KINETIC INVESTIGATION OF FAMOTIDINE S-OXIDATION REACTION BY MEANS OF POTASSIUM CAROATE USING IODOMETRIC METHOD

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Famotidine(FMT),3-[2-(diaminomethyleneamino)thiazol-4ylmethylthio]-N-sulfamoylpropionamidine, is a histamine H2-receptor antagonist (H2-RA) which competitively inhibits the action of histamine on the H2-receptors of parietal cells and thereby reduces the gastric acid secretion under daytime and nocturnal basal conditions. It is easily oxidized and the metabolites are S-oxides which can be impurities in the medical preparation. The metabolite has no pharmacological activity on gastric acid secretion. It is produced in the form of powder substance and tablets containing 20 or 40 mg of API and other pharmaceutical formulations.

The purpose of the present work is to study kinetics of Famotidine S-oxidation products formation by means of Caro's acid.

All materials were of the analytical reagent grade, and the solutions were prepared with twice-distilled water. Famotidine pure substance (ac No. FMC/1508003, FM-1507002V 24/08/2015, Nakoda Chemicals Ltd, product-E-P) was used as received. Famotidine preparation, tablets, 20 mg, produced by PJSC "Kyivmedpreparat", Ukraine was used for the research. The oxidant was $KHSO_5$, potassium caroate in the form of a triple potassium salt of Caro's acid, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Acros Organics). The choice of the reagent was determined by its rather high oxidative capacity, $E^0 = 1.84$ V, easy availability, and satisfactory solubility in water, and also by sufficiently high stability in the use and storage.

Kinetic studies were carried out in water medium under second-order conditions with potassium caroate at the temperature 293 K. The reaction was followed by estimating the unreacted Caro's acid as a function of time by using the iodometric method. The isolated iodine was titrated against standard sodium thiosulfate solution using starch as indicator.

To determine the stoichiometry of the reaction, peroxyacidic titration of standard solutions was carried out. Values of pH influencing the rate, rate constants and product yield of oxidation by potassium caroate have been studied. Metamorphosis of the kinetic curves 1/c vs t are given on the Figure 1. The linear dependence reveals the second order reaction. As it is seen from the plot in the pH value interval 2.3-8.4 the rate of chemical reaction increases.

The formation of Famotidine S-oxide is immediate (during the first minute). The observed rate constants k_{obs} show the formation of FMT sulfone. The reaction rate is fast during the first 20 min, but later the reaction slows down.

The oxidation depth is controlled to a greater extent by the pH of the reaction mixture. In solution caroate exists as HSO_5^- and SO_5^{2-} ions and they are weak and strong nucelophile respectively. It is suggested that the reaction proceeds through an nucleophilic attack of the oxidant (HSO_5^-) on the electrophilic site sulfur S of formed in the first step of reaction FMT sulphoxide (Fig. 2, a) by meance a mechanism involving displacement of terminal oxygen of the peroxide group. A cyclic

intermediate undergoes intramolecular rearrangement to give FMT sulphone (Fig. 2, b) as the product. This, in particular, points to a linear dependence of the observed reaction rate constant on the mole fraction of the dianion of the Caro's acid ($k_{obs} = 129.5 \cdot \alpha_{SO_5^{2-}} + 15.183$, $r = 0.990$).

A hypothetic mechanism scheme based on these observations is proposed (Figure 2.):

