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Title page

Transporters Involved in Metformin Pharmacokinetics and Treatment Response

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Abstract

Metformin, widely used as first-line treatment for type 2 diabetes, exists primarily as a hydrophilic cation at physiological pHs. As such, membrane transporters play a substantial role in its absorption, tissues distribution, and renal elimination. Multiple organic cation transporters are determinants of the pharmacokinetics of metformin, and many of them are important in its pharmacological action, as mediators of metformin entry into target tissues. Further, a recent genomewide association study (GWAS) in a large multi-ethnic population implicated polymorphisms in SLC2A2, encoding the glucose transporter, GLUT2, as important determinants of response to metformin. Here, we describe the key transporters associated with metformin pharmacokinetics and response.
Introduction

Metformin is among the world’s most widely prescribed drugs, and is used primarily for the treatment of type 2 diabetes (T2D). Metformin and its structurally related analog, phenformin, are derivatives of guanidine, which was discovered in the extracts of the plant *Galega officinalis* (French Lilac) in the 1920s\(^1\). Metformin improves peripheral and liver sensitivity to insulin, reduces glucose production in the liver, increases insulin-stimulated uptake and utilization of glucose by peripheral tissues, decreases appetite, and causes weight reduction\(^2\). In recent years, new indications for metformin use in clinical practice have emerged. In particular, a number of studies have shown that metformin can positively influence multiple cardiovascular disease risk markers, including improvement of serum lipid profiles and modulation of inflammatory markers, and possibly reduce risk for cancer\(^2-5\).

Metformin is an oral agent. With a pKa of 11.5 and a low logP value, \(-1.43\), metformin is mostly ionized at physiological pHs\(^6\). Thus, rapid passive diffusion of metformin through cell membranes is unlikely. Excretion of unchanged metformin in the urine is its major mode of elimination, and metabolites of the drug have not been identified\(^6\). In addition to filtration in the kidneys, the drug is eliminated by active tubular secretion. According to the Biopharmaceutics Drug Disposition Classification System (BDDCS)\(^7\), metformin, with its high solubility and poor metabolism, belongs to Class 3, suggesting that absorptive transporters are necessary for intestinal absorption to overcome its poor permeability. Furthermore, the large apparent volume of distribution of metformin indicates significant tissue uptake\(^8-10\). Thus, transporters appear to play important roles in the absorption, distribution, and elimination of metformin. Many studies have shown that metformin is a substrate of various polyspecific organic cation transporters, which are important determinants of pharmacokinetics, including OCT1 (SLC22A1), OCT2 (SLC22A2), OCT3 (SLC22A3), MATE1 (SLC47A1), MATE2 (SLC47A2), PMAT (SLC29A4), and OCTN1 (SLC22A4)\(^11-16\) (Fig. 1.1, Table 1). In addition, a recent study
showed that metformin is a substrate of the thiamine transporter, THTR-2 (SLC19A3)\textsuperscript{17}, which may play a role in its intestinal absorption and renal re-absorption.

In the last 50 years, more than 100 publications have performed or discussed metformin pharmacokinetics studies, which Kajbaf \textit{et al.} have listed and discussed in the recent review\textsuperscript{18}. The highly variable metformin pharmacokinetic parameters may be due to variation in dose size, dose form, subject ethnicity, genetics, study design, sample size, and analytic methods. Here, we summarize the major properties and pharmacokinetic parameters of metformin (Table 2). In terms of pharmacodynamics, a GWAS indicated that the glucose transporter 2, GLUT2 (SLC2A2) has a significant impact on metformin response\textsuperscript{19}. That is, genetic polymorphisms of SLC2A2 were associated at genomewide level significance with glycemic response to the drug in 8,000 patients with T2D.

