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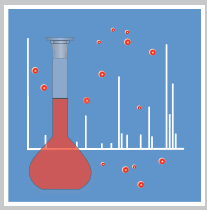

Highlights of Analytical Sciences in Switzerland

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Analytical Strategy to Characterize Drug–Plasma Interactions: From High Throughput to In-depth Analysis

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Launching a drug is a complex and time-consuming process that requires 15–20 years. It usually costs around 1 billion dollars and is rather risky: only one out of 10,000 studied compounds will eventually reach the market. Among the different challenges the pharmaceutical industry has to face to produce better drug candidates, it is essential to reduce the attrition rates during drug development by developing compounds with improved pharmacokinetics. Plasma protein binding (PPB) is an important drug characteristic that has strong implications for *in vivo* performance. It is widely accepted that only the free drug fraction can cross membrane barriers, be distributed to tissues, and elicit a pharmaceutical response. Moreover, the effect of a drug (pharmacological or toxicological) is related to the exposure of a patient to the free drug in plasma rather than to the total drug concentration. The binding of a drug to plasma proteins (albumin and α_1-acid glycoprotein), by regulating the free drug fraction, is thus considered an important parameter to be determined during the drug research process. Nowadays, the most widely used techniques for PPB measurement are equilibrium dialysis and ultrafiltration. However, these techniques have some limitations, which narrow their application in the current high-throughput pharmaceutical environment.

Our proposed methodology takes into account the requirements and specificity of the different stages of the drug research process. During the early stages of the drug discovery phase, the number of compounds to test is huge and detailed analysis cannot be performed on every molecule. Therefore, a screening step by affinity chromatography is first applied to identify strongly bound compounds (>85%) that are likely to cause drug safety issues or severe adverse effects. Affinity chromatography requires only a single analysis per compound to obtain an estimation of its affinity for a protein. Moreover, using a highly selective detector, such as mass spectrometry, compound pooling can be performed to further enhance the throughput. In a second step, the strong binders are studied with techniques that produce more information on the binding process (*i.e.* affinity constant, stoichiometry, kinetics of the interaction), even though they are more time-consuming. For this purpose, surface plasmon resonance biosensor and capillary electrophoresis, for drug-albumin and drug–α_1-acid glycoprotein, respectively, are particularly well adapted. **The developed strategy shows great potential to enhance the pharmacokinetic profile of drug candidates.**

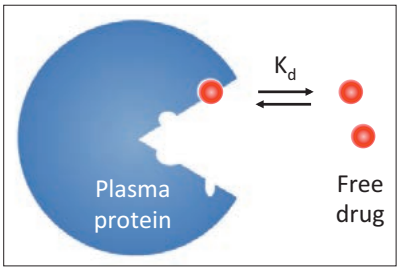

Fig. 1. Binding equilibrium between a plasma protein and a drug. K_d represents the dissociation constant.

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Reference

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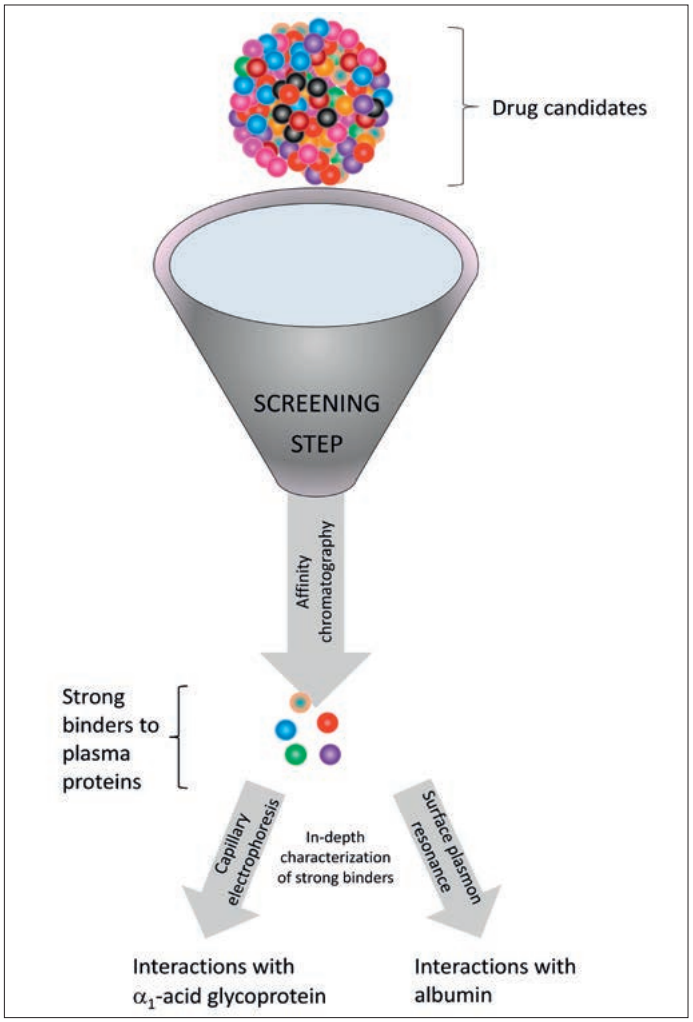

Fig. 2. Proposed methodology to assess drug–plasma protein interactions.

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