Ozonation of ranitidine: effect of experimental parameters and identification of intermediates

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Abstract

The aim of this study was to reveal the effects of various operational parameters on the ozonation kinetics of the histamine-2 blocker drug ranitidine (RAN) in aqueous solutions and to detect and identify possible transformation products (TPs) of RAN produced during the ozonation experiments.

The influence of the solution's pH value, the initial concentrations of the oxidant and analyte, the matrix effect and the organic matter presence on RAN's removal were evaluated. Results indicated high reactivity of RAN with molecular aqueous ozone. Initial ozone concentration and pH were proven major process parameters. Alkaline pH values and increased ozone initial concentrations promoted degradation kinetics and overall mineralization. Although RAN mineralization at neutral and acidic pH was restricted (maximum 22%), it increased at pH 10. Dissolved Organic Matter (DOM) acts as an antagonistic agent to RAN degradation, limiting its % removal. The effect of inorganic ions in the matrix did not seem to affect RAN ozonation.

Eleven (11) TPs were identified and structurally elucidated, using Reversed Phase (RP) and HILIC LC-Q-ToF-MS. Most of the TPs (P-304, P-315b, P-299b, P-333, P-283) are generated by the attack of ozone at the double bond or the adjacent secondary amine, with the abstraction of NO_2 moiety, forming TPs with an aldehyde group and an imine C=N bond. Oxidized derivatives with a carboxylic group (P-315a, P-331a, P-331b, P-299a) are also formed. Ranitidine S-oxide was identified as an ozonation product (P-330) and its structure was confirmed through the analysis of a reference standard. P-214, was also produced during ozonation, through the C-N bond rupture adjacent to the NO_2 moiety. HILIC was successfully used complementary to RP, either for the successful separation and identification of isomeric TPs or for the elution of new TPs that were not eluted in the RP chromatographic system. Retention time (t_R) prediction was also used as a complementary tool for the identification of TPs. The obtained results supported the proposed structures, since the predicted t_R of most compounds in both RP and HILIC were in accordance with the experimental ones.

Keywords: ozonation; ranitidine; degradation kinetics; transformation products; LC-Q-TOF-MS; retention time prediction