International Journal of Pharmaceutics 520 (2017) 14–20

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Original Research Article

Interaction of pharmaceutical excipients with organic cation transporters

Sirima Soodvilai[a], Sunhapas Soodvilai[b,c], Varanuj Chatsudthipong[b], Tanasait Ngawhirunpat[a], Theerasak Rojanarata[a], Praneet Opanasopit[a,*]

[a] Pharmaceutical Development of Green Innovations Group (PDGIG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand
[b] Department of Physiology, Faculty of Science, Mahidol University, Bangkok, Thailand
[c] Research Center of Transport Proteins for Medical Innovation, Faculty of Science, Mahidol University, Bangkok, Thailand

ARTICLE INFO

Article history:
Received 23 August 2016
Received in revised form 6 January 2017
Accepted 20 January 2017
Available online 25 January 2017

Keywords:
Tween
Drug transporters
Kidney
Liver
Excipients

ABSTRACT

Increasing evidences have shown that many pharmaceutical excipients are not pharmacologically inert but instead have effects on several transport function of uptake and efflux drug transporters. Herein, we investigated whether the excipients frequently used in many drug formulations affect transport function of organic cation transporters (OCTs) that are responsible for elimination of cationic drugs. Our finding revealed that solubilizing agents, Tweens, showed the most significant effect rbOCT1/2-mediated [^{3}H]-MPP$^+$ uptake in heterologous expressing cells. The haft inhibitory concentration (IC_{50}) values of Tween 20, Tween 60, and Tween 80 for OCT1 were 85 ± 1.12, 50 ± 1.26, 106.00 ± 1.20 μg/ml, respectively, while the IC_{50} values for OCT2 were 295 ± 1.48, 42 ± 1.15, 185 ± 1.20 μg/ml, respectively. The inhibitory effect of Tween 20, Tween 60 and Tween 80 on OCT2-mediated [^{3}H]-MPP$^+$ uptake in the human renal proximal tubular cells (RPTEC/TERT1 cells) was found and the IC_{50} values was similar to heterologous OCT2 expressing cells. Interestingly, Tween 20, Tween 60 and Tween 80 exhibited less inhibitory effect on OCT1 functions in HepG2 cells expressing OCT1 compared with heterologous OCT1 expressing cells. In addition, clearance of [^{3}H]-MPP$^+$ was reduced in mice receiving Tween 20 compared with vehicle. The present study provides the first evidence revealing that Tweens, solubilizing excipients, could inhibit transport function of OCT1 and OCT2 which play crucial roles for pharmacokinetics, drug–drug interactions and tissue deposition of many cationic drugs.

1. Introduction

Pharmaceutical excipients are important in pharmaceutical formulations facilitate their preparations for example, surfactants are extensively used in pharmaceutical formulations to improve dissolution of poorly soluble drugs (Strickley, 2004; Engel et al., 2012; Paus et al., 2015; Elder et al., 2016). In addition, the excipients could also help in improving patient acceptability. The excipients commonly used in pharmaceutical formulations include solvents such as dimethyl sulfoxide (DMSO), propylene glycol (PG) and polyethylene glycol (PEG); cyclodextrins and surfactants (Cremophor, Tween, and Span) (Goole et al., 2010). Although, excipients have been considered to be inert, the emerging data demonstrate that numerous excipients may directly or indirectly alter the transport activity of drug transporters (Goole et al., 2010). Previous studies reported that the numbers of surfactants/excipients inhibited the transport activity of P-glycoprotein (P-gp), a member of the human ABC transporters that actively transport xenobiotics out of cells. For instance, Cremophor EL, Tween80 and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) inhibited P-gp and subsequently increased absorption of its substrates (Yamagata et al., 2007). Moreover, Cremophor EL, Tween 20, Span 20, Pluronic P85 and Brij 30 could inhibit efflux of [^{3}H]-mitoxantrone, a substrate of breast cancer resistance protein (BCRP) (Yamagata et al., 2007, 2009). Recently, excipients commonly used in drug delivery system as self-emulsifying have been shown to interact with human multidrug resistance related protein 2 (MRP2) (Li et al., 2013). The excipients might alter their incorporated drug pharmacokinetics which subsequently affects its therapeutic efficacy and/or enhancing adverse side effects (Goole et al., 2010).

* Corresponding author at: Pharmaceutical Development of Green Innovations Group (PDGIG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand. Tel.: +66-34-255800; fax: +66-34-255941.
E-mail address: opanasopit_p@su.ac.th (P. Opanasopit).

