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Short communication

Integrating *in vitro* pharmacokinetic screening and QSPR modeling for enhanced drug candidate selection

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Introduction

Drug discovery and development is a complex and costly process with high attrition rates, as many promising candidates fail during preclinical and clinical stages. A major cause of these failures is unfavorable pharmacokinetic behavior, including poor absorption, low bioavailability, inadequate distribution, rapid metabolism, and metabolite-associated toxicity. Pharmacokinetic and safety issues are estimated to account for around 40–50% of failures in early development, particularly during preclinical studies and Phase I trials (Kenakin, 2024; Palmer et al., 2022). Traditionally, pharmacokinetic properties have been evaluated using animal models, which, although informative for ADMET profiling, are limited by ethical concerns, high costs, and imperfect translation to human systems. These limitations have driven the adoption of the 3Rs principles (Replacement, Reduction, and Refinement) in pharmaceutical research, promoting alternative methods that reduce animal use while maintaining scientific validity (Vitale and Ricceri, 2022). In this context, advanced *in vitro* techniques combined with computational modeling offer a promising strategy to overcome ethical and scientific limitations, enabling early identification of compounds with poor pharmacokinetic profiles and improving the efficiency and success rate of drug development.

In vitro pharmacokinetic evaluation

One of the most widely used *in vitro* techniques is the Parallel Artificial Membrane Permeability Assay (PAMPA), which evaluates passive diffusion through an artificial lipid membrane and is used to predict intestinal, blood-brain barrier, skin, and corneal permeability. Its main advantages are simplicity, high throughput, low cost, and good reproducibility, while the main disadvantage is inability to predict active transport (Kansy et al., 2004; Bošković et al., 2024). Biopartitioning micellar chromatography (BMC) is a chromatographic method that mimics drug–membrane interactions using micellar mobile phases, allowing estimation of lipophilicity and partitioning behavior, which are crucial for pharmacokinetics (Molero-Monfort et al., 2001). Electrochemical methods simulate oxidative metabolism, enabling the study of metabolites, toxicity, and compound stability. Electrochemical methods also enable the simulation of drug binding to human serum albumin, which impacts their distribution (Bošković et al., 2024; Nikzad and Rafiee, 2024). Modern chromatographic techniques, such as immobilized artificial membrane (IAM) chromatography, use stationary phases containing phosphatidylcholine to mimic biological membranes and assess protein binding and metabolic stability (Tsopelas et al., 2024).

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The role of *in silico* modeling and QSPR approaches

Rapid advances in computational chemistry and machine learning have significantly changed drug candidate evaluation. Quantitative Structure-Property Relationship (QSPR) modeling establishes mathematical relationships between molecular descriptors and experimentally measured physicochemical or pharmacokinetic properties, enabling prioritization of compounds with favorable profiles (Chen et al., 2024; Dobričić et al., 2024). Modern machine learning methods, including random forests, support vector machines, artificial neural networks, and deep learning, are capable of capturing complex nonlinear relationships between molecular structure and biological activity. The greatest benefit is achieved when experimental and computational approaches are integrated. This enables early identification of pharmacokinetic liabilities, for example by incorporating permeability data from PAMPA or chromatographic retention data into QSPR models to predict absorption. This integrated approach supports the design of compounds with balanced pharmacokinetic and pharmacodynamic properties, allowing simultaneous optimization of activity, ADME characteristics, and safety, thereby increasing the likelihood of clinical success.

Conclusion

Pharmacokinetic limitations remain a major cause of drug candidate attrition in pharmaceutical development, making early and reliable prediction of drug behavior essential. *In vitro* techniques such as PAMPA, biopartitioning micellar chromatography, electrochemical methods, and immobilized artificial membrane chromatography, provide valuable experimental data while supporting the 3Rs principles. QSPR models enable prediction of key molecular properties and support rational drug design. The integration of experimental and computational approaches improves decision-making, reduces costs and animal testing, and increases the likelihood of identifying safe and effective drug candidates.

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