Lidocaine Degradation using Fenton-Like Processes with Copper: Effect of the complex formation and pH of the solution

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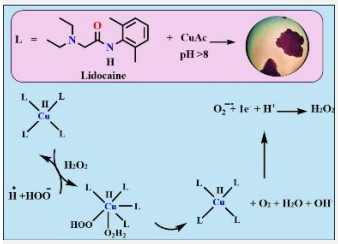

This study used a Fenton-like advanced oxidation process to investigate the impact of Cu(II) complexation on the degradation of lidocaine, a commonly used local anesthetic in dental treatments. The optimal ratio for the coordination compound formation and the effect of pH on the degradation rate were identified, achieving complete removal of lidocaine within 60 minutes under basic conditions. The reactivity of copper(II) was favored at high peroxide concentrations, which facilitates the oxidation of organic molecules by reducing the coordination around the metal center.

Introduction

Advanced Oxidation Processes (AOPs) are capable of breaking down organic and persistent compounds that traditional methods are ineffective to decompose [1]. These compounds often include pharmaceuticals and chemicals used in agriculture, industry, and households; such as pesticides and detergents. They usually retain their identity and toxicity, and primarily comes from urine and feces excretion, or from improper disposal of the unused pharmaceuticals. AOPs work by reactive oxygens species (ROS) that enable oxidative reactions to remove contaminants [2].

The Fenton system is an AOP, which employs Fe(II) as a catalyst along with H_2O_2 to produce radical species like HO•. However, its effectiveness is limited at neutral and basic pH due to the low availability of Fe(II) in solution, which tends to form insoluble aqua complexes, reducing ROS formation. To overcome this limitation and broaden the applicable pH range, chelating agents are used to prevent iron precipitation and keep it soluble. Additionally, some studies have showed that pharmaceuticals can act as metal complexing agents due to the presence of functional groups like carboxylic acid, amide, amine, sulfur, and hydroxyl in their structures. Similarly, the Fenton process can use copper as a catalyst for converting H_2O_2 into reactive oxidizing species through the Cu(II)/Cu(I) redox cycle, which is part of homogeneous Fenton-like processes. This copper-based system shows better performance at neutral pH, likely due to copper's higher solubility compared to iron over a broader pH range (3.0-10.0). The main goal of this study is to evaluate in a wide pH range the effect of Cu(II) complexation with iron on the photo-degradation of lidocaine in presence of H_2O_2.

Material and Methods

Synthesis of the iron-lidocaine complex

Lidocaine (2 mmol, 0.180 g) was measured and dissolved in 50 mL of water. Subsequently, with continuous stirring, a molar amount of $Cu(CH_3COO)_2.H_2O$ metal salt was added to achieve stoichiometric ratios (1:1, 1:2, 1:3, Metal: Lidocaine). The mixture was stirred for 2 hours under refluxing conditions, followed by pH adjustment to 5, 8, and 10.

Degradation process

Experiments were carried out using 100 mL of 30.6 µM metal-lidocaine of 1:2 ratio solution under constant stirring. Then, the amount of oxidant (H_2O_2) was added to reach a final concentration of 500 µM. Subsequently, 0.75 mL aliquots were taken at intervals of 5, 10, 20, 30, 40 and 60 min. To remove residual H_2O_2, 50 µL of 80 mM sodium metabisulfite was added to each sample. The degradation of lidocaine was monitored by high-performance liquid chromatography (HPLC) with specific UV detection, and a mixture of acetonitrile and formic acid was used.

Results and Discussion

During the synthesis of the complex, it was noted that a 1 mM copper solution had a blue color, whle lidocaine is colorless When lidocaine was added in a stoichiometric ratio of 1:2, the pH of the solution changed to 5 and a green colour was noted, which is attributed to Cu ions in solution. However, upon adjusting the pH to 8 and 10, the solution turned violet, indicating that the complex formation occurs at pH levels higher than 8. This behavior is consistent with the ability of lidocaine to exist in both ionized and non-ionized forms (pKa of 7.9). Under basic conditions, lidocaine is in its neutral form, which is liposoluble, while under acidic conditions, it becomes positively charged.

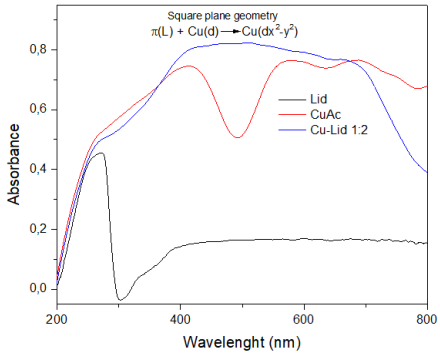

Figure 1. Absorption spectrum of Lidocaine, Copper Acetate, and copper-Lidocaine-complex 1:2 at pH 10.

The formation of the complex was characterized by diffuse reflectance spectroscopy (Figure 1). The mixture of copper ion with lidocaine in a stoichiometric ratio of 1:2 showed a strong absorption band at 490 nm, associated with the electronic transition to the copper d orbitals (dx^2-y^2), attributed to a square planar geometry due to the coordination of the nitrogen atoms present in the structure of lidocaine towards the metal center [5].

Figure 2 shows the degradation of lidocaine using the Cu(II)/H2O2 system. After 1 h of treatment, complete removal of the pharmacuetic is observed when working at pH 8. At the same time, 89% removal was found at pH 10. However, a minimal removal was observed under circum-neutral pH conditions. This is related to the low conversion of Cu(II) to Cu(I) through the conventional reduction pathway (Reaction 1)

$$Cu^{2+} + H_2O_2 \rightarrow Cu^{+} + HO_2^{\bullet} + H^{+} \qquad (1)$$

This suggests that the degradation pathway improves under basic pH, which is attributed to the formation of a Cu(II)-peroxo complex under these conditions (Reaction 2-5)

$$H_2O_2 \rightleftharpoons H^{+} + HOO^{-} \qquad (2\text{-}5)$$
$$Cu^{II}L + HOO^{-} \rightleftharpoons Cu^{II}L(OOH)$$
$$Cu^{II}L(OOH) + H_2O_2 \rightleftharpoons Cu^{II}L(OOH)(H_2O_2)$$
$$Cu^{II}L(OOH)(H_2O_2) \rightleftharpoons Cu^{II}L + O_2 + H_2O + OH^{-}$$

A mechanism is proposed in which the peroxide or hydroperoxide anion (HOO^-) coordinates with the metal, forming a stable Cu(II)-peroxo complex. Once formed, this complex becomes the primary active oxidant in the system, enhancing the reaction rate with the drug.

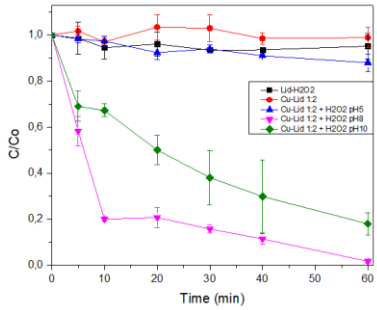

Figure 2. Degradation of Cu-Lid 1:2 ratio at pH 5, pH 8 and pH 10.

Conclusions

The copper-lidocaine complex was synthesized in a 1:2 stoichiometric ratio. The degradation of lidocaine through the Fenton-like process is influenced by the pH of the medium. The rate of drug elimination increases at pH 8, likely due to the formation of a stable Cu(II)-peroxo complex, which serves as the primary oxidant in this system.

Acknowledgments

Project of *SGR BPIN 587*

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