In vitro-in silico approach to access the potential of alcohol-induced dose dumping: Ibuprofen case
S. Cvijić, A. Lipovac, M. Lukić, S. Beloica, I. Aleksić, J. Paroјčić
University of Belgrade - Faculty of Pharmacy, 11000 Belgrade, Serbia
jelena.parojcic@pharmacy.bg.ac.rs

Purpose: Co-administration of alcohol beverages with sustained-relase (SR) oral dosage forms may pose a risk to patients due to potential alcohol-induced dose dumping (ADD). Regulatory guidances provide general recommendations regarding the assessment of ADD, emphasizing that suitable in vitro dissolution tests (e.g. 2 h in 0.1 M HCl containing 5-40% v/v ethanol) should be carried out to identify the risk of ADD. In addition, in silico modelling could be used to correlate in vitro data to the corresponding pharmacokinetic outcome. The aim of this study was to investigate the applicability of in vitro-in silico approach to access a potential ADD, using ibuprofen (IBU) SR tablets as model formulations.

Methods: IBU solubility was tested in different media (0.1 M HCl pH 1.1 without/with addition of 5 and 40% ethanol, and USP buffers pH 6.8 and pH 7.4). Drug dissolution from the investigated matrix tablets (SR1-based on xanthan gum, SR2-based on stearic acid) was tested in the paddle apparatus, using media change method (pH 1.1 without/with addition of 5 or 40% ethanol for 2 h, pH 6.8 for 2 h, pH 7.4 for 20 h). The obtained dissolution data, incorporated in the previously developed and validated IBU-specific gastrointestinal absorption model were used for in silico simulations (Simcyp® Population-Based Simulator, v. 14.1; Certara™, USA) of drug plasma concentration-time profiles (1).

Results: Increase in IBU solubility at pH 1.1 in the presence of 40% ethanol (17.01 mg/ml compared to 0.08 mg/ml in aqueous media) indicated that concomitant intake of alcohol might induce dose dumping from SR tablets in the stomach. Dissolution data revealed that 5% ethanol in acidic medium had no significant effect on drug dissolution rate. However, IBU dissolution during the first 2 hours was notably increased in media containing 40% ethanol (Fig. 1). Increase in media pH resulted in the increased drug dissolution from lipid matrix based formulation, while release from the hydrophilic matrix tablets was less affected. Differences in in vitro drug release were reflected in the respective in silico predicted ibuprofen pharmacokinetic profiles (Fig. 2). The obtained in silico data indicate that the observed changes in drug release rate would not result in plasma concentrations beyond the therapeutic window (up to 50 µg/ml (2)). Simulation based on hypothetical dissolution scenario, illustrating the ‘worst case’, demonstrated that even 100% IBU release in the stomach (profile V100) would not lead to toxic concentrations in plasma (> 100 µg/ml (2)).

Conclusions: The presented IBU case demonstrated superiority of the combined in vitro-in silico approach over simple in vitro testing for ADD risk assessment. It merits further investigation and could complement formulation development of sustained release dosage forms.

References: