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Stability of loperamide hydrochloride in aqueous solutions as determined by high performance liquid chromatography

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Summary

The stability of loperamide hydrochloride at 90 ± 0.2 °C in different pH solutions with various buffer species (acetate, phosphate and borate) at a constant buffer concentration of 0.1 M and ionic strength of 0.5 has been studied using a developed stability-indicating high-performance liquid chromatographic method. This analytical procedure shows a linear response range at concentrations of 2 to 10 μg/ml with a correlation coefficient greater than 0.99. The observed rate of degradation was found to follow apparent first order kinetics with respect to loperamide hydrochloride. The maximum stability of loperamide hydrochloride was shown to be at an approximate pH of 4.5. The catalytic effect of specific acid–base and water on the degradation of loperamide hydrochloride aqueous solution was expected; however, general acid–base catalysis from different buffer species is possible but needs to be studied further.

Introduction

Loperamide hydrochloride (Sigma Chemical Co., St. Louis, MO; Fig. 1), 4-[*p*-chlorophenyl]-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidine-butyramide hydrochloride, is a synthetic antidiarrheal agent. It inhibits peristaltic activity by a direct effect on the circular and longitudinal muscles of the intestinal wall to lower intestinal mobility and alter electrolyte movement through the bowel. It is indicated for the control and systematic relief of acute non-specific diarrhea and chronic diarrhea associated with inflammatory bowel disease. Solid and liquid dosage forms of loperamide hydrochloride (Imodium, Janssen Pharmaceutica Inc., Piscataway, NJ) are currently available on the market.

Over the years, loperamide hydrochloride has been assayed quantitatively by UV spectropho-

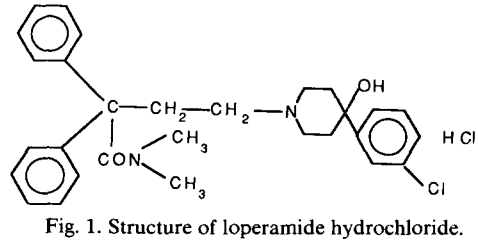

Fig. 1. Structure of loperamide hydrochloride.

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tometry (U.S. Pharmacopeia, 1985, Clarke, 1975) and colorimetry (The Extra Pharmacopeia, 1977). However, as yet, no information concerning a stability-indicating high-performance liquid chromatographic (HPLC) method for the determination of loperamide hydrochloride and its degradation products has been reported. The purposes of this investigation were to (1) develop a rapid, precise and reliable high-performance liquid chromatographic method which would show stability-indicating capability, and (2) study the pH-dependent stability of loperamide hydrochloride in aqueous solutions.

Materials and Methods

Kinetic studies

Nine buffer solutions of varying buffer species with a constant buffer concentration (0.1 M) and fixed ionic strength (0.5) were prepared at each specific pH (acetate buffer: pH 3.0, 4.0, 4.5 and 5.0; phosphate buffer: pH 5.5, 6.0 and 7.0; and borate buffer: pH 8.0 and 9.0). Sample solutions were prepared by dissolving loperamide hydrochloride in a suitable volume of the above buffer solutions to make 8 μg/ml. The ionic strength of these solutions was adjusted with potassium chloride. The solutions were sealed into type I glass ampules (2 ml, Wheaton Scientific, Millville, NJ) and stored in a dark oven (Model 18EM, GCA Corporation, Chicago, IL) maintained at 90 ± 0.2°C for up to 46 days. Samples were taken immediately after preparation and from the oven after 5, 17, 30 and 46 days of storage and immediately placed in a freezer (−20°C) until all samples for the 46 days had been collected. Before analysis, the samples were removed from the freezer, equilibrated to room temperature, and mixed in a vortex mixer (Super-Mixer, Lab-Line Instruments Inc., Melrose Park, IL). The pH value for each sample was checked (Orion 901 Microprocessor Ionalizer, Orion Research Inc., Cambridge, MA) to ensure no significant pH change at each designated sampling time compared to initial conditions. The concentration of loperamide hydrochloride was determined in triplicate by a stability-indicating reversed-phase HPLC method.