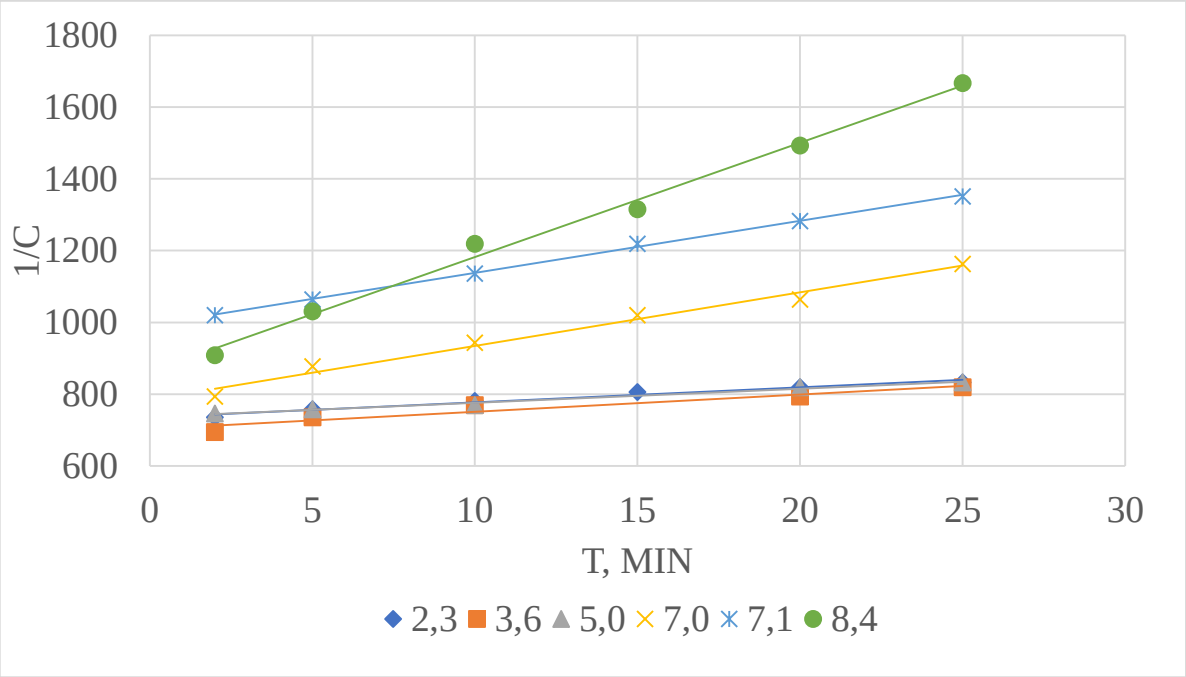

Fig. 1. Dependence of k (1/c) on pH. c(FMT) = $5 \cdot 10^{-4}$ mol L^{-1}; $c(KHSO_5) = 2 \cdot 10^{-4}$ mol L^{-1}

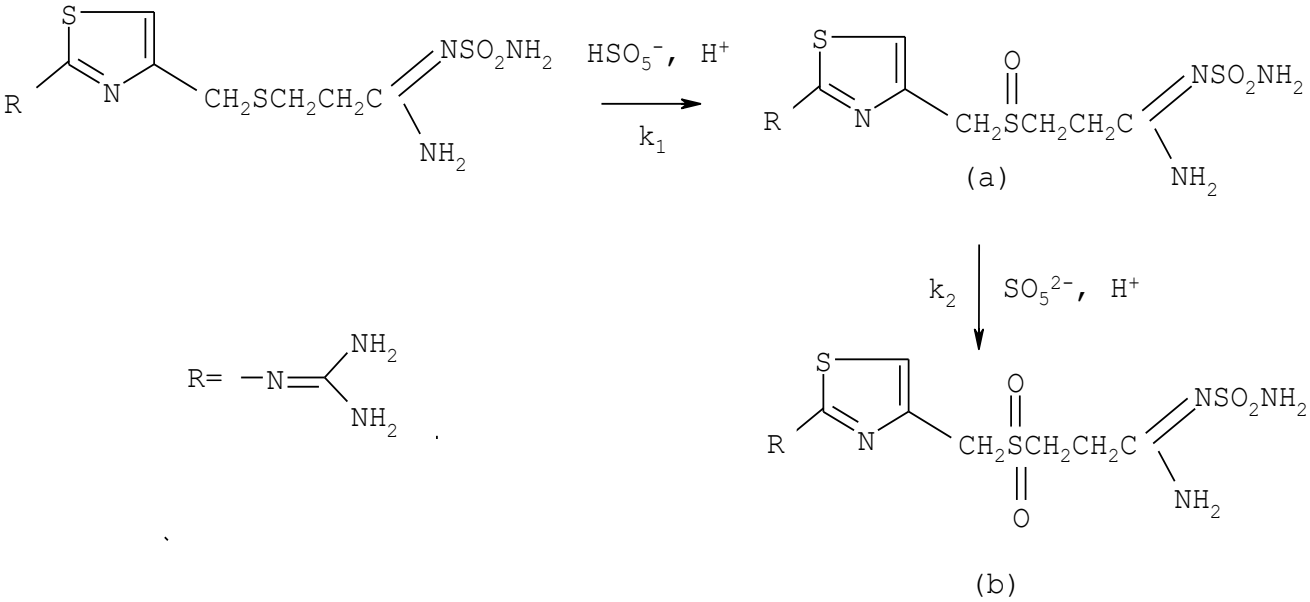

Fig. 2. The scheme of Famotidine S-oxide and sulfone formation ($k_1 \gg k_2$).

The kinetics of Famotidine S-oxide and sulfone formation by means of potassium caroate have been studied. The optimal condition for the Famotidine sulfone formation have been proposed (pH=7.0, t=20 min).