Clearly transporters are critical in both the pharmacokinetics and pharmacodynamics of metformin. In fact, in part based on elegant mechanistic drug-drug interaction studies carried out in the Sugiyama laboratory, regulatory agencies recommend that metformin be used as a probe drug in both \textit{in vitro} and \textit{in vivo} studies to evaluate potential drug-drug interactions that involve the renal drug transporters, OCT2 and MATE\textsuperscript{1}\textsuperscript{26-29}. Though candidate gene studies implicate genetic polymorphisms in many of the pharmacokinetic transporters in the disposition of metformin, a large study in type 2 diabetic patients, failed to identify significant associations between genetic variants in metformin pharmacokinetic transporters and glycemic response to the drug\textsuperscript{30}. These interesting, but seemingly contradictory studies, will be discussed in this mini-review, which summarizes our current understanding of metformin transporters, and highlights the transporters that play a role in metformin pharmacokinetics and pharmacodynamics including those that mediate clinically important drug-drug interactions involving metformin.
Transporters involved in metformin intestinal absorption

Metformin is primarily taken orally as the hydrochloride salt, in a tablet form. After oral administration, metformin is slowly absorbed from the proximal small intestine (duodenum)\textsuperscript{10,31,32}. An inverse relationship was observed between the dose ingested and the relative absorption. That is, a greater fraction of metformin is absorbed after lower doses than after higher doses\textsuperscript{9}. Specifically, the bioavailability (F) of metformin is reduced from 86\% to 42\% after oral doses of metformin ranging from 250 mg to 2000 mg\textsuperscript{9}. Though bioavailability for most drugs is determined by absorption and metabolism in the gastrointestinal tract as well as hepatic metabolism, because metformin is not metabolized its bioavailability is determined primarily by intestinal absorption. These data, which suggest that metformin absorption is mediated by a saturable absorption process\textsuperscript{9,14,33}, are consistent with a major role of intestinal influx transporters in the oral absorption of metformin.

To date, several transporters have been implicated in metformin intestinal absorption. The plasma membrane monoamine transporter (PMAT; SLC29A4), identified in 2004, accepts structurally diverse hydrophilic organic cations as substrates, such as 1-methyl-4-phenylpyridinium (MPP\textsuperscript{+}), tetraethylammonium, serotonin, dopamine, epinephrine, norepinephrine, guanidine, and histamine\textsuperscript{34,35}. In immunofluorescence studies\textsuperscript{36}, Xia et al. showed that PMAT is primarily targeted to the apical membrane of polarized epithelial cells. Kinetic studies indicate that metformin has an apparent $K_m$ of 1.32 mM for PMAT\textsuperscript{14}, which is in the range of other organic cation transporters (Table 1). In addition, PMAT-mediated metformin uptake rate versus concentration is sigmoidal, with a Hill coefficient >2 and is greatly stimulated by acidic pHs. The finding that metformin’s uptake rate is greater at pH 6.6 than at pH 7.4, is consistent with intestinal physiology. For example, the pH in the intestinal lumen can be as low as 6\textsuperscript{14}. These data suggest that the naturally acidic environment in the intestinal lumen can
serve as a driving force to promote PMAT-mediated uptake of metformin.

Transporters in the SLC22 family also appear to play a role in metformin intestinal absorption. The organic cation transporters, OCT1 (SLC22A1) and OCT3 (SLC22A3), are expressed in the small intestine, and metformin is an excellent substrate of both transporters (apparent $K_m$ of 1.47 mM for OCT1 and 1.10 mM for OCT3) (Table 1). OCT3 is localized to the brush border membrane of enterocytes, and appears to play a role in metformin absorption. Using genetically engineered mice, Chen et al. showed that Oct3 deletion significantly reduced the bioavailability of metformin$^{15}$. After oral doses, a significantly lower bioavailability was observed in Oct3 knockout mice compared with wild-type mice at a dose of 50 mg/kg metformin$^{15}$. These data suggested that OCT3 plays an important role in metformin absorption in vivo. OCT1 is localized to the basolateral membrane of the enterocyte, and is suspected to play a major role in metformin absorption by mediating its flux across the basolateral membrane of enterocytes to the portal circulation$^{37,38}$.

