Research Article ISSN 2689-1050

Chemical & Pharmaceutical Research

Evaluation of Imidapril Degradation Kinetics in Aqueous Solution

Chika J Mbah*, Philip F Uzor, Chinwe M Onah and Chinwe N Oha

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

***Correspondence:**
Chika J Mbah, Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

Received: 06 Oct 2025; **Accepted:** 07 Nov 2026; **Published:** 21 Nov 2026

Citation: Chika J Mbah, Philip F Uzor, Chinwe M Onah, et al. Evaluation of Imidapril Degradation Kinetics in Aqueous Solution. Chem Pharm Res. 2026; 8(2): 1-5.

ABSTRACT

Imidapril is a dipeptide-type, dicarboxylate-containing, non-sulfhydryl angiotensin converting enzyme inhibitor clinically employed in the treatment of essential hypertension, chronic congestive heart failure, and type 1 diabetic nephropathy. The purpose was to investigate imidapril degradation kinetics under acidic and alkaline hydrolysis. The degradation kinetics was carried out in various pH solutions (pH 1.00 – 10.00); ionic strength solutions (0.10 - 0.50), buffer solutions (0.05M - 0.20M) and temperatures 323 – 353 degrees Kelvin. High performance liquid chromatography met.hod was utilized in the kinetic degradation analysis. The method was considered to be accurate, precise, specific and linear over the concentration range of 1- 6 µg/ml. The degradation reaction was observed to follow apparent first-order rate kinetics and the rate constants for the decomposition were obtained from plots of logarithm percent drug concentration remaining versus time. The degradation was specific hydrogen ion and hydroxide ion catalyzed reactions respectively. Calculated activation energies were 65.22 and 59.46 kJ/mol for acidic (pH 1.04) and alkaline (pH 10.02) hydrolysis respectively. In conclusion, imidapril degradation kinetics occurred under acidic and alkaline conditions and followed apparent first-order rate kinetics.

Keywords

Imidapril degradation kinetics, pH-rate profile, temperature effect on imidapril degradation kinetics.

Introduction

Imidapril (IMD), is a dipeptide-type, dicarboxylate-containing, non-sulfhydryl angiotensin converting enzyme inhibitor (ACE-I), clinically used as an antihypertensive agent to treat essential hypertension, chronic congestive heart failure, and type 1 diabetic nephropathy [1,2].

The IUPAC chemical name for imidapril is (4S)-3-{(2S)-2-[((2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl)amino]propanoyl}-1-methyl-2-oxoimidazolidine-4-carboxylic acid, (Figure 1).

As an ACE inhibitor, imidapril decreases total peripheral vascular resistance without an increase in heart rate or cardiac contractility. It also increases renal blood flow and reduces renal vascular resistance mainly due dilatation of the efferent arterioles. Its free base has molecular formula $C_{20}H_{27}N_3O_6$, a molecular mass of 405.45 g/mol, and melting point of 139 to 140 ^{0}C. As a hydrochloride salt the molecular formula $C_{20}H_{28}ClN_3O_6$, and a molecular mass of 441.91 g/mol and exclusively available in the form of tablets [3].

Drug degradation has been associated with problems such as (i) deterioration of drug quality (loss of active ingredient, formation of degradation impurities or loss of excipients activity) and (ii) clinical consequences (alternations of its potency, toxicity, bioavailability) leading to lack of desired biological activity [4]. Therefore, the International Conference on Harmonization (ICH) requires stress testing to elucidate the inherent stability characteristics of active substances [5]. Previous studies have reported the kinetics of degradation of imidapril hydrochloride in (i) finished dosage [6]; (ii) pure solid form [7]; (iii) aqueous alkaline solution [8,9]. Hitherto, little or no study has been carried out on the degradation kinetics of imidapril base, thus in the present study we examined

the influence of acid-base catalysis, temperature on the kinetics of degradation of imidapril base in aqueous solution.

