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THE EFFECT OF SURFACTANTS AND pH MODIFYING AGENTS ON THE DISSOLUTION AND PERMEATION OF PIMOBENDAN

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PURPOSE

Solubility and permeability are two key parameters for establishing *in vitro-in vivo* correlation for poorly water-soluble active pharmaceutical ingredients (APIs). While the solubility of the API is altered when using solubilizing agents as formulation additives, recent studies demonstrate that also effective permeability of the API may change due to the addition of these excipients[1]. This study aimed to show the importance of early screening of solubility and permeability in presence of additives to achieve the expected bioavailability of the API. In this work, the effect of surfactants and microenvironmental pH modifiers were in focus, and pimobendan as a poorly water-soluble API was chosen as the model drug.

METHOD(S)

Pimobendan (PIMO, 334 g/mol) was received from Lavet Ltd. (Kistarcsa, Hungary). Two PIMO brand formulations were obtained from commercial trade. The formulation additives (SDS, PEG 6000 (Macrogol 6000), Gelucire, Citric acid, Malic acid, Tartaric acid) were sourced from Sigma-Aldrich Co. Llc. (St. Louis, MO, USA) and Merck Ltd. (Budapest, Hungary)

The pH-dependent equilibrium solubility of PIMO was studied at 37 °C in pH 1.2 (HCl), pH 3.0, pH 4.5, and pH 6.5 phosphate buffer using the traditional shake-flask method[2] with *in situ* fiber optic UV spectroscopic endpoint detection by the Rainbow Dynamic Dissolution Monitor instrument (Pion Inc., Billerica, MA). The equilibrium solubility of PIMO (10 mg) was also studied in the presence or absence of formulation additives at pH 4.5.

The parallel artificial membrane permeability assay (PAMPA) method was used to study the excipient effect of the permeation of PIMO following the protocol described by Avdeef[3], applying the GIT PAMPA Explorer assay kit and instrumentation (Pion Inc.).

The brand formulations of PIMO were tested using µFLUX (Pion Inc., Billerica MA, USA) apparatus to investigate the complex formulation effect on membrane flux. The test system consists of a donor and an acceptor chamber separated by an artificial membrane (PVDF, polyvinylidene-fluoride, 0.45 µm, 1.54 cm2) impregnated with 25 µL GIT lipid to form a lipophilic barrier between the donor and acceptor chambers.

RESULT(S)

In the case of pH modifiers, the equilibrium solubility of the API increased even in the presence of low amounts of formulation additives (see Table 1.), while the permeability decreased significantly (Figure 1). No negative effect was observed for two surfactants at low additive levels, but these additives also exhibited a slightly negative effect on permeability when used at higher concentrations (Figure 1).

In line with the results of the solubility and permeability measurements, in the simultaneous dissolution-permeation studies the surfactants-containing formulation (Product A contains Macrogol 6000 and Gelucire) was found to be slightly better than the pH-modifier-containing one (Product B contains malic acid) (Figure 2). It can be due to the phenomenon that the dissolution of the active substance can be enhanced by these surfactants without any significant permeability reducing effect at the concentrations used in the formulation.

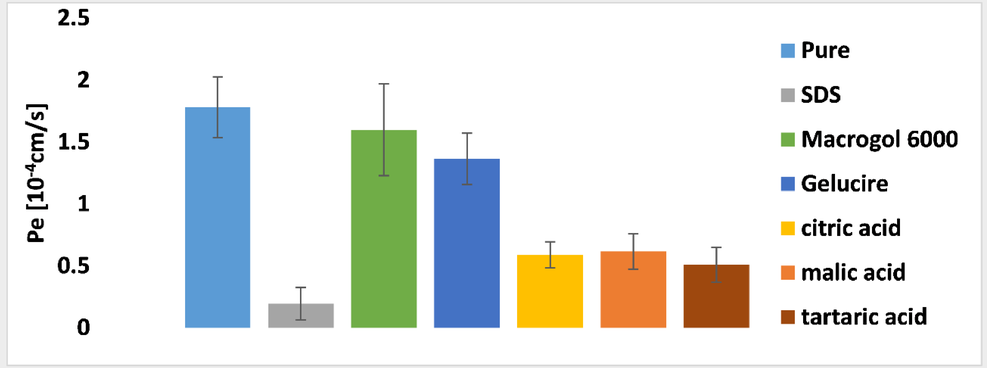

Figure 1. Effective permeability values of PIMO at higher additive concentrations

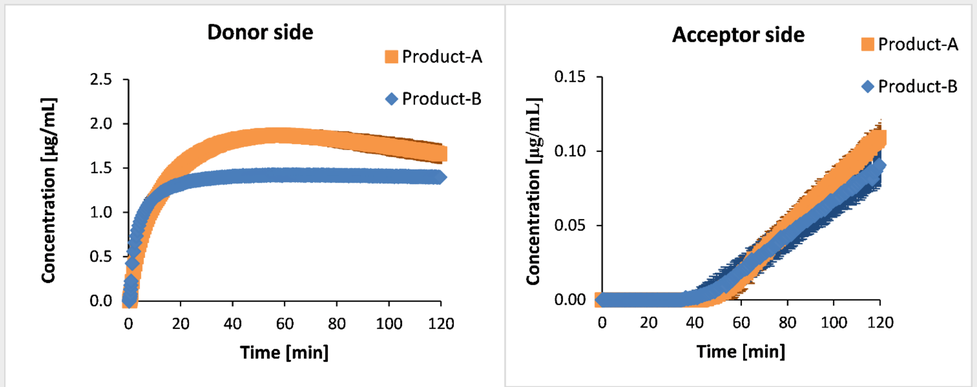

Figure 2. Concentration curves at donor and acceptor side of uFlux in case of Product-A and Product-B formulation

Table 1. Equilibrium solubility of PIMO in presence of different additives

additive	additive concentration [µg/mL]	pH	equilibrium solubility of PIMO [µg/mL]
pure PIMO	-	4.5	1.04 ± 0.06
SDS	84	4.5	2.97 ± 0.09
PEG 6000	36	4.5	1.09 ± 0.09
Gelucire	12	4.5	0.98 ± 0.09
citric acid	100	4.3	1.17 ± 0.14
malic acid	100	4.3	1.12 ± 0.08
tartaric acid	100	4.2	1.51 ± 0.16

CONCLUSION(S)

The results obtained from the present study clearly demonstrate the importance of studying drug-additive interactions in every step of formulation development and, based on these, the selection of the appropriate quality and quantity of additives. In addition, the results also underline the significance of performing simultaneous dissolution-permeation studies to predict bioavailability.

REFERENCE

1: Arik Dahan and Jonathan M. Miller, The Solubility–Permeability Interplay and Its Implications in Formulation Design and Development for Poorly Soluble Drugs; AAPS J. 2012 Jun; 14(2): 244–251.

2: Baka, E.; Comer, J. E. A.; Takács-Novák, K. Study of Equilibrium Solubility Measurement by Saturation Shake-Flask Method Using Hydrochlorothiazide as Model Compound. J. Pharm. Biomed. Anal. 2008, 46 (2): 335–341.

3: A. Avdeef, Absorption and drug development: Solubility, Permeability, and Charge State, John Wiley and Sons, United States, 2nd edn., 2012.