Carnitine/organic cation transporter (OCTN1; SLC22A4), another transporter within the SLC22A family, was also previously shown to be involved in metformin absorption$^{13}$. OCTN1 localizes to the apical membrane of enterocytes in the small intestine of mice and humans. In vitro experiments show that OCTN1 mediates the uptake of metformin in human embryonic kidney 293 cells transfected with the mouse OCTN1 gene though the uptake of metformin is much lower than the uptake of the typical substrate [3H] ergothioneine (ERGO). The study suggests the possible involvement of OCTN1 in the intestinal absorption of metformin$^{13}$.

Additionally, Han et al. demonstrated that the serotonin reuptake transporter (SERT; SLC6A4) transports metformin with a $K_m$ of 4 mM in vitro$^{24}$. Paroxetine, a selective serotonin reuptake inhibitor ($K_i = 0.8$ nM for SERT)$^{39}$, inhibited OCT1-, 2-, 3-, and SERT-mediated metformin uptake in single transporter-expressing cell systems with IC$_{50}$ values of 1.0 ± 0.2 µM,
11.9 ± 1.2 µM, 6.4 ± 1.3 µM, and 6.0 ± 0.6 nM, respectively. Further, SERT appears to contribute to metformin uptake across the apical membrane in Caco-2 cell monolayers. These data suggest that SERT may contribute to the intestinal absorption of metformin.

Recently, Liang et al. demonstrated that thiamine transporter 2 (THTR-2; SLC19A3), the main transporter for intestinal thiamine absorption, transported metformin with a $K_m$ of 1.15 mM in cells stably expressing human THTR-2. The uptake mechanism for human THTR-2 was pH and electrochemical gradient sensitive. In particular, at low pH’s metformin uptake by THTR-2 was enhanced. These data suggest that THTR-2 contributes to the intestinal absorption of metformin, and may be a target for metformin-nutrient interactions. Taken together, a number of transporters have involved in metformin intestinal absorption. However, the relative contribution of individual transporters to intestinal absorption is not clear at this point, and will depend upon their expression levels and kinetic properties. Further information on regional expression of transporter proteins in the intestine on both basolateral and apical surfaces and well-constructed PBPK models are needed.

**Transporters involved in metformin tissue distribution**

In humans, the volume of distribution ($V_d$) of metformin has been reported to range from 63 to 276 L after intravenous administration. After oral administration $V_d/F$ estimated during multiple dosing with 2000 mg metformin daily is approximately 600 L. The large $V_d$ indicates significant tissue uptake of metformin and suggests that membrane transporters may be major determinants of the tissue distribution of metformin. In fact, in a previous study of the pharmacokinetics of metformin, we observed a lower oral volume of distribution ($V_d/F$) in the individuals carrying reduced function alleles of OCT1 (R61C, G401S, 420del, or G465R), an important hepatic transporter.
OCT3 also plays a role in metformin tissue distribution. The transporter is detected in almost all tissues and is expressed at high levels in adipose tissue, lung, prostate, and skeletal muscle in humans and rodents. Further, OCT3 is expressed in the blood brain barrier, placenta, and salivary glands. Using the Oct3 knockout mouse model, Chen et al. showed a 2-fold decrease in the apparent volume of distribution of metformin in knockout compared with wildtype mice after intravenous doses of metformin. Similar results were observed in another published study. Consistent with its reduced volume of distribution, metformin tissue-to-plasma ratios were significantly lower in the liver, muscle, and adipose tissue in knockout mice, indicating an important role of OCT3 in tissue distribution. Additionally, recent whole-body PET imaging study in humans showed that $^{11}$C-metformin was primarily taken up in the liver, kidney, urinary bladder, and to a lesser extent in the salivary glands, skeletal muscle, and intestines. Mechanistic studies in mice showed that $^{11}$C-metformin uptake in the kidney and liver increased in the presence of the MATE-selective inhibitor, pyrimethamine, suggesting an important role of MATEs in the pharmacokinetics of metformin. Taken together, data from animal and human studies demonstrate that metformin has a broad tissue distribution and that transporters play an important role in the distribution of the drug.

