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Review

Introduction to *in vitro* estimation of metabolic stability and drug interactions of new chemical entities in drug discovery and development

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Abstract:
Determination of metabolic properties of a new chemical entity (NCE) is one of the most important steps during the drug discovery and development process. Nowadays, *in vitro* methods are used for early estimation and prediction of *in vivo* metabolism of NCEs. Using *in vitro* methods, it is possible to determine the metabolic stability of NCEs as well as the risk for drug-drug interactions (DDIs) related to inhibition and induction of drug metabolic enzymes. Metabolic stability is defined as the susceptibility of a chemical compound to biotransformation, and is expressed as *in vitro* half-life ($t_{1/2}$) and intrinsic clearance (CL_{int}). Based on these values, *in vivo* pharmacokinetic parameters such as bioavailability and *in vivo* half-life can be calculated. The drug metabolic enzymes possess broad substrate specificity and can metabolize multiple compounds. Therefore, the risk for metabolism-based DDIs is always a potential problem during the drug development process. For this reason, inhibition and induction *in vitro* screens are used early, before selection of a candidate drug (CD), to estimate the risk for clinically significant DDIs. At present, most pharmaceutical companies perform *in vitro* drug metabolism studies together with *in silico* prediction software and automated high-throughput screens (HTS). Available data suggest that *in vitro* methods are useful tools for identification and elimination of NCEs with unappreciated metabolic properties. However, the quantitative output of the methods has to be improved. The aim of this review is to highlight the practical and theoretical basis of the *in vitro* metabolic methods and the recent progress in the development of these assays.

Key words:
drug metabolism, metabolic stability, drug interactions, high-throughput screens, cytochrome P450