Publication

In vitro safety cardiovascular pharmacology studies: impact of formulation preparation and analysis.

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Abstract

Collection of formulation samples is required for GLP in vitro studies to check the exposure of the test system and allow reliable determinations of safety margins. In vitro studies conducted in-house were investigated to evaluate problems of solubility, stability and adsorption of the formulations. Terfenadine was used as reference substance to illustrate the purpose. Lowered target concentrations of test substances in in vitro studies can be attributed to the solubility limitation in the superfusion medium, the low stability under frozen conditions (24% of the final solutions stable at -20 °C) and/or the adsorption on the superfusion tubing (30% of the studies). Terfenadine also showed a limited solubility (measured concentrations ranging from 0.597 µM to 0.833 µM instead of 1 µM) and a loss of substance through the superfusion tubing from -30.2% to -39.2% with dimethylsulfoxide, ethanol or methanol. Terfenadine solubility was improved with 2-hydroxypropyl-β-cyclodextrin, no adsorption was observed, but its capacity to block the hERG channel was decreased. It is recommended to determine the substance solubility in appropriate buffers, to evaluate possible adsorption during method validation (formulation samples collected after superfusion), and to prepare fresh formulation each testing day with immediate analysis in absence of stability data. This strategy clearly favors single-site as opposed to multi-site studies.