**Transporters involved in metformin renal elimination**

The major clearance pathway of metformin is renal elimination. As noted earlier, metformin is cleared in the kidney by both filtration in the glomerulus and tubular secretion. The estimated population mean renal clearance ($CL_R$) of metformin is $507 \pm 129$ mL/min in healthy adults and diabetic patients with good renal function, consistent with active tubular secretion. Metformin is a substrate of several organic cation transporters expressed in the kidney. OCT2 (SLC22A2) is mainly expressed on the basolateral membrane of renal tubule cells, where it mediates entry of metformin into the tubule cells and, together with MATE1 (SLC47A1) and MATE2 (SLC47A2), mediates the secretion of metformin into urine.
A number of drug-drug interaction studies have demonstrated a role for MATE1 in metformin renal elimination\textsuperscript{28,29,49,50}. An elegant \textit{in vitro} and \textit{in vivo} studies from the Sugiyama laboratory, clarified previously confusing data. That is, his research group determined that the H2-receptor antagonist, cimetidine, previously thought to be an OCT2 inhibitor, reduced metformin renal clearance by inhibiting MATEs predominantly\textsuperscript{29}. Further, pyrimethamine, an antimalarial drug and a selective inhibitor of MATEs (over OCT2) reduced metformin renal clearance\textsuperscript{28,51,52}. Surprisingly, in a recent study of the effect of the H2-receptor antagonist, famotidine on metformin pharmacokinetics, there was some evidence that the renal clearance of metformin increased after famotidine\textsuperscript{53}, consistent with the drug inhibiting a re-absorptive transporter for metformin in the kidney. Though speculative, the transporter may be THTR-2, as discussed previously, because of its role as a re-absorptive transporter\textsuperscript{50}. In addition to drug-drug interaction studies, which have provided mechanistic information on the transporters involved in metformin renal elimination, human genetic studies have contributed immensely to our understanding of transporters involved in metformin renal elimination. In particular, in candidate gene studies in healthy volunteers, \textit{SLC22A2} and \textit{SLC47A1/SLC47A2} polymorphisms have been associated with changes in the pharmacokinetics and/or pharmacodynamics of metformin\textsuperscript{54-56}.

Studies in genetically engineered mice have complemented and extended human genetic and drug-drug interaction studies focused on metformin. In an \textit{Oct1/2} double-knockout mice, metformin clearance is reduced substantially and secretion is totally abolished in the \textit{double} knockout mice. Further, the volume of distribution is reduced 3.5-fold in the double knockout mice\textsuperscript{57}. Similarly, \textit{Mate1} knockout mice exhibit a 2-fold increase in systemic exposure to metformin as compared to their wildtype counterparts, presumably as a result of reduced renal clearance of the drug.\textsuperscript{48} In addition, lactic acidosis, a severe adverse effect of metformin, is associated with increased metformin exposure. Reduced MATE function has been shown to
cause elevations in metformin concentrations, which represents a risk factor for metformin-induced lactic acidosis\textsuperscript{58}. Collectively, the data suggest that OCT2, MATE1 and MATE2 play critical roles in the renal secretory clearance and toxicity of metformin.

**Transporters involved in metformin pharmacologic action**

In terms of pharmacodynamics, studies in mice have demonstrated important roles for organic cation transporters. In particular, the liver is a major site of action for metformin, which reduces hepatic glucose production\textsuperscript{1,3,32}. OCT1 and OCT3 are expressed on the sinusoidal membrane of hepatocytes and play a major role in the uptake of metformin from blood into the hepatocytes\textsuperscript{59}. In 2002, elegant studies from the Sugiyama group showed that OCT1 is responsible for the hepatic uptake and intestinal distribution of metformin\textsuperscript{60,61}. Further, reduced hepatic metformin concentrations have been shown to affect metformin response in mice\textsuperscript{62}. In particular, the hepatic accumulation of metformin was significantly greater in wildtype mice than in \textit{Oct1} knockout mice after a single oral dose of the drug. Consistent with its lower accumulation, the activation of AMP-activated protein kinase (AMPK), a biomarker of metformin action, was substantially reduced in livers from \textit{Oct1} knockout mice. Metformin significantly reduced fasting plasma glucose levels by more than 30% in wildtype mice fed high-fat diets but not in the \textit{Oct1} knockout mice\textsuperscript{63}.