http://dx.doi.org/10.1016/j.ijpharm.2017.01.042
0378-5173/

Organic cation transporters (OCTs) play crucial roles in pharmacokinetics and pharmacodynamics of many cationic drugs, at the level of OCTs is of high clinical relevance (International Transporter C. et al., 2010). Three members of the OCTs (SLC22A) family including OCT1, OCT2, and OCT3 have been cloned and characterized, (Schomig et al., 1998; Hosoyamada et al., 1999). Human OCT1 and OCT2 are highly expressed in liver and kidney, respectively, whereas OCT3 is ubiquitously expressed in multiple tissues such as skeletal muscles, brain, placenta, liver, and kidney (Jonker and Schinkel 2004; Koepsell et al., 2007). OCTs play a crucial role in excretion of a wide range of organic cations, including endogenous compounds and therapeutic agents (Okuda et al., 1999; Jonker and Schinkel 2004; Urakami et al., 2004; Wright and Dantzler, 2004; Otsuka et al., 2005). OCTs transport many drugs such as beta-blockers, quinidine, cisplatin, morphine, metformin, phenoxybenzamine, prazosin, procainamide, and cimetidine (Ciarimboli et al., 2005; Kimura et al., 2005; Koepsell et al., 2007). Thus, the renal OCTs are important determinant of drug efficacy and toxicity (Ciarimboli et al., 2005; Wright 2005; Choi and Song, 2008). It has been reported that metformin fails to reduce fasting plasma glucose in type 2 diabetes patients who have mutation of OCT1 which is explained by decreasing hepatic uptake of metformin (Shu et al., 2007). Furthermore, cimetidine which is a substrate of OCT1and OCT2 significantly increased the plasma concentration of metformin and reduced its hepatic and renal clearance (Somogyi et al., 1987; Wang et al., 2003). These evidences indicated that OCT1 and OCT2 play a vital role in pharmacokinetic and drug disposition.

Since, pharmaceutical excipients are shown to interact with efflux transporters; therefore, the aim of this study was to investigate whether pharmaceutical excipients frequently used in many drug formulations affected transport function of OCT1 and OCT2. The pharmaceutical excipients including surfactants, solubilizing agent, and suspending agents were evaluated on

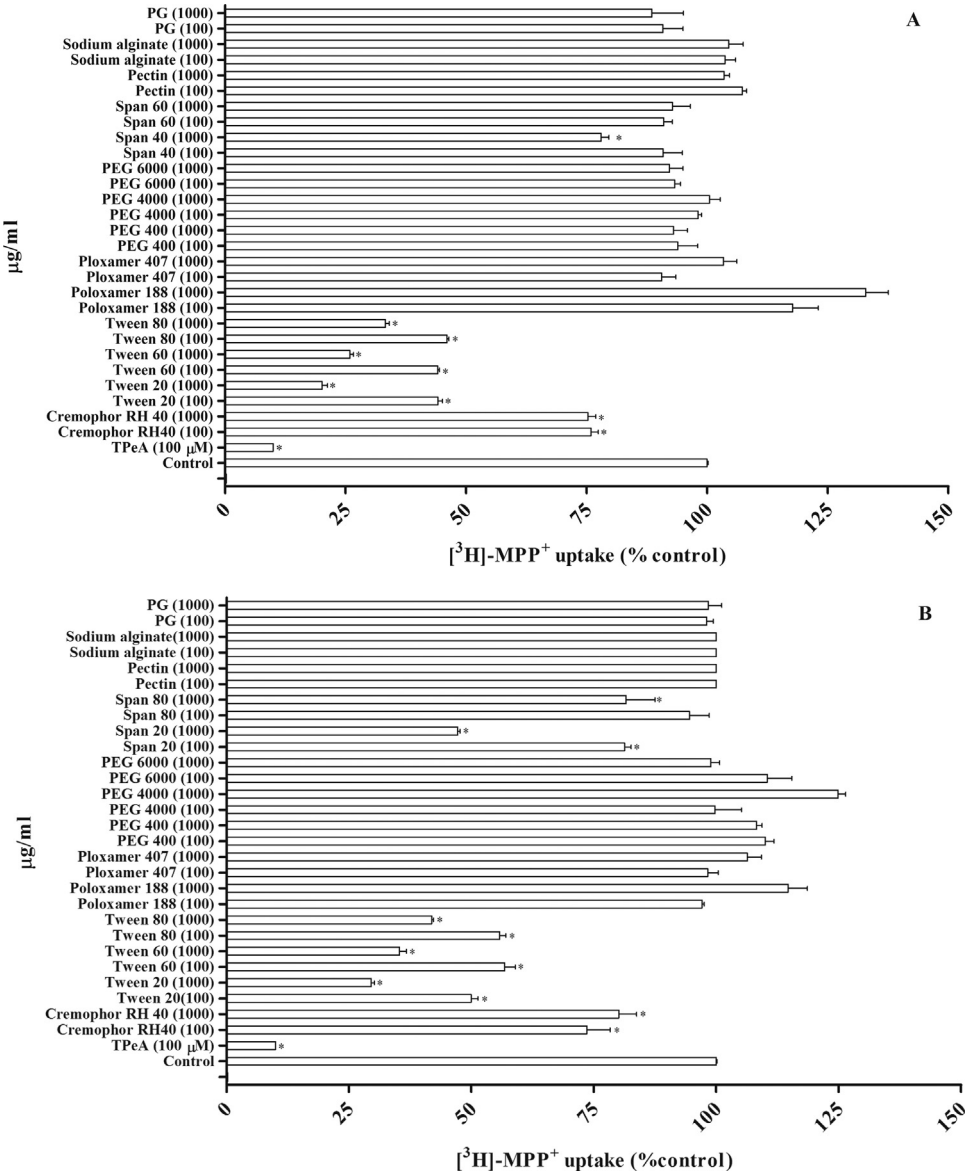

Fig. 1. Inhibitory effect of various excipients on the uptake of [^{3}H]-MPP$^+$ in (A) rbOCT1-CHO-K1 and (B) rbOCT2-CHO-K1. Uptake of [^{3}H]-MPP$^+$ (10 nM) was measured in the presence or absence of excipients. Tetrapentylammonium (TPeA) (100 μM) were used as positive control. The data are expressed as mean ± S.E. from three independent experiments, expressed as percentage of control. $^*P < 0.05$ compared with control.