SESSION II

WEDNESDAY, MAY 24th, 2017

CHAIRPERSONS:

Monika Waksmundzka-Hajnos

and Roman Kaliszan

7.

Illustration of the new hybrid optimization method for preparative chromatography column separation using enantiomeric mixtures as a model

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In this study a robust method of scale up chromatography column separation on the basis of few experiments in analytical and preparative scale has been presented involving test system with mixture of two enantiomeric compounds: omeprazole and etiracetam. The processes have been numerically optimized applying the general rate model and utilizing a hybrid optimization method where global simulated annealing procedure was combined with local simplex algorithm.

The objective function was productivity and the decision parameters were: adsorbent particle diameter, column length and injection time with maximum flow rate assumed. The results have been experimentally verified in both analytical and pilot-scale at maximum allowed backpressures of 80 and 200 bar, respectively, representing contemporary standard equipment.

In this study we have shown that at least for our cases the shorter columns are more suitable utilizing packing materials with smaller particle sizes. In both investigated process scales a column length of 10 cm was found to be optimal. We also have shown that increasing the allowed maximum pressure 2.5 times resulted in around 1.5 times higher productivity. Another benefit of operating under elevated pressure levels was 40% solvent consumption reduction.

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8.

Towards 'sweet spot' approach: *In silico* estimation of lipophilicity profile for a set of drug transporters

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Finding a balance between desired drug potency and its physicochemical properties called 'sweet spot', important for creating a molecule's pharmacokinetic or pharmacodynamics profile is still a challenging issue in rational drug discovery. The *a priori* calculation of the molecular descriptors, crucial for the compound bioavailability and hence critical for the prospective drug candidate is necessary to make predictions of chosen property profiles. Lipophilicity is generally regarded as a first-rate physicochemical parameter increasingly relevant to characterization of both the pharmacokinetic (ADMET) and pharmacodynamic aspects of drug-receptor/enzyme interactions which often correlates well with bioactivity of chemicals. Quantitative assessment of the lipophilic characteristics of potential drug molecules is indispensable for efficient development of ADMET-tailored structure-activity models; therefore reliable procedures for deriving logP from molecular structure are desirable.

A number of modern drugs are not available to the patients due to their poor aqueous solubility and permeability. Generally, modification/optimization of poor permeability through membranes can be solved by selecting appropriate excipients to function as transporting components of a dosage form. Numerous compounds of different chemical structures were evaluated/applied as absorption promoters - cholic acid is one of the most important human bile acids as a relevant class of compounds with a range of pharmacological activities.

A range of various software logP predictors for estimation of the numerical lipophilic values for a set of cholic acid derivatives have been employed and subsequently crossed-compared with the experimental parameter. Thus, the empirical lipophilicity (R_M) was compared with the corresponding logP characteristics calculated using alternative methods for deducing the lipophilic features. The mean values of the selected molecular descriptors that average over the chosen calculation methods (*consensus* clogP) were subsequently correlated with R_M parameter. As an additional experiment, the IVE-PLS methodology for an ensemble of descriptors retrieved from DRAGON 6.0 software have been applied for a set of drug transporters. To investigate the variations within the ensemble of cholic acid derivatives PCA and SOM procedures were employed to visualize the major differences in the performance of drug promoters with respect to their lipophilic profile.

In the current study a range of calculation methods was employed to analyze the experimental and *in silico* data, but one should be aware that '*statistical unicorns beasts exist on paper not in reality*', therefore we should not blindly follow theoretical estimators and sometimes do the experiments.

9.

Whole Body Autoradiography combined with HPLC

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Autoradiography is the method to discover and detect radioactivity Whole body autoradiography (WBA) became a useful tool in pharmacology in time to follow distribution of the radiolabelled compounds in the body.

Toguzov and Tikhonov considered human and animal body as a complex chromatographic system. In living organisms various pseudo-chromatographic processes take place and retardation of the compounds studied is based on their size and lipophilicity. Moreover, it is based on affinity binding of compounds to receptors and to other binding sites of the body (R.T. Toguzov and Yu.V. Tikhonov: Natural chromatographic systems in biological objects. In "Chromatography, the State of the Art", H. Kalász and L.S. Ettre, Eds., Akadémiai Kiadó, Budapest, 1985, pp. 153-160).

WBA serves to scout radiolabelled compounds and certain segments of the drug, while HPLC determines both parent compound and its metabolites in the body compartments. Selegiline (an antiparkinsonian drug) was radiolabelled, and its fate in male Wistar rats was analyzed. WBA made possible to illustrate the progress of distribution of selegiline. Novel binding sites could be found for selegiline, and significance of these binding sites has been analyzed for its non-labeled analogues.

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