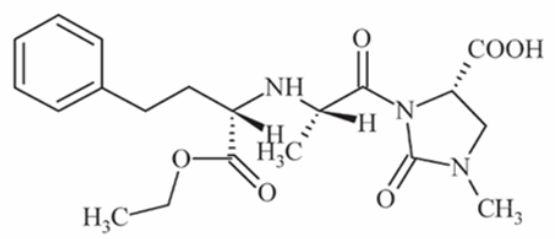


Figure 1: Chemical structure of Imidapril.

Experimental Section

Materials

Imidapril (Tanatril) was purchased from Northumbria Pharma Ltd (United Kingdom).

HPLC grade methanol and reagent grade concentrated hydrochloric acid, sodium hydroxide pellets, potassium biphthalate, potassium phosphate, and boric acid were purchased from Fischer Scientific, USA. Ultra-pure water was prepared from Milli-Q water purification system procured from Millipore (Bangalore, India).

Instruments

All separations were carried out with Shimadzu LC-6A pump, AS 2000 autosampler, Kratos spectroflow 783 detector (Spectra Physics, USA) and Merck analytical column (LiChrospher RP-18, 250 mm × 4 mm i.d., 5 µm particle size). The mobile phase consisted of methanol-phosphate buffer (40:60) and was degassed by vaccum pump filtration. The injection volume was 20 µl at room temperature and a flow rate of 1 ml/min.

Preparation of standard solution

Stock solution was prepared by dissolving 10 mg of imidapril in a volumetric flask and diluted to volume with methanol to obtain a 500 µg/ml stock solution. The stock solution was diluted to 10 ml in a volumetric flask with methanol (50 µg/ml solution). Serial dilutions were made from the 50 µg/ml solution to obtain solutions of 1, 2, 3, 4, 5 and 6 µg/ml. Portions of 1.0 mL standard solution were mixed with 1.0 mL of internal standard and injected on to the chromatograph. The injection volume was 10µL. The peak area ratios were plotted against concentrations of imidapril to construct the calibration graph.

The aqueous buffer solutions preparation

The buffer solutions were HCl-KCl, pH 1-3; biphthlate-NaOH, pH 5; KH_2PO_4- NaOH, pH 6-7 and H_3BO_3-NaOH-KCl, pH 8-10. Constant ionic strength (0.4mol/l) was maintained for each buffer by adding calculated amount of potassium chloride. The solutions were freshly prepared and the pH values were determined with pH meter (ThermoOrion, USA) model 330 equipped with a combination glass electrode.

Kinetic studies

The kinetic degradation studies were performed in buffer solutions at 70 ± 0.2°C. The total buffer concentration was 0.1 mol/l and at a constant ionic strength (0.4). A 1.0 ml of imidapril methanol solution (50µg/ml) was transferred into vials, followed by the addition of 4 ml of buffer solution (pH 1.04) to each of the vials and capped. The samples were placed inside the water bath maintained at 70±0.2°C for eight hours. At appropriate intervals, the vials were withdrawn from the bath, cooled and the solutions were injected into the chromatograph. The same procedure was carried out for the other pH values. All samples were analyzed in triplicate.

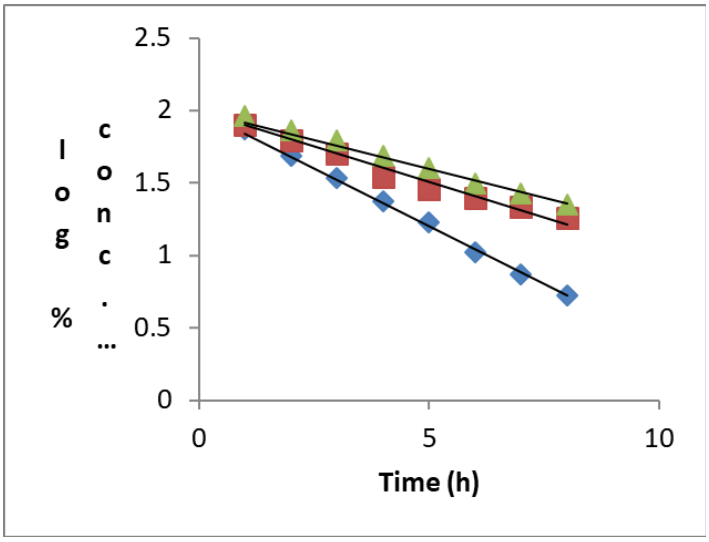
The influence of ionic strength on the degradation of imidapril was investigated with solutions of ionic strength of 0.1, 0.2, 0.3, 0.4, 0.5, respectively and at pH 1.04 and pH 10.02 respectively. Also, buffer species effect on the degradation of imidapril was studied with solutions of molar strength of 0.05M, 0.1M, 0.15 M, 0.2M, respectively and at pH 1.04 and pH 10.02 respectively and a constant ionic strength (0.4). Furthermore, the effect of temperature on the hydrolytic reaction of imidapril was determined at temperatures ranging from 50 to 80°C at pH 1.04 and pH 10.02 respectively and a constant ionic strength (0.4).

