Savez farmaceutskih udruženja Srbije
Pharmaceutical Association of Serbia

Univerzitet u Beogradu - Farmaceutski fakultet
University of Belgrade - Faculty of Pharmacy

VI KONGRES FARMACEUTA SRBIJE
sa međunarodnim učešćem

ZBORNIK SAŽETAKA

VI SERBIAN CONGRESS OF PHARMACY
with international participations

ABSTRACT BOOK

15-19. oktobar 2014.
Beograd, hotel Crowne plaza

October 15th-19th, 2014
Belgrade, Hotel Crowne plaza

The Application of PAMPA and QSPR Analysis for the Design of Novel 17β-Carboxamide Steroids with Improved Skin Retention/Permeability Ratio

M. Dobričić, K. Nikolic, B. Marković, S. Vladimirov, O. Čudina
Department of Pharmaceutical Chemistry, University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia

The parallel artificial membrane permeability assay (PAMPA) is a simple and rapid test intended to estimate passive membrane permeability. The aim of this study was to predict skin permeability and retention of novel twenty-two 17β-carboxamide steroids using PAMPA and to create quantitative structure-property relationship (QSPR) models which would be used for the design of novel derivatives with improved skin retention/permeability ratio. These compounds are potentially new soft drugs with fewer side effects than traditional glucocorticoids. PAMPA was performed at isocratic conditions (pH=5.5), using the mixture of isopropyl myristate and silicone oil (30:70, v/v) as the artificial membrane. Selected molecular descriptors of the optimized structures of tested compounds were calculated in Chem3D Ultra 9.0.1, MarvinSketch and Dragon software. PLS-, MLR- and ANN-QSPR models were created in SIMCA P+ 12.0 and STATISTICA and validated by use of statistical parameters. The PAMPA parameters (log*Pe* and *R*) were calculated and six QSPR models created (PLS(log*Pe*), MLR(log*Pe*), ANN(log*Pe*), PLS(*R*), MLR(*R*) and ANN(*R*)). On the basis of the most reliable QSPR models (PLS(log*Pe*) and ANN(*R*)), molecular descriptors with the most significant influence on skin permeability and retention were identified and the derivatives with possibly improved skin retention/permeability ratio designed. The PAMPA parameters (log*Pe* and *R*) of designed compounds were predicted by use of these QSPR models and best derivatives were selected. The combination of *in vitro* (PAMPA) and *in silico* (QSPR) approach could be used for the design of novel 17β-carboxamide steroids with improved skin retention/permeability ratio.

vladimir@pharmacy.bg.ac.rs

Uticaj micelarnih rastvora surfaktanata na protolitičke ravnoteže ACE inhibitora

M. Popović[1], G. Popović[2], D. Agbaba[1]
[1]Katedra za farmaceutsku hemiju, [2]Katedra za opštu i neorgansku hemiju, Farmaceutski fakultet, Univerzitet u Beogradu, Srbija

ACE inhibitori su lekovi koji se koriste u terapiji hipertenzije i drugih kardiovaskularnih poremećaja. Zbog prisustva jedne ili više jonizujućih grupa (karboksilna, tiolna, primarna i sekundarna amino grupa) u hemijskom pogledu predstavljaju kiseline i amfolite. Poznavanje pK_a vrednosti lekova neophodno je za predviđanje jonizacije pri fiziološkim uslovima, ali na očekivanu jonizaciju mogu uticati i drugi molekuli prisutni u biosredini. Za procenu farmakološkog ponašanja relevantniji su podaci o fizičko-hemijskim osobinama lekova dobijeni ispitivanjem u prisustvu micela. Cilj ovog rada bio je da se primenom micelarnih rastvora surfaktanata, kao pojednostavljenih modela biomembrana, ispita uticaj anjonskog natrijum-dodecilsulfata (SDS), katjonskog cetiltrimetilamonijum-bromida (CTAB), nejonskog surfaktanta 4-oktilfenol polietoksilata (TX-100) na kiselo-bazne ravnoteže devet ACE

