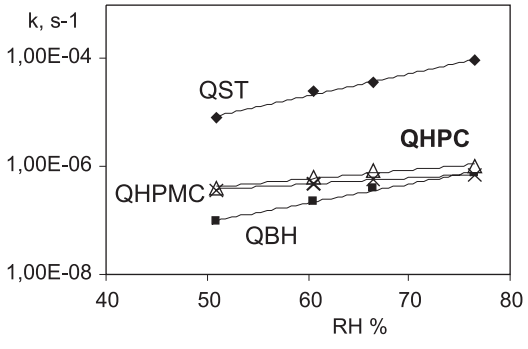
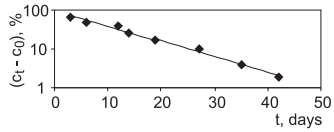
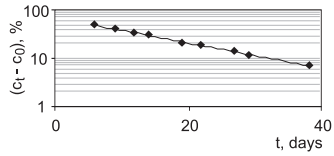
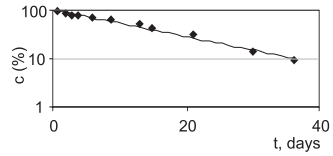
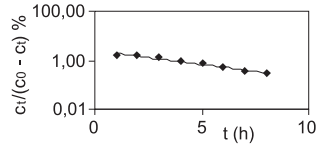


Figure 2. Plots of the relationship $ln\ k_i = f(RH\%)$ characterising the degradation reaction of QHCl in the presence of hydroxypropyl cellulose (**QHPC**), hydroxypropylmethyl cellulose (**QHPMC**), glyceryl behenate (**QBH**) or magnesium stearate (**QST**), at 318 K and relative humidities 50.9 – 76.4%

Table 1. Catalytic effects in solid phase of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, glyceryl behenate and magnesium stearate on stability of quinapril hydrochloride at 318 K and 76.4% relative humidity

QHCl in the presence of hydroxypropyl cellulose *Kinetic model:* reversible first-order *Kinetic equation:* $\ln (c_t - c_e) = \ln (c_0 - c_e) - k\,t$	
	$ln\ k_i = a\ (RH\%) + b =$ $(0.03797 \pm 0.016) \cdot RH\% - (16.61 \pm 0.62)$ $SD_a = 0.0038$; $SD_b = 0.24$; $r = 0.991$
QHCl in the presence of hydroxypropylmethyl cellulose	
Kinetic model: reversible first-order *Kinetic equation:* $\ln (c_t - c_e) = \ln (c_0 - c_e) - k\,t$	
	$ln\ k_i = a\ (RH\%) + b =$ $(0.02575 \pm 0.016) \cdot RH\% - (16.10 \pm 0.42)$ $SD_a = 0.0026$; $SD_b = 0.16$; $r = 0.990$
QHCl in the presence of gliceryl behenate	
Kinetic model: first-order *Kinetic equation:* $\ln c_t = \ln c_0 - k\,t$	
	$ln\ k_i = a\ (RH\%) + b =$ $(0.0712 \pm 0.011) \cdot RH\% - (20.25 \pm 0.76)$ $SD_a = 0.0037$; $SD_b = 0.24$; $r = 0.998$
QHCl in the presence of magnesium stearate	
Kinetic model: autocatalytic second-order *Kinetic equation:* $\ln c_t/(c_0 - c_t) = C + k\,t$	
	$ln\ k_i = a\ (RH\%) + b =$ $(0.0940 \pm 0.034) \cdot RH\% - (14.51 \pm 1.68)$ $SD_a = 0.0037$; $SD_b = 0.24$; $r = 0.990$

c_t, c_e and c_0 denote concentration of QHCl in synthetic mixture at time t, t_e (equilibrium time) and 0, respectively; C – represents a parameter of the lag time; k is the first-order rate constant; SD_a – standard deviation of slope a, SD_b – standard deviation of inercept *b*

The kinetic of degradation of QHCl in presence of HPC, HPMC, ST and BH

Determination of the rate constants

The concentration changes of QHCl in the presence of HMC and HPMC, at constant and different humidities, produced the linear relationship $\ln (c_t - c_e) = f(t)$. However, the decay of QHCl in presence of GB demonstrated straight line relationship $\ln c_t = f(t)$. The relationship $c_t = f(t)$ for change of QHCl in the presence of ST is characterized by sigmoidal curve. Semilogarithmic plots of the equation: $c_t/(c_0 - c_t) = f(t)$ were linear for the degradation of QHCl in the presence of ST (Table 1).

The effect of humidity

The influence of relative humidity on the stability of QHCl in the presence of excipients presented above is described by the equation $ln\ k_i = aRH\% + b$. The slope value describes the influence of relative humidity on the stability of the examined compound (Tab. 1 and Fig. 2).

CONCLUSION

HPC, HPMC, BG and ST influence the character of the kinetics of QHCl degradation. A linear relation was found between the rate constant of QHCl degradation in the presence of HPC, HPMC, ST, BG and the air relative humidity in the range 50.9 – 76.4% (Fig. 2). The influence of relative humidity on the QHCl degradation in the presence of HPC, HPMC, ST or BH differs, as indicated by various slopes of the line $ln\ k_i = a(RH\%) + b$ (Tab. 1). The least significant effect of the air relative humidity on the QHCl stability was observed in the presence of HPMC (slope a = 0.02575), whilst the most significant degradation of QHCl occurred in the presence of GB (slope a = 0.0712). The fastest degradation of QHCl was observed in the presence of magnesium stearate ($k = 1.564 \pm 0.06 \times 10^{-4}\ s^{-1}$), and the slowest degradation rate appeared in the presence of glyceryl behenate ($k = 5.41 \pm 0.30 \times 10^{-7}\ s^{-1}$) under the same conditions (Fig. 2).

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Received: 04. 08. 2009