HPLC analysis

The HPLC consisted of a dual piston pump (Model 6000A, Waters Associates, Milford, MA), a dual UV absorbance detector (Model 440, Water Associates, Milford, MA) set at 201 nm, and a μ-Bondapak C_{18} column (3.9 mm × 30 cm with 10 μm packing, Waters Associates, Milford, MA). The mobile phase was a mixture (v/v) of methanol, 0.2 M phosphate buffer (pH 3.0) containing 0.005 M heptanesulfonic acid sodium salt and acetonitrile (12 : 10 : 1) at a flow rate of 3.0 ml/min. The absorbance of loperamide hydrochloride and its degradation products was recorded using a strip-chart recorder (Omniscribe, Houston Instrument, Austin, TX) at a speed of 0.5 cm/min. The stability-indicating nature of this HPLC assay was determined by forcibly degrading a sample of loperamide hydrochloride solution at pH 8.0 and 90 ± 0.2°C for 85 days. Standard curves were constructed each day for calibration over a range of 2 μg/ml to 10 μg/ml. A control solution was assayed after every 10 samples to ensure the reproducibility of the HPLC procedure. The concentration of loperamide hydrochloride was determined by comparing its peak height to that of external standard solutions. The initial concentrations of each drug solution were designated as 100%; all subsequent concentrations were expressed as a percentage of the initial concentration.

Results and Discussion

The correlation coefficient of the detector linearity for loperamide hydrochloride at a concentration range of 2 μg/ml to 10 μg/ml was found to be greater than 0.99. The reproducibility for loperamide hydrochloride at this concentration range was also calculated and shown to be less than ±3.0% S.D. ($n = 3$). Fig. 2 illustrates the HPLC chromatogram of loperamide hydrochloride solution stored at pH 8.0 and 90 ± 0.2°C for 85 days. The degradation products were eluted separately and were detected without apparent interference with the peak of interest. At least 3 degradation compounds were detected and the retention times for loperamide hydrochloride and

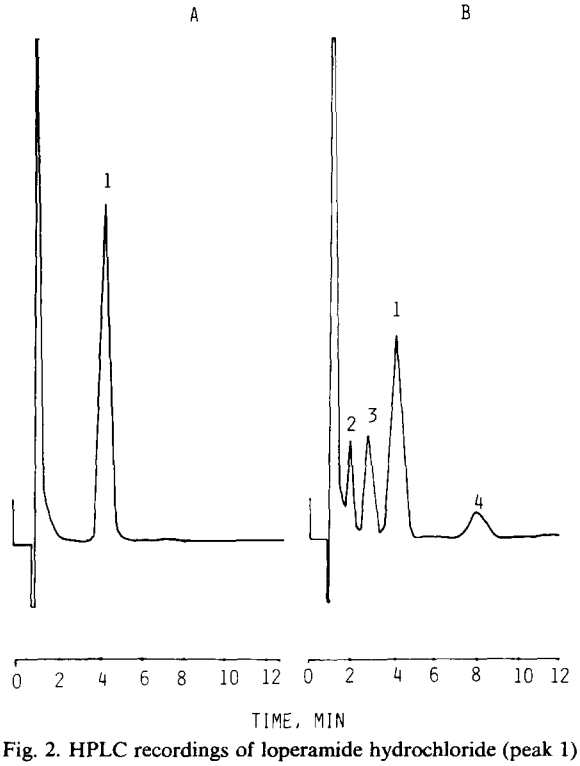

Fig. 2. HPLC recordings of loperamide hydrochloride (peak 1) and its degradation products (peak 2, 3, and 4) when stored at pH 8.0 (ionic strength 0.5) solution and 90±0.2°C for (A) 0, and (B) 85 days.

its degradation products were found to be 4.4, 2.1, 3.0 and 8.2 min, respectively.

Degradation kinetics

Data showing the stability of loperamide hydrochloride solution (8 μg/ml) over the pH range of 3.0–9.0 at 90 ± 0.2°C are listed in Table 1. The results indicate an overall apparent first order degradation kinetics with respect to the loperamide hydrochloride at constant pH, ionic strength (0.5), buffer concentration (0.1 M) and temperature (90 ± 0.2°C) as shown in Fig. 3. The observed rate constant were obtained from the slopes of the semi-log plots of concentration vs. time by statistical regression analysis. The correlation coefficients for all the pH conditions were greater than 0.97. The buffer capacities were sufficient to maintain constant pH values as evidenced by no observed pH change for all the solutions throughout the entire period of study. The half-

