APPLICATION OF MOLECULAR MODELLING TO BIOPHARMACEUTIQUE PROPERTIES SCREENING

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The study of the biopharmaceutical properties (i.e. the behaviour of the drug in the body in term of absorption, tissue distribution, biotransformation, drug-drug interactions, and elimination) are more and more included in new drugs research programs. While pharmacological studies give information on the activity and selectivity of new drugs, biopharmaceutical properties deal with the ability of new drugs to reach the target with the lowest inter- or even intra-subject variability and the best safety ratio, the combination of both domains making the success of future clinical phases and post AMM drug life. Even with the most recent LCMSMS equipment combined with powerful in vitro models, the biopharmaceutical screening is still not compatible with HTS, and not possible in some chemical series because of technical limitations.

Some molecular modelling tools using virtual chemical probes to calculate interaction descriptors allow the analysis of the possible interactions between the drugs and the component of biological matrix, and thus can be today used to mathematically models and thus to predict such in vitro or in vivo interactions. For example, the aqueous solubility depends directly from the interactions with water while the passage through a membrane depends more on interactions with the lipid parts and polar heads of the phospholipids. The affinity for a protein such as an efflux transporter (PgP) or a Cytochrome P450 depends on the easiness of the interaction between the enzyme and the drug. The rate of metabolism include in addition some chemical reactivity while the metabolic pathways refer more to the most probable drug positions within the active site of an enzyme. These models can be used to describe, to explain and even to predict the behavior of a drug in the body. This also open new possibilities to analysis rapidly the high quantity of information to be managed during drug discovery steps.

The way how these in *silico* models can be used to optimize at the earliest steps the ADME properties of new drugs for absorption, distribution, metabolism, and elimination will be presented using examples.