

APPLICATION OF SIMULTANEOUS pH AND ORGANIC SOLVENT GRADIENT RP HPLC IN DETERMINATION OF PHARMACOKINETICS-AFFECTING PARAMETERS OF DRUGS

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Pharmacokinetics and toxicity (ADMET – absorption, distribution, metabolism, excretion, toxicity) of xenobiotics depend on their pK_a and lipophilicity. Therefore, there is a need for methods allowing fast testing of drug candidates for these properties.

We developed theoretical and experimental basis of determination of compound's pK_a and lipophilicity ($\log k_w$) employing reversed phase high-performance chromatography (RP HPLC) with simultaneous gradient of pH and organic solvent content in mobile phase. Advantages of our approach are that it can be applied to compound mixtures and it requires only minute amounts of substances.

A comprehensive theory of the combined pH/organic modifier gradient has recently been elaborated [1]. According to the theory, the determination of $\log k_w$ and pK_a consists in a series of gradient runs of programmed changes of pH and/or methanol content in the eluent and of different duration of the gradients. From a set of 18 retention data both the aqueous pK_a value and the $\log k_w$ value for both the ionized and the nonionized forms of the analyte are determined. A brief description of experimental procedure and computation steps will be given.

Verification of reliability of the acidity and lipophilicity parameters determined with the new method was done for a series of 100 acidic and basic analytes. A good agreement with the literature data is demonstrated.

[1] Wiczling, P., Markuszewski, M.J., Kaliszan, M., Kaliszan, R. Anal. Chem. 77, 449-458, 2005.