TABLE 1

Degradation rates and half-lives of loperamide hydrochloride

Buffer	pH	Rate (10^3/day)	Estimated half-life (days)
Acetate	3.0	6.30	110.0
Acetate	4.0	3.37	205.4
Acetate	4.5	1.72	402.6
Acetate	5.0	2.44	284.3
Phosphate	5.5	2.83	245.1
Phosphate	6.0	3.75	184.9
Phosphate	7.0	7.69	90.1
Borate	8.0	14.67	47.2
Borate	9.0	17.82	38.9

Buffer concentration (0.1 M) and ionic strength (0.5) of various pH solutions were constant. Temperature 90±0.2°C.

lives of loperamide hydrochloride, calculated based on the $t_{1/2} = 0.693/(\text{rate})$ equation are also shown in Table 1. Depending on the pH and also the buffer species of the solution, the half-lives ranged from 39 to 403 days for the degradation of loperamide hydrochloride at a pH range of 3.0–9.0

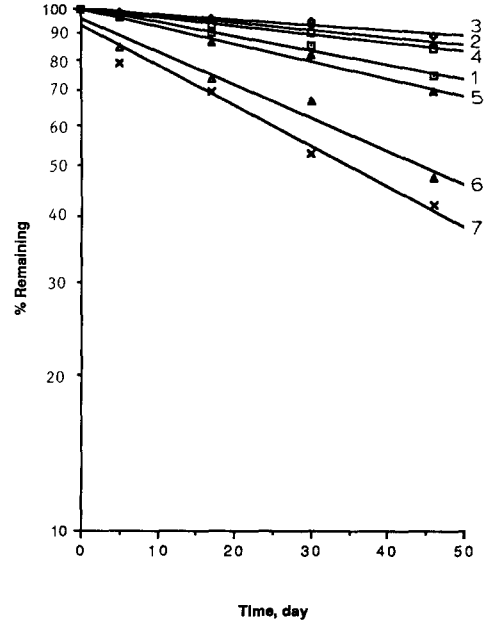

Fig. 3. Apparent first-order degradation kinetics of loperamide hydrochloride in various pH solutions (0.1 M) at 90±0.2°C and $\mu = 0.5$. 1, pH 3.0; 2, pH 4.0; 3, pH 5.0; 4, pH 6.0; 5, pH 7.0; 6, pH 8.0; 7, pH 9.0.

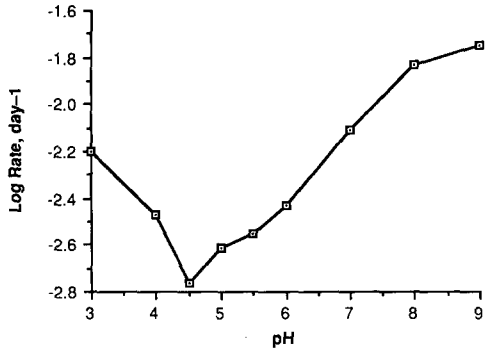

Fig. 4. pH–rate profile of the degradation of loperamide hydrochloride at constant buffer concentration (0.1 M), ionic strength (0.5) and $90 \pm 0.2°$ C.

at $90 \pm 0.2°$ C. The pH-dependent stability of loperamide hydrochloride aqueous solution is shown as pH–rate profile in Fig. 4. The results showed a maximum stability of loperamide hydrochloride at a pH of about 4.5. Based on the pH and buffer species of the solution, the overall degradation kinetics of loperamide hydrochloride can be described by the following general form.

$$-\frac{d[\text{loperamide HCl}]}{dt} = k_{obs}\,[\text{loperamide HCl}]$$

or $k_{obs} = k_0 + k_{H^+}\,[H^+] + k_{OH^-}[OH^-] + \Sigma k_i\,[\text{buffer}_i]$ where k_{obs}, k_0, k_{H^+}, k_{OH^-} and k_i are the rate constants of the entire reaction, the catalysis of water, hydrogen ion, hydroxyl ion and the buffer species present in solution, respectively.

The catalytic effect from various buffer species was possible but not studied in detail in this investigation. However, specific acid–base and water catalysis on the degradation of loperamide hydrochloride aqueous solution was significant. The temperature effect and degradation mechanism of loperamide hydrochloride are not clear and need to be studied further.

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