inhibitora (kaptopril, cilazapril, enalapril, fosinopril, lizinopril, perindopril, kvinapril, ramipril i zofenopril). Potenciometrijskom titracijom su određene pK_a vrednosti u prisustvu surfaktanata (10^{-2} M), na temperaturi 25 °C i pri konstantnoj jonskoj sili 0.1 M (NaCl). Na osnovu eksperimentalnih podataka vrednosti su izračunate primenom kompjuterskog programa Hyperquad. Upoređivanjem sa pK_a vrednostima određenim bez prisustva surfaktanata, pod istim uslovima, uočeno je pomeranje pK_a vrednosti od +1.90 do -1.54 jedinice. Jonizacija karboksilne podložnija je uticaju surfaktanata od jonizacije amino grupe, a od primenjenih surfaktanata najveći uticaj na kiselo-bazne ravnoteže ispoljava SDS. Pomeranja pK_a vrednosti ACE inihitora u prisustvu surfaktanata ukazuju na postojanje složenih interakcija između suprotnih naelektrisanja jonizovanih kiselih i baznih grupa ACE inhibitora i naelektrisanih ili polarnih površina micela. Dobijeni rezultati pružaju bolji uvid u ponašanje ovih lekova u fiziološkim uslovima, naročito jer jonizujuće grupe direktno učestvuju u interakciji sa enzimom.

The Effects of Micellar Solutions of Surfactants on Protolytic Equilibria of ACE Inhibitors

M. Popović[1], G. Popović[2], D. Agbaba[1]
[1]Department of Pharmaceutical Chemistry, [2]Department of General and Inorganic Chemistry, Faculty of Pharmacy, University of Belgrade, Serbia

ACE inhibitors are drugs applied in the treatment of different cardiovascular disorders. Because to the presence of carboxyl, thiol, primary and secondary amino ionizable groups these compounds represent acids and ampholytes. Knowledge of pK_a values of drugs is necessary for prediction of their ionization under physiological conditions, but expected ionization can be affected by other molecules present in bioenvironment. For estimation of pharmacological behavior more relevant data are obtained in presence of micelles.

The aim of this study was to investigate the effects of micellar solutions of surfactants, anionic sodiumdodecylsulfate (SDS), cationic cetyltrimethylammonium bromide (CTAB), non-ionic 4-octylphenol polyethoxylates (TX-100) as biomembrane models on acid-base equilibria of nine ACE inhibitors (captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, and zofenopril). Determinations of pK_a values in presence of surfactants (10^{-2} M) were performed at 25 °C and constant ionic strength of 0.1 M (NaCl). Based on experimental data values were calculated by computer program Hyperquad. Comparison with pK_a values determined in absence of surfactants under the same conditions revealed the shift from +1.90 to -1.54 units, which demonstrated a significant effect of surfactants on ionization of ACE inhibitors. Carboxyl group ionization was more susceptible than amino group and among surfactants employed, SDS expressed the most prominent effect on acid–base equilibria. Shifts of pK_a values demonstrate complex interactions between the opposite charge of ionizable groups of ACE inhibitors and polar or charged micelle surfaces. Estimation provides a better insight into their pharmacological behavior, especially since ionizable groups are involved in interaction with enzyme.

marija.popovic@pharmacy.bg.ac.rs

The effects of micellar solutions of surfactants on protolytic equilibria of ACE inhibitors

M. Popović[1], G. Popović[2], D. Agbaba[1]
[1]Department of Pharmaceutical Chemistry and [2]Department of General and Inorganic Chemistry, Faculty of Pharmacy, University of Belgrade