Kinetic calculations

To ascertain the reaction order, we plotted the time versus the remaining concentration of the imidapril ($C = C_0$–kt, zero-order process), logarithm of the drug concentration ($\log C = \log C_0$–kt, first-order process) and the reciprocal of the drug concentration ($1/C = 1/C_0$–kt, second order process), where C_0 is the concentration of the reactants at time zero, C is the concentration after reaction time t and k is the reaction rate constant. The best observed fit from obtained correlation coefficients (r) indicated the reaction order. In this study, the best observed fit indicated the reaction order to be first-order, therefore the rate constants were determined from the slopes of linear plots of logarithm of percent imidapril concentration remaining versus time. For the degradation kinetics analysis performed at different temperatures, $\ln k_i = \ln A = -Ea/RT$, where: k_i = reaction rate constant in temperature $_i$, A = frequency coefficient or factor, Ea = energy of activation [J mol^{-1}], R = universal gas constant (8.314 J K^{-1} mol^{-1}), T = temperature (Kelvin, K). The straight-line plot $\ln k_i = f(1/T)$ was obtained for each reaction.

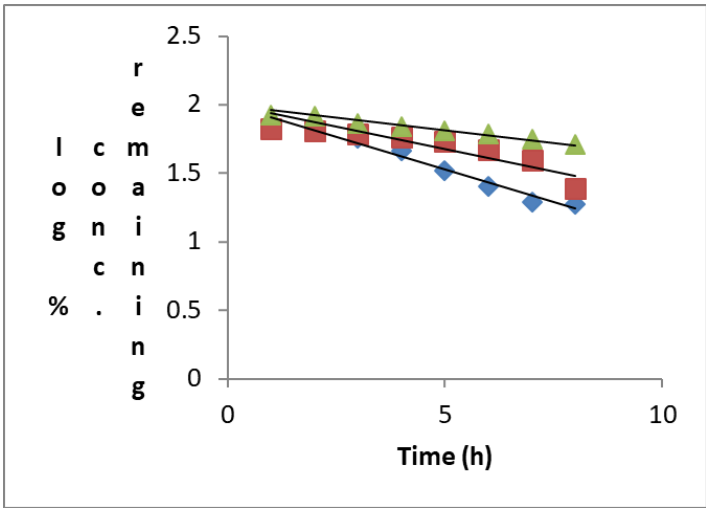
Results

The evaluation of the detector linearity demonstrated that imidapril was linear in the concentration range of 1-6 µg/ml. The correlation coefficient obtained from the regression equation describing the peak area ratio versus concentration relationship is 0.9995. The kinetics of imidapril degradation was evaluated as a function of the decrease in drug concentration. The plots of concentration, log of concentration and reciprocal of concentration versus time permitted the determination of the reaction order through correlation coefficients analysis. Subsequently plots (Figure 2) of log percentage of drug concentration remaining against time for acidic and alkaline conditions respectively show linear relationship indicating a first-order reaction.



----- pH 1.04
---- pH 2.02
Δ-----Δ pH 3.05

Figure 2A: Plot of log percentage of drug concentration remaining versus time under acidic conditions.



----- pH 10.02
---- pH 9.04
Δ-----Δ pH 8.01

Figure 2B: Plot of log percentage of drug concentration remaining versus time under alkaline conditions.

The results of calculated first-order rate constants from plots 2A and 2B respectively are given in Table 1.

