P33

Molecular modeling of prostate specific antigen (PSA) and the design of compounds modulating its activity

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Prostate cancer is the most common cancer of males in industrialized countries. Its incidence has increased significantly due to PSA screenings and aging of the population. Common drug therapy has side effects affecting the patients' quality of life and some of the drugs eventually become inefficient. The objective of this research is to develop new drug molecules using computer-aided drug design (CADD). CADD is extremely important method in modern drug design. Recently, the crystal structure of PSA was published. However, crystal structures with bound ligands still lack. As such, a comparative model of PSA is developed using molecular modeling and dynamics. With the protein model, binding modes of PSA activating cyclic peptides are studied using molecular docking. Moreover, together with the crystal structure PSA model is used for virtual screening of novel drug candidates. Successful in silico models make it possible to predict the pharmacokinetic profile of novel drug candidates.

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P34

Solvent-mediated solid phase transformations of carbamazepine—Effects of simulated intestinal fluid and fasted state simulated intestinal fluid

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Solvent-mediated transformations of carbamazepine anhydrate (CBZ (A)) were investigated in Simulated Intestinal Fluid, a simple USP buffer medium, and in FaSSIF, which contains sodium taurocholate (STC) and lecithin. Raman spectroscopy (in situ) was utilized to reveal the connection between the changes in solid phase composition and dissolution rate while simultaneously detecting the solid state and the dissolved amount of CBZ. Initial dissolution rate was higher in FaSSIF due to better wetting and solubilization effects, while the solid phase data revealed that the crystallization of carbamazepine dihydrate (CBZ (D)) was inhibited in both dissolution media, albeit by different mechanisms. In SIF this inhibition was related to extensive needle growth, in FaSSIF to plate-like counterparts. These results underline the importance of biologically representative dissolution media linking the in vitro dissolution results of metastable solids to their in vivo dissolution behaviour.

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P35

Developing an extended compartmental absorption and transit model for per oral controlled drug delivery

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Computational methods have potential to decrease the length of time prior to submissions to regulatory authorities and to reduce the number of experiments in drug development. A pharmacokinetic compartmental absorption and transit model (CAT) is useful in predicting the per oral drug absorption in the small intestine. For controlled delivery, it is necessary to expand the model to take into account release and absorption in the colon. In this work, an extended CAT model was built based on pharmacoscintigraphic studies of a controlled release (CR) delivery system. Three colon segment compartments were introduced in the model. The extended design allows modeling of formulation transit, controlled drug release and absorption in the entire colon. The simulated plasma profiles were correlated with the in vivo findings. New model was tested by varying the parameters for transit, absorption and elimination. The model is useful in assessing the potential kinetics of CR medication.

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P36

Utilizing ion mobility spectrometry combined with mass spectrometry for analysis of pharmaceutical compounds

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Drift tube ion mobility spectrometry (IMS) is a time-of-flight technique which utilizes the characteristic ion mobilities of the gas phase ions for separation and detection of chemical species. In IMS instrument an applied drift voltage drives ions through drift tube where collisions occur between ions and neutral drift gas molecules. The separation of compounds is achieved based upon the different drift times of the ions through the drift tube. The drift time of an ion depends on its characteristic ion mobility. Furthermore, the mobility of an ion in an inert gas depends on the charge, reduced mass and collision cross section of the ion. In this study a self-made IMS instrument combined with commercial triple quadrupole mass spectrometer (IMS-MS) was utilized for analysis of pharmaceutical compounds. Four drugs (verapamil, metoprolol, propranolol and antipyrine) were chosen for the