Preliminary study on screening the intermolecular interactions of organic cation drugs from BSC Class III (case study Metformin)

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Among the orally administered drugs, about 40% share the properties of organic cations (protonated bases) or neutral bases at physiological pH, which indicates one important point for studying their transport mechanisms [1]. Antineoplastic platinum compounds [2,3], the histamine H_2 receptor antagonist cimetidine [4], the antiviral drugs (acyclovir, gancyclovir, lamivudine and zalcitabine) [5-7], the antidiabetic drug metformin [8,9], and the antiarrhythmic drug quinidine [10], are the identified to be transported by the organic cation transporters OCT1, OCT2 and OCT3 (membrane transporters) [2]. The case study of drug model (DM) metformin (MET), that according to Biopharmaceutical Classification System (BCS) belongs to the class III drugs (high solubility, low permeability) [11], emphasizes the importance of non-covalent interactions of this dication drug with range of ligands selected from the GRAS (Generally Recognized as Safe by FDA for food additives list) [12].

MET (*N,N*-dimethylbiguanide) is the only approved hypoglycemic drug of the biguanide class used in oral therapy of type 2 diabetes, marketed as hydrochloride, embonat (pamoate) and *p*-chlorophenoxy acetate salt [13]. Because of the biguanide π-conjugated system, MET in solution can exist in three resonance-stabilized forms, *i.e.* as neutral molecule (MET), monoprotonated ($METH^+$) or diprotonated ($METH^{2+}$) cation, with dissociation constants in water typical of biguanides:

Metformin = L; [HL]/[L][H] pK_{a1}(N−H^+)~12.40; [H_2L]/[HL][H] pK_{a2}(N−H^+)= 2.96 (NIST database)

The high basicity of pK_{a1} and the difference between the pK_a values qualify MET as organosuperbase and determine the stability of its monoprotonated form $METH^+$ within a wide range of pH [14]. Patterns of charge assisted H-bonding between MET and ligands are expected to be useful in predicting its absorption and transportation. Comparable study on predicting ligands for OTC1 by docking, applying High-Throughput Screening (HTS) and *in silico* modeling [15], offer an opportunity for growing the molecular crystals of MET with drugs, that are uses in combo- therapy with MET, as well with excipients and food ingredients, thus by generating the crystallographic, thermodynamic and spectroscopy data MET-ligand interactions, contributes the development of delivery systems with enhanced permeability of BSC class III drug models.

References

1. Neuhoff S, Ungell AL, Zamora I, Artursson P. pH-dependent bidirectional transport of weakly basic drugs across Caco-2 monolayers: implications for drug–drug interactions. *Pharm. Res.*20(8), 1141–1148 (2003).

2. Zhang S, Lovejoy KS, Shima JE *et al.* Organic cation transporters are determinants of oxaliplatin cytotoxicity. *Cancer Res.*66(17), 8847–8857 (2006).

3. Yonezawa A, Masuda S, Yokoo S, Katsura T, Inui KI. Cisplatin and oxaliplatin, but not carboplatin and nedaplatin, are substrates for human organic cation transporters (SLC22A1–3 and MATE family). *J. Pharmacol. Exp. Ther.*319(2), 879–886 (2006).

4. Barendt WM, Wright SH. The human organic cation transporter (hOCT2) recognizes the degree of substrate ionization. *J. Biol. Chem.*277(25), 22491–22496 (2002).

5. Takeda M, Khamdang S, Narikawa S *et al.* Human organic anion transporters and human organic cation transporters mediate renal antiviral transport. *J. Pharmacol. Exp. Ther.*300(3), 918–924 (2002).

6. Jung N, Lehmann C, Rubbert A *et al.* Relevance of the organic cation transporters 1 and 2 for antiretroviral therapy in HIV infection. *Drug Metab. Dispos.*36(8), 1616–1623 (2008).

7. Minuesa G, Volk C, Molina-Arcas M *et al.* Transport of lamivudine (3TC) and high-affinity interaction of nucleoside reverse transcriptase inhibitors with human organic cation transporters 1, 2, and 3. *J. Pharmacol. Exp. Ther.*329(1), 252–261 (2009).

8. Kimura N, Masuda S, Tanihara Y *et al.* Metformin is a superior substrate for renal organic cation transporter OCT2 rather than hepatic OCT1. *Drug Metab. Pharmacokinet.*20(5), 379–386 (2005).

9. Nies AT, Koepsell H, Winter S *et al.* Expression of organic cation transporters OCT1 (SLC22A1) and OCT3 (SLC22A3) is affected by genetic factors and cholestasis in human liver. *Hepatology*50(4), 1227–1240 (2009).

10. Hasannejad H, Takeda M, Narikawa S *et al.* Human organic cation transporter 3 mediates the transport of antiarrhythmic drugs. *Eur. J. Pharmacol.*499(1–2), 45–51 (2004).

11. Cheng CL, Yu LX, Lee HL, Yang CY, Lue CS, Chou CH., Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: bridging evidence for metformin immediate-release tablet. Eur J Pharm Sci.;22(4):297-304 (2004).

12. http://www.accessdata.fda.gov/scripts/fdcc/?set=SCOGS

13. Rojas et al., Metformin: an old but still the best treatment for type 2 diabetes, Diabetology & Metabolic Syndrome 2013, 5:6.

14. Desai D, Wong B, Huang Y, Ye Q, Tang D, Guo H, Huang M, Timmins P. Surfactant-mediated dissolution of metformin hydrochloride tablets: wetting effects versus ion pairs diffusivity J Pharm Sci. 2014, 103(3):920-6.

15. Chen EC, Khuri N, Liang X, Stecula A Chien HC, Yee SW, Huang Y, Sali A, Giacomini KM. Discovery of Competitive and Noncompetitive Ligands of the Organic Cation Transporter 1 (OCT1; SLC22A1). J Med Chem. 2017 Apr 13;60(7):2685-2696.