The plot was constructed from the logarithm of the observed pseudo first-order rate constants versus the pH values. The pH-rate profile indicated that the degradation of imidapril was acid and base catalyzed. The catalytic effect of buffer species utilized in the kinetic study was determined at constant pH (10.02), ionic strength (μ=0.4) and temperature (70±0.2°C) and varying only the buffer concentration. The results (Table 2) showed that the rate constant was unaffected by buffer concentration.

Table 1: First-order rate constant of imidapril in aqueous solution.

pH	Buffer	k_{obs} $(h^{-1})^x$	$t_{1/2}$ (h)
	Hydrochloric acid		
1.04		0.3848±0.22	2.13
2.02		0.2353±0.31	2.95
3.05		0.1872±0.28	3.70
	Biphthalate		
5.03		0.0947±0.48	7.32
	Phosphate		
6.04		0.0487±0.53	14.23
7.02		0.0768±0.62	9.06
	Borate		
8.01		0.0824±0.66	8.42
9.04		0.1276±0.51	5.43
10.02		0.2267±0.43	3.06

Temperature: 70 ± 0.2°C; Ionic strength (μ): 0.4 mol/l, x: Mean ± RSD (%); n = 3.

The pH-rate profile for the degradation of imidapril at 70±0.2 °C is shown in (Figure 3).

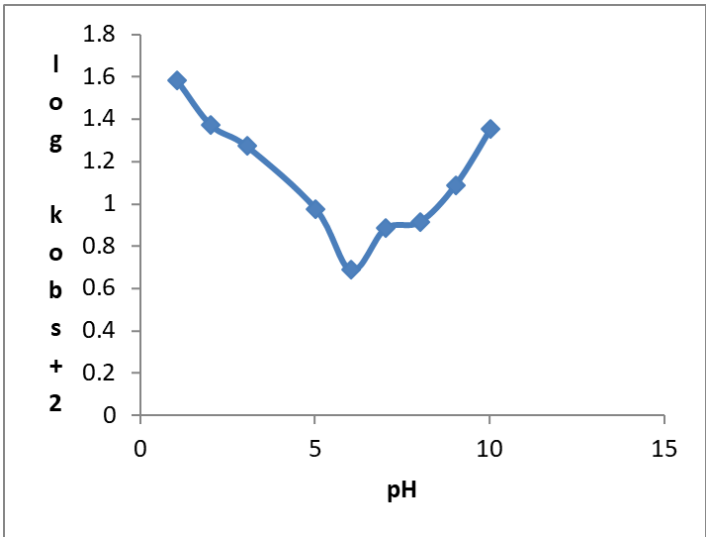


Figure 3: Plot of log first-rate constant versus pH.

Table 2: Effect of buffer concentration and ionic strength on the first-order rate constant of Imidapril.

Buffer concentration		Ionic strength	
$(mol/l)^y$	k_{obs} $(h^{-1})^x$	KCl $(mol/l)^z$	k_{obs} $(h^{-1})^x$
0.05	0.2257±0.43	0.100	0.3895±0.31
0.10	0.2241±0.37	0.200	0.3871±0.29
0.15	0.2287±0.54	0.300	0.3882±0.43
0.20	0.2264±0.29	0.400	0.3826±0. 37
		0.500	0.3841±0. 53

y:70 ± 0.2°C; pH 10.02; H_3BO_3-NaOH-KCl, z: 70 ± 0.2° C; pH 1.04; HCl-KCl ; x: Mean ± RSD (%); n=3.

The influence of ionic strength on the degradation of imidapril was also investigated by keeping the buffer concentration (0.1mol/l), pH (1.04) and temperature (70 ± 0.2°C) constant but varying only

the ionic strength. The results (Table 2) showed no kinetic salt effect for the degradation of imidapril.

The effect of temperature on the hydrolytic reaction of imidapril in solution was studied at temperature ranging from 50 to 80°C, constant ionic strength (μ = 0.4) and measuring the pseudo-first-order rate constants at pH 1.04 and pH 10.02 respectively. The data results are given in Table 3. A plot of logarithm apparent first-order rate constant against the reciprocal of the absolute temperature is given in Figure 4.

