
HYPHENATION OF ELECTROCHEMISTRY, LIQUID CHROMATOGRAPHY AND MASS SPECTROMETRY AS A COMPLEMENTARY TOOL IN DRUG METABOLISM STUDIES

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In the human body, the biotransformation of drugs can be described as a series of metabolic reactions, ideally transforming xenobiotics into less toxic and more polar compounds, which can be easily excreted from the human body. In many cases, the metabolic pathway is initiated by oxidation reactions (phase I metabolism), being catalysed by enzymes of the cytochrome P450 superfamily. To investigate the metabolites generated during the oxidative phase I metabolism, *in vivo* and *in vitro* experiments are widely applied. As reactive metabolites tend to undergo covalent binding to cellular macromolecules, the isolation and identification of the metabolites in these experiments is often hampered. Thus, a purely instrumental method has been developed using an electrochemical cell coupled online to HPLC-ToF/MS (EC-LC-MS).

The EC-LC-MS system has been proven its utility in a number of metabolic studies, including the detection of reactive metabolites of drugs like acetaminophenone and amodiaquine¹. Recent instrumental developments have enlarged the application window for this technique. Using electrochemical thin layer cells with platinum or boron doped diamond (BDD) working electrodes enables the electrochemical generation of hydroxy radicals. Thus, for the first time aliphatic and allylic hydroxylation processes of drugs can be simulated in an online EC-LC-MS setup². The experimental EC-LC-MS set-up has been further extended by different detection techniques. Based on inductively coupled plasma mass spectrometry (ICP/MS) detection, providing low limits of detection and elementspecific quantification, iodine containing drugs like amiodarone³ or arsenic containing drugs like melarprosol can be studied in an EC-LC-ICP/MS set-up. A simple set-up, consisting of the direct hyphenation of electrochemistry and mass spectrometry has been established as valuable tool in fast screening of oxidative labile sites in drugs. By plotting three-dimensional “mass voltammograms”, potential oxidation products can be predicted at an early stage of drug development.

The detailed comparison between electrochemistry, conventional microsomal based approaches and *in vivo* experiments for different drug molecules has underlined the fact that electrochemistry is a valuable complementary tool to study oxidation product of pharmaceuticals. EC-LC-MS has the potential to predict metabolites which can not be foreseen in microsomal approaches due to either binding of reactive metabolites to cellular macromolecules or due to the different distribution of P450 enzymes in each organism.

¹ Lohmann W., Karst U., *Anal Bioanal Chem*, **2008**, 391, 79

² Baumann A., Schubert B., Oberacher H., Karst U., *J Chromatogr A*, **2009**, 1216, 3192

³ Lohmann W., Meermann M., Möller I., Scheffer A., Karst U., *Anal Chem*, **2008**, 80, 9769