In addition to OCT1, OCT3 plays a role in the pharmacologic effects of metformin. Again, studies in genetically engineered mouse study have strongly suggested that metformin has therapeutic effects in peripheral tissues. For example, metformin treatment significantly reduced blood glucose AUC after an oral glucose tolerance test in wildtype but not \textit{Oct3} knockout mice\textsuperscript{15}. Correspondingly, phosphorylated AMPK and expression levels of the insulin-sensitive glucose transporter, GLUT4, increased in adipose tissue in response to metformin in wildtype mice, but to a much lesser extent in \textit{Oct3} knockout mice\textsuperscript{15}. Interestingly, Lee \textit{et al}. 
demonstrated that OCT3 is highly expressed in salivary glands and plays a role in metformin accumulation in salivary glands, which may induce taste disturbances associated with the drug. These data suggest that OCT3 plays a major role in the uptake of metformin into multiple tissues, thereby modulating the therapeutic and toxicological effects of metformin peripherally.

In terms of metformin pharmacologic action, human genetic studies associating transporters and glycemic response have shown complex and somewhat contradictory results, which may due to differences in study design, sample size, and different end-point measurements. Recently, in a large meta-analysis in almost 8,000 patients with T2D, Dujic et al. showed that polymorphisms in transporters involved in metformin pharmacokinetics (SLC22A1, SLC22A2, SLC22A4, SLC47A1, and SLC47A2) have no significant impact on glycemic response to the drug. Though transporters clearly play a role in metformin pharmacokinetics, and indeed genetic polymorphisms in various transporters may modulate the pharmacokinetics of metformin, they do not appear to be critical to the pharmacodynamics of the drug in diabetic populations. Recently, in a large human genome-wide association study (GWAS), Zhou et al. showed a strong association between SLC2A2 genetic variants and glycemic response to metformin (HbA1c reduction) in diabetic patients. GLUT2 is highly expressed in the liver and plays an important role in glucose homeostasis. The generally accepted role of GLUT2 in the liver is to take up glucose following meals and to release glucose into the blood during fasting. Previous studies have shown that one of the major actions of metformin is inhibition of hepatic gluconeogenesis. Though speculative, GLUT2, which is responsible for the last step (glucose release) in the gluconeogenesis pathway, may be a target of metformin. That is, metformin may reduce its function (or expression) resulting in reduced hepatic glucose output. Individuals with reduced function variants of SLC2A2 may be particularly sensitive to this effect and respond better. Further studies to understand the
underlying mechanism of GLUT2 in metformin action and genetic variants in GLUT2 on modulation of metformin action are warranted.

Conclusion
Clearly the available data today provide strong evidence that multiple membrane transporters are critical determinants of the absorption, disposition and pharmacologic action of metformin. Given that metformin is transported into different tissues by various transporters and has pharmacologic effects in the liver as well as in peripheral tissues, combined factors that modulate transport function including genetic polymorphisms, concomitant medications, and underlying disease may contribute to metformin response. Dr. Yuichi Sugiyama and his colleagues have contributed immensely to our understanding of the mechanisms of metformin transport. Their groundbreaking studies identifying OCT1 as the major liver transporter for metformin, together with their elegant studies focused on understanding the mechanisms of transporter-mediated drug-metformin interactions paved the way to our current understanding of the pharmacologic mechanisms of one of the world’s most widely prescribed drugs. We look forward to new studies from his group and others applying computational methods to analyze and predict the complex pharmacokinetics and pharmacodynamics of metformin.
Figure Legend

Figure 1. Diagram of major transporters involved in metformin disposition. Arrows show the direction of transport that has been observed in in vivo studies in mammals.

References


24. Han T, Proctor WR, Costales CL, Cai H, Everett RS, Thakker DR. Four Cation-Selective


Metabolism and Disposition. 2009;37(3):555–559.