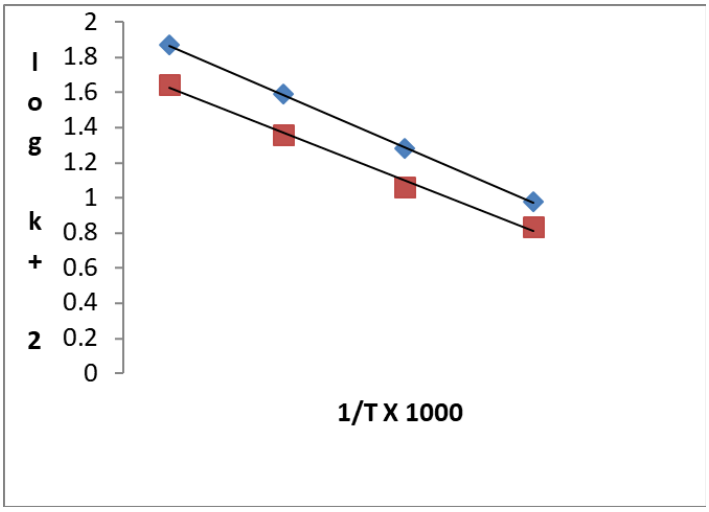


Figure 4: Plot of logarithm of observed first-order rate constant versus reciprocal of absolute temperature.
(log k_{obs} +2 versus $1/T\times10^3$); upper curve (□------□) represents pH 1.04; lower curve (□-----□) represents pH 10.02.

Table 3: Effect of temperature on the pseudo-first order rate constant of Imidapril.

pH	Temperature(°C)	k_{obs} (h^{-1})	$t_{50\%}$	$t_{90\%}$	Ea (KJ mol^{-1})
1.04					65.22
	25	0.0122	56.8	8.6	
	50	0.0948	7.3	1.1	
	60	0.1907	3.6	0.56	
	70				
	80				
10.02					59.46
	25	0.0100	69.3	10.6	
	50	0.0684	10.1	1.5	
	60	0.1158	6.0	0.92	
	70	0.2274	3.0	0.47	
	80	0.4522	1.5	0.23	

Discussion

The detector linearity depicting imidapril to be linear in the concentration range studied confirmed that Beers law was obeyed. The pseudo-first order kinetic plots of log percentage of imidapril concentration remaining versus time obtained under acidic and alkaline conditions showing linear relationship permitted the reaction rate constants to be calculated for different pH values investigated. The pH-rate profile which indicated the degradation of imidapril to be acid and base catalyzed allowed the reaction to be described by the following equation: $k_{obs} = k_H[H^+] + k_{OH}[OH^-] + k_o$ [1], where k_H and k_{OH} are the second-order rate constant for the hydrogen ion and hydroxide ion-catalyzed degradation respectively, k_o is the first-order rate constant of spontaneous or water catalyzed degradation, k_{obs} is the overall observed rate constant. The apparent first-order rate constant for water-catalyzed as well as the second-order rate constant for hydrogen ion and hydroxide ion catalyzed degradation were found to be 4.87×10^{-2} h^{-1}, $5.035\times10^{-1}mol^{-1}h^{-1}$ and $4.353\times10^{-5}mol^{-1}h^{-1}$respectively. The k_o was evaluated from the intersection of the acid and base catalyzed pH-rate profile plots while k_H and k_{OH} were obtained from the intercepts in the low and high pH regions respectively of $\log(k_{obs}-k_o)$ versus pH plots. The rate constant of imidapril being not affected by varying buffer concentration indicated lack of general base catalysis. The rate constant of imidapri was also not significantly altered by varying ionic strength (the addition of different amounts of potassium chloride) of the kinetic solutions.

