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PHYSIOLOGICALLY BASED MODELING IN THE DEVELOPMENT OF NOVEL DRUGS: DIGITAL WINDOW TO DRUG'S JOURNEY THROUGH THE BODY

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The application of computer-based (*in silico*) modeling&simulation tools has become a global trend in different areas of science, including pharmaceutical sciences. These methods have been increasingly used in different phases of formulation development, starting with defining a sound formulation strategy, through the selection of drug dose and optimal formulation for clinical studies, to the prediction of drug absorption/disposition in different populations, identification of potential drug-drug interactions, prediction of bioequivalence study outcomes and justification of biowaivers (1). *In silico* tools for the prediction of drug bioperformance incorporate the so called physiologically-based models i.e., systems of data on physiological conditions and processes a drug undergoes in the organism, with an adequate mathematical background to describe these processes. As such, these models allow prediction of the expected therapeutic outcomes following drug administration, and offer a distinctive opportunity to test hypotheses and identify the underlying mechanisms responsible for the phenomena a drug undergoes *in vivo*. In other words, they act as a digital window to "drug's journey through the body". Physiologically-based models have been upgraded continuously, and relatively simple models evolved into the model-based drug development platforms, initiating a transformational change in drug formulation research&development. Opposed to the traditional "trial&error" methods, the outcomes of *in silico* modeling are based on the knowledge of *in vivo* processes, and planning of the optimal formulation strategy depending on drug biopharmaceutical properties and physiological characteristics of the target population. The selected examples will demonstrate the basic principles of *in silico* modeling in the development of pharmaceutical formulations.

References

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PRIMENA FIZIOLOŠKI ZASNOVANOG MODELOVANJA U RAZVOJU INOVATIVNIH LEKOVA: DIGITALNI PROZOR U PUTOVANJE LEKA KROZ ORGANIZAM

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Primena računarski podržanih (*in silico*) metoda modelovanja i simulacija postala je globalni trend u različitim oblastima nauke, uključujući i farmaceutske nauke. Poslednjih godina ove metode nalaze sve širu primenu u različitim fazama razvoja leka, od definisanja strategije za razvoj formulacije, preko izbora odgovarajuće doze leka i optimalne formulacije za kliničke studije, do predviđanja apsorpcije i dispozicije leka u različitim populacijama pacijenta, identifikacije potencijalnih lek-lek interakcija, predviđanja ishoda studija biološke ekvivalencije i argumentovanja *biowaiver*-a (1). Programi za *in silico* simulaciju/predviđanje "ponašanja leka u organizmu" predstavljaju tzv. fiziološki-zasnovane modele, bazirane na saznanjima o fiziološkim uslovima i procesima kojima lek podleže u organizmu, kao i primeni odgovarajućih matematičkih relacija kojima je ove procese moguće opisati. Stoga predstavljaju korisno sredstvo, ne samo za predviđanje očekivanih terapijskih ishoda koji prate primenu leka, već i za testiranje hipoteza, odnosno, identifikaciju mehanizama koji su odgovorni za fenomene kojima lek podleže *in vivo*. Drugim rečima, predstavljaju digitalni prozor u "putovanje leka kroz organizam". Fiziološki-zasnovani modeli se kontinuirano unapređuju, te su relativno jednostavni modeli evolirali u tzv. model-zasnovane platforme za razvoj lekova, što je na neki način pokrenulo revoluciju u oblasti istraživanja i razvoja lekova. Za razliku od tradicionalnih metoda „pokušaja i greške", ishodi *in silico* modelovanja su zasnovani na poznavanju procesa koji se dešavaju *in vivo* i planiranju optimalne strategije za razvoj formulacije, u zavisnosti od biofarmaceutskih svojstava lekovite supstance i fizioloških karakteristika ciljane populacije pacijenata. U ovom izlaganju će, na odabranim primerima, biti prikazani osnovni principi *in silico* modelovanja u razvoju formulacija farmaceutskih preparata.

Literatura

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