# Acid Decomposition of Omeprazole in the Absence of Thiol: A Differential Pulse Polarographic study at the Static Mercury Drop Electrode (SMDE)

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*Received 16 August 2005; revised 2 October 2005; accepted 17 October 2005*

*Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20546*

**ABSTRACT:** The reactions of omeprazole, a potent proton pump inhibitor (PPI), were investigated in the absence of a nucleophile. Reactions were monitored, using differential pulse polarography (DPP) at the static mercury drop electrode (SMDE), in solutions buffered to pH values ranging from 2.0 to 8.0. The fast, sensitive, and selective electrochemical technique facilitated to repeat recordings of successive voltammograms [peak current (nA) vs. peak potential (volts vs. Ag/AgCl saturated with 3.0 M KCl)]. The DPP signals of omeprazole and its degradation products, believed to be due to sulfur functional group (the principal site of electrode reaction), gave advantages over the previously employed UV detection technique. The latter primarily relied on pyridine and benzimidazole analytical signals, which are common reaction products of PPI in aqueous acidic solutions. After peak identification, the resulting current (nA)-time (s) profiles, demonstrated that omeprazole undergoes degradation to form two main stable compounds, the first is the cyclic sulfenamide ($D^+$), previously believed to be the active inhibitor of the $H^+$, $K^+$-ATPase, the second is omeprazole dimer. This degradation is highly dependant on pH. Unlike previous studies which reported that the lifetime of $D^+$ is few seconds, the cyclic sulfenamide ($D^+$) was found to be stable for up to 5–20 min. The results further indicated that omeprazole converts into the cyclic sulfenamide in an irreversible reaction, consequently, $D^+$ and sulfenic acid (an intermediate which rapidly converts into $D^+$) were not interconvertable. The present work suggested that the sulfenic acid is the active inhibitor *in vivo*. In addition, the omeprazole reactions, in the absence of the thiol, were not as complicated as were previously reported.
 J Pharm Sci 95:384–391, 2006
**Keywords:** omeprazole; acid decomposition; differential pulse polarography; cyclic sulfenamide; sulfenic acid

## INTRODUCTION

Omeprazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyrinylmethyl-sulfinyl)-1H-benzimidazol ($C_{17}H_{19}N_3O_3S$, f. wt. 345.42 g/mol) is a potent proton pump inhibitor (PPI), consisting of a substituted pyridine ring, connected to a substituted benzimidazole ring by a $CH_2SO$ chain, as shown in the structure below. Omeprazole is amphoteric with pKa values of 3.98 for accepting a proton on the pyridine nitrogen atom, and 8.7 for releasing a proton from the NH group of the benzimidazole.[1]

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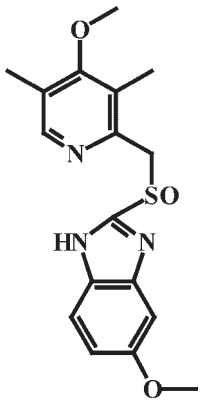
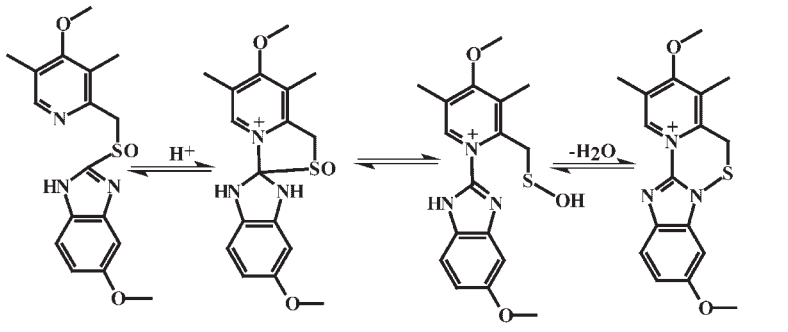
Journal of Pharmaceutical Sciences, Vol. 95, 384–391 (2006)



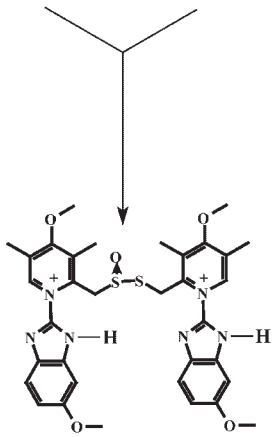
omeprazole

Omeprazole is a weak base, thus concentrates in the parietal cell (the most acidic cell in the body) containing the $H^+$, $K^+$-ATPase enzyme which is responsible for acid production.[2]

Several attempts have been made to understand the chemical conversions and the mechanism of action of omeprazole. Among others, these have included: isolation, structure elucidation, and characterization of both intermediates and decomposition products in the acidic media.[3–7] Reversed phase HPLC coupled with UV detection, and indirect UV spectrophotometry have been used to understand the degradation of omeprazole in acidic media; both in the absence and in the presence of 2-mercaptoethanol.[1–7] Previously employed analytical techniques suffered from at least two major drawbacks, which adversely affected an accurate prediction of omeprazole acid conversion scheme[1] and hindered the proper estimation of the rate of formation of the cyclic sulfenamide ($D^+$), believed to be the active inhibitor. The employed RP-HPLC technique was limited by (1) long-lag time from the moment when the reaction was stopped, to that at which compounds were eluted from the HPLC column (2) UV detection suffered from lack of specificity, since the core molecular structure of reactants, intermediates, and products contain essentially the same chromophoric species which exhibited similar UV spectra. In spite of these drawbacks, it also had limited sensitivity which hindered the detection of trace levels of intermediates. Following a kinetic study, a reaction mechanism have been proposed. Previous researchers suggested that all steps in the reaction scheme, except that which forms the dimer, were reversible as detailed in the reaction scheme below.[1]



omeprazole dihydrobenzimidazole sulfenic acid sulfenamide (D+)



omeprazole dimer