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Amorphous solid dispersion (ASD)formulation of the low-solubility drug rifaximine allows overcoming the solubility-permeability tradeoff

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The aim of this work was to assess the efficiency of different rifaximine amorphous solid dispersions (ASDs) in achieving and maintaining supersaturation and to investigate the solubility-permeability interplay when increasing the apparent solubility via ASD formulations. Spray-dried ASDs of rifaximine in different hydrophilic polymers were prepared and their ability to achieve and maintain supersaturation over 24 h was assessed. Then, rifaximine's apparent intestinal permeability was investigated as a function of increasing supersaturation in-vitro using the parallel artificial membrane permeability assay (PAMPA) model and in-vivo using the single-pass rat intestinal perfusion model. The efficiency of the different ASDs to achieve and maintain supersaturation of rifaximine was found to be highly polymer dependent, and the Copovidone:HPC-SL formulation was found to be superior to the other ASDs, allowing supersaturation of 200× that of the crystalline solubility for over 20 hours. Rifaximine flux across the intestine from supersaturated solutions was increased, and the apparent intestinal permeability was constant, irrespective of the degree of supersaturation. In conclusion, while with other solubility-enabling approaches (e.g., surfactants, cyclodextrins, cosolvents), it is not enough to increase the apparent solubility, but to strike the optimal solubility–permeability balance, which limits the chances for successful drug delivery, the amorphous form emerges as a more advantageous strategy, in which higher apparent solubility (i.e., supersaturation) will be readily translated into higher drug flux and overall absorption.

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