ACE inhibitors are drugs applied in the treatment of different cardiovascular disorders. Because to the presence of carboxyl, thiol, primary and secondary amino ionizable groups these compounds represent acids and ampholytes. Knowledge of pK_a values of drugs is necessary for prediction of their ionization under physiological conditions, but expected ionization can be affected by other molecules present in bioenvironment. For estimation of pharmacological behavior more relevant data are obtained in presence of micelles. The aim of this study was to investigate the effects of micellar solutions of surfactants, anionic sodiumdodecylsulfate (SDS), cationic cetyltrimethylammonium bromide (CTAB), non-ionic 4-octylphenol polyethoxylates (TX-100) as biomembrane models on acid-base equilibria of nine ACE inhibitors (captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, and zofenopril). Determinations of pK_a values in presence of surfactants (10^{-2} M) were performed at 25 °C and constant ionic strength of 0.1 M (NaCl). Based on experimental data values were calculated by computer program Hyperquad. Comparison with pK_a values determined in absence of surfactants under the same conditions revealed the shift from +1.90 to -1.54 units, which demonstrated a significant effect of surfactants on ionization of ACE inhibitors. Carboxyl group ionization was more susceptible than amino group and among surfactants employed, SDS expressed the most prominent effect on acid−base equilibria. Shifts of pK_a values demonstrate complex interactions between the opposite charge of ionizable groups of ACE inhibitors and polar or charged micelle surfaces. Estimation provides a better insight into their pharmacological behavior, especially since ionizable groups are involved in interaction with enzyme.

Marija Popović,
Vojvode Stepe 450, 11000 Belgrade, Serbia
+381 11 3951219
+381 11 3972840
marija.popovic@pharmacy.bg.ac.rs

Uticaj micelarnih rastvora surfaktanata na protolitičke ravnoteže ACE inhibitora

M. Popović[1], G. Popović[2], D. Agbaba[1]
[1]Katedra za farmaceutsku hemiju, [2]Katedra za opštu i neorgansku hemiju, Farmaceutski fakultet, Univerzitet u Beogradu

ACE inhibitori su lekovi koji se koriste u terapiji hipertenzije i drugih kardiovaskularnih poremećaja. Zbog prisustva jedne ili više jonizujućih grupa (karboksilna, tiolna, primarna i sekundarna amino grupa) u hemijskom pogledu predstavljaju kiseline i amfolite. Poznavanje pK_a vrednosti lekova neophodno je za predviđanje jonizacije pri fiziološkim uslovima, ali na očekivanu jonizaciju mogu uticati i drugi molekuli prisutni u biosredini. Za procenu farmakološkog ponašanja relevantniji su podaci o fizičko-hemijskim osobinama lekova dobijeni ispitivanjem u prisustvu micela. Cilj ovog rada bio je da se primenom micelarnih rastvora surfaktanata, kao pojednostavljenih modela biomembrana, ispita uticaj anjonskog natrijum-dodecilsulfata (SDS), katjonskog cetiltrimetilamonijum-bromida (CTAB), nejonskog surfaktanta 4-oktilfenol polietoksilata (TX-100) na kiselo-bazne ravnoteže devet ACE inhibitora (kaptopril, cilazapril, enalapril, fosinopril, lizinopril, perindopril, kvinapril, ramipril i zofenopril). Potenciometrijskom titracijom su određene pK_a vrednosti u prisustvu surfaktanata (10^{-2} M), na temperaturi 25 ^oC i pri konstantnoj jonskoj sili 0.1 M (NaCl)**.** Na osnovu eksperimentalnih podataka vrednosti su izračunate primenom kompjuterskog programa Hyperquad. Upoređivanjem sa pK_a vrednostima određenim bez prisustva surfaktanata, pod istim uslovima, uočeno je pomeranje pK_a vrednosti od +1.90 do -1.54 jedinice. Jonizacija karboksilne podložnija je uticaju surfaktanata od jonizacije amino grupe, a od primenjenih surfaktanata najveći uticaj na kiselo-bazne ravnoteže ispoljava SDS. Pomeranja pK_a vrednosti ACE inihitora u prisustvu surfaktanata ukazuju na postojanje složenih interakcija između suprotnih naelektrisanja jonizovanih kiselih i baznih grupa ACE inhibitora i naelektrisanih ili polarnih površina micela. Dobijeni rezultati pružaju bolji uvid u ponašanje ovih lekova u fiziološkim uslovima, naročito jer jonizujuće grupe direktno učestvuju u interakciji sa enzimom.

Marija Popović,
Vojvode Stepe 450, 11000 Beograd, Srbija
+381 11 3951219
+381 11 3972840
marija.popovic@pharmacy.bg.ac.rs