Table 1. Summary of Metformin Transporters

<table>
<thead>
<tr>
<th>Transporter name</th>
<th>Km (mM)</th>
<th>Major Tissues</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>THTR-2 (SLC19A3)</td>
<td>1.15</td>
<td>Intestine and Liver</td>
<td>Liang et al. 2015\textsuperscript{17}</td>
</tr>
<tr>
<td>OCT1 (SLC22A1)</td>
<td>1.47</td>
<td>Liver and Kidney</td>
<td>Kimura et al. 2005\textsuperscript{20}, Li et al. 2011\textsuperscript{21}</td>
</tr>
<tr>
<td>OCT2 (SLC22A2)</td>
<td>1.07</td>
<td>Kidney</td>
<td>Choi et al. 2007\textsuperscript{22}</td>
</tr>
<tr>
<td>OCT3 (SLC22A3)</td>
<td>1.10</td>
<td>Multiple tissues (liver, skeletal muscle, fat, and brain)</td>
<td>Chen et al. 2015\textsuperscript{15}</td>
</tr>
<tr>
<td>MATE1 (SLC47A1)</td>
<td>0.23</td>
<td>Kidney and Liver</td>
<td>Chen et al. 2009\textsuperscript{23}</td>
</tr>
<tr>
<td>MATE2 (SLC47A2)</td>
<td>1.05</td>
<td>Kidney</td>
<td>Masuda et al. 2006\textsuperscript{16}</td>
</tr>
<tr>
<td>PMAT (SLC29A4)</td>
<td>1.32</td>
<td>Intestine</td>
<td>Zhou et al. 2002\textsuperscript{14}</td>
</tr>
<tr>
<td>OCTN1 (SLC22A4)</td>
<td>NA*</td>
<td>Gastrointestinal tract</td>
<td>Nakamichi et al. 2013\textsuperscript{13}</td>
</tr>
<tr>
<td>SERT (SLC6A4)</td>
<td>4</td>
<td>Intestine</td>
<td>Han et al. 2015\textsuperscript{24}</td>
</tr>
</tbody>
</table>

\* No Km was reported. Significant uptake in overexpressing cells compared to mock cells.

\* Table is modified from a previous publication\textsuperscript{17}.
Table 2. Summary of Metformin Properties and Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (base free), g/mol</td>
<td>129.16</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>logP</td>
<td>-1.43</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>pKa</td>
<td>2.8, 11.5</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protein binding</td>
<td>negligible</td>
<td>DrugBank</td>
</tr>
<tr>
<td>Bioavailability (F), %</td>
<td>55</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Volume of distribution (V&lt;sub&gt;a&lt;/sub&gt;), i.v., L</td>
<td>63 to 276</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apparent volume of distribution (V&lt;sub&gt;d&lt;/sub&gt;/F), oral, L</td>
<td>~ 600</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renal clearance (CL&lt;sub&gt;r&lt;/sub&gt;), mL/min</td>
<td>~ 500</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;; Gong et al., 2012&lt;sup&gt;25&lt;/sup&gt;; DrugBank</td>
</tr>
<tr>
<td>Apparent total clearance (CL/F), oral, mL/min</td>
<td>~ 1140</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;; DrugBank</td>
</tr>
<tr>
<td>Plasma half-life (t&lt;sub&gt;1/2, plasma&lt;/sub&gt;), h</td>
<td>5 to 6</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;; Gong et al., 2012&lt;sup&gt;25&lt;/sup&gt;; DrugBank</td>
</tr>
<tr>
<td>Blood half-life (t&lt;sub&gt;1/2, blood&lt;/sub&gt;), h</td>
<td>17 to 20</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;; DrugBank</td>
</tr>
<tr>
<td>Average plasma concentration at steady state, C&lt;sub&gt;ave, ss&lt;/sub&gt;, mg/L</td>
<td>1.4</td>
<td>Graham et al., 2011&lt;sup&gt;b&lt;/sup&gt;; DrugBank</td>
</tr>
<tr>
<td>Therapeutic concentration, mg/L</td>
<td>0.129 to 90</td>
<td>Kajbaf et al., 2016&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>* DrugBank (https://www.drugbank.ca/drugs/DB00331)</sup>