Mechanism of drug release from levofloxacin-monomer conjugates.

Igor Chekhtman[1], Richard J. Prankerd[1]

[1]Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia 3052

The release of drug from highly soluble drug-polymer conjugates is adequately described by a pseudo-first order kinetic process. However, release from poorly soluble polymers is more complex and less thoroughly understood. This study investigated the mechanism of levofloxacin release from drug-monomer conjugates; these are building blocks for drug-polymer conjugates designed for site-specific treatment of bacterial infections. Degradation of a levofloxacin monomer (4-((3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy)carbonyl)phenyl-levofloxacin or LVX-pHB-THE) was studied at 37.0±0.1° C in buffered solutions of varying pH, and in different mixtures of normal and heavy water. Mathematical modelling (Micromath® Scientist 3.0) was applied to kinetic data for detailed analysis. The pH-rate profile describing LVX-pHB-THE degradation was typical of activated esters. Specific acid, specific base catalysis, and spontaneous water attack, are dominant at low pH(<2.0), high pH(>8.0) and intermediate pH(3.0-6.0), respectively. An inflection in the profile is observed between pH 6.0-8.0. This deviation was ascribed to changes in ionisation of acid/base functional groups on the molecule. Mathematical modelling supported the presence of two such groups. Curvature in observed rate constant vs. atom fraction of deuterium data was consistent with a two-proton (single water molecule) transition state model. Hydrolysis of LVX-pHB-THE can be described by a pseudo-first order process and rate constants are shown to be influenced by the monomer ionisation state. The transition state structure may involve co-ordination of a single water molecule at the carbonyl carbon. However, when incorporated into a drug-polymer conjugate, the reactivity of the ester bond (and, therefore, drug release) may be affected by changes within the polymer microenvironment (i.e., microclimate pH, K_a of ionisable groups and/or changes in water activity).