The relationship between the reaction rate constant and temperature was described by Arrhenius equation. The linearity of Arrhenius plots indicated that the degradation mechanism was not with a change in temperature within the temperature range investigated. This signified single degradation mechanism thus justifying the extrapolation of the results to obtain rate constants at 25◦C. The extrapolated rate constants at 25◦C are 1.22×10^{-2} (pH1.04) and 1.00×10^{-2} (pH10.02) respectively. Arrhenius equation [10] was utilized to calculate activation energies as well as the frequency factors for the hydrolytic reaction. The activation energies are 65.22 kJ/mol (pH 1.04) and 59.46 kJ/mol (pH 10.02) respectively while the frequency factors are 3.29×10^9 (pH 1.04) and 2.65×10^8 (pH 10.02) respectively. The calculated Ea values obtained for imidapril hydrolysis display a higher stability of the drug acidic than alkaline conditions. The high values of the frequency factors show that there was large proportion of collisions between hydrogen ions, hydroxide ions and imidapril molecules during the hydrolytic reactions. The most effective collisions occurred at pH 1.04 than pH 10.02. Basing on the transition state theory, we obtained further information from the kinetic investigation, by calculating the entropy of activation (ΔS), heat of activation (ΔH) and free energy change (ΔG) respectively. Substitution of the values obtained for rate constants at 25◦C and the activation energy into the relevant thermodynamic equations [11], these thermodynamic parameters were evaluated. The evaluated values are 211.27J/K/mol, 63.04KJ/mol and 83.88 KJ/mol for the entropy of activation (S), heat of activation (H) and free energy change (G) respectively.

As previous investigation [6], has reported the degradation products of imidapril to be diketopiperazine derivative and imidaprilat respectively, no attempt was made in this present study to determine the degradation products and specific degradation pathways for imidapril.

Conclusion

Imidapril when subjected to degradation stress conditions was

found to be labile under alkaline/acidic hydrolysis. The degradation under these conditions followed first-order reaction kinetics. The active ingredient was mostly stabilized at pH of 6.04.

Acknowledgement

The authors are grateful to the Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria, Nsukka, for providing the facilities utilized in the study.

References

1. Hayashi K, Nunami J, Kato N, et al. Studies on angiotensin converting enzyme inhibitors. 4. Synthesis and angiotensin converting enzyme inhibitory activities of 3-acyl-1-alkyl-2-oxoimidazolidine-4-carboxylic acid derivatives. J Med Chem. 1989; 32: 289-295.
2. Robinson DM, Curran MP, Lyseng-Williamson KA. Imidapril: a review of its use in essential hypertension, Type 1 diabetic nephropathy and chronic heart failure. Drugs. 2007; 67: 1359-1378.
3. Harahap Y, Prasetyo V, Sandra M, et al. Comparative bioavailability study of two imidapril tablet formulations in Indonesian healthy subjects. Sys Rev Pharm. 2021; 12: 1540-1544.
4. Yoshioka S, Stella VJ. Stability of drugs and dosage forms. New York: Kluwer Academic Publishers. 2002.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH harmonised tripartite guideline: validation of analytical procedures: text and methodology Q2(R1). Geneva: ICH. 2005.
6. Stanisz B, Regulska K. Kinetics of degradation of imidapril hydrochloride in finished dosage formulations. Acta Pol Pharm. 2013; 70: 737-742.
7. Regulska K, Stanisz B. Kinetics and mechanism of solid-state imidapril hydrochloride degradation and its degradation impurities identification. Cent Eur J Chem. 2013; 11: 754-762.
8. Abdulla SA, Frag EY, Ahmed HE. Kinetic study of the alkaline degradation of imidapril hydrochloride using a validated stability indicating HPLC method. RSC Adv J. 2016; 73: 1-6.
9. Hegazy MA, Eissa MS, Abd El-Sattar OI, et al. Determination of a novel ACE inhibitor in the presence of alkaline and oxidative degradation products using smart spectrophotometric and chemometric methods. J Pharm Anal. 2014; 4: 132-143.
10. Singh S, Bakshi M. Guidance on conduct of stress tests to determine inherent stability of drugs. Pharm Tech. 2000; 24: 1-14.
11. Zimmer KD, Shoemaker R, Ruminski RR. Synthesis and characterization of a fluxional Re(I) carbonyl complex fac-[Re(CO)3(Dpop′)Cl] with the nominally tri-dentate ligand dipyrido(2,3-a:3′,2′-j)phenazine (Dpop′). Inorg Chim Acta. 2006; 359: 1478-1484.

© 2026 Chika J Mbah, et al. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License