formulation aspects. The results of preformulation measurements indicate that these polymers can be used as potential carriers in ophthalmic drug delivery.

de Kanter, R. et al. (2016). "Physiologically-based pharmacokinetic modeling of macitentan: Prediction of drug-drug interactions." *Clin Pharmacokinet* 55(3):369–380.

INTRODUCTION: Macitentan is a novel dual endothelin receptor antagonist for the treatment of pulmonary arterial hypertension (PAH). It is metabolized by cytochrome P450 (CYP) enzymes, mainly CYP3A4, to its active metabolite ACT-132577. METHODS: A physiological-based pharmacokinetic (PBPK) model was developed by combining observations from clinical studies and physicochemical parameters as well as absorption, distribution, metabolism and excretion parameters determined in vitro. RESULTS: The model predicted the observed pharmacokinetics of macitentan and its active metabolite ACT-132577 after single and multiple dosing. It performed well in recovering the observed effect of the CYP3A4 inhibitors ketoconazole and cyclosporine, and the CYP3A4 inducer rifampicin, as well as in predicting interactions with S-warfarin and sildenafil. The model was robust enough to allow prospective predictions of macitentan-drug combinations not studied, including an alternative dosing regimen of ketoconazole and nine other CYP3A4-interacting drugs. Among these were the HIV drugs ritonavir and saquinavir, which were included because HIV infection is a known risk factor for the development of PAH. CONCLUSION: This example of the application of PBPK modeling to predict drug-drug interactions was used to support the labeling of macitentan (Opsumit).

De Paula, W. X. et al. (2018). "A long-lasting oral preformulation of the angiotensin II AT1 receptor antagonist losartan." *Drug Dev Ind Pharm* 44(9):1498–1505.

Losartan (Los), a non-peptidic orally active agent, reduces arterial pressure through specific and selective blockade of angiotensin II receptor AT1. However, this widely used AT1 antagonist presents low bioavailability and needs once or twice a day dosage. In order to improve its bioavailability, we used the host: guest strategy based on beta-cyclodextrin (betaCD). The results suggest that Los included in betaCD showed a typical pulsatile release pattern after oral administration to rats, with increasing the levels of plasma of Los. In addition, the inclusion compound presented oral efficacy for 72 hours, in contrast to Los alone, which shows antagonist effect for only 6 hours. In transgenic (mREN2)L27 rats, the Los/betaCD complex reduced blood pressure for about 6 d, whereas Los alone reduced blood pressure for only 2 d. More importantly, using this host: guest strategy, sustained release of Los for over a week via the oral route can be achieved without the need for encapsulation in a polymeric carrier. The proposed preformulation increased the efficacy reducing the dose or spacing between each dose intake.

Dorati, R. et al. (2018). "Development of a topical 48-H release formulation as an anti-scarring treatment for deep partial-thickness burns." *AAPS Pharm Sci Tech* 19(5):2264–2275.

The purpose of this study was to develop pirfenidone (PF) ointment formulations for a dose finding study in the prophylactic treatment of deep partial-thickness burns in a mouse model. A preformulation study was performed to evaluate the solubility of PF in buffers and different solvents and its stability. Three different formulations containing 1, 3.5, and 6.5% w/w PF were prepared and optimized for their