

Improving brain penetration using elacridar—A P-glycoprotein and BCRP inhibitor

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Abstract. The central nervous system (CNS) is a site for a myriad of disorders and diseases, such as schizophrenia, Alzheimer's disease, and Parkinson's disease. Many medications targeting these illnesses remain challenged due to efflux transporters forming a blood-brain barrier (BBB). To combat such challenges, elacridar shown promise at inhibiting such transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), therefore improving brain penetration. However, as an early clinical candidate, many remain unknown about elacridar's pharmacokinetic (PK) properties in the human body. This paper aims to obtain a better understanding of elacridar's pharmacokinetic profile and predict the optimal dose and dose interval for its application in the clinic. To begin with, a series of basic PK models were created using fundamental PK equations and the models were fit to elacridar clinical data to obtain elacridar-specific PK parameters. Next, elacridar preclinical PK as well as in vitro inhibition assay were used to determine the therapeutic window. Our final, multiple-dose extravascular PK model reveals that the most convenient and effective dose regimen is 900 mg BID (bis in die; twice per day). With this elacridar PK model, researchers can leverage elacridar human PK to improve clinical outcomes.

Keywords: Blood-Brain Barrier, Pharmacokinetics Modeling, Elacridar, Efflux Transporters

1. Introduction

The central nervous system (CNS) disorders, including psychiatric and neurological conditions such as Alzheimer's disease, Parkinson's disease, schizophrenia, depression, epilepsy, and multiple sclerosis, affect a significant portion of the global population. These disorders can have a profound impact on patients' quality of life, making it a significant unmet medical need for effective treatments.

Currently, many CNS disorders lack satisfactory treatment options. While medications are available for some conditions, they often suffer from limited efficacy, significant side effects, or only the ability to address the symptoms but not the underlying causes. Developing drugs that can penetrate the brain and target specific disease mechanisms hold the potential to improve patient outcomes [1]. Given the significant burden of CNS disorders and limited treatment options available, there is a high demand for CNS drugs that can effectively penetrate the brain and reach the target.

One of the major challenges researchers face is developing drugs that can effectively penetrate the blood-brain barrier (BBB). BBB is a highly restricted barrier that separates the bloodstream from the brain, protecting the brain from potentially harmful substances [2]. While the BBB is crucial for maintaining brain homeostasis, it also poses challenges when developing drugs that need to reach the

brain. The BBB contains efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), that actively pump drugs out of the brain back into the bloodstream [3]. These transporters recognize a broad range of structurally diverse compounds and can significantly limit the brain penetration of potential therapeutics. Overcoming the efflux transporters' activity is a major challenge in achieving sufficient drug concentrations in the brain.

Elacridar is a known P-gp and BCRP inhibitor that has potential to overcome the efflux activity of the transporters and therefore enhance drug penetration across the BBB [4]. By inhibiting the efflux transporters at the BBB, elacridar can enhance the influx of these transporters' substrates (such as paclitaxel and topotecan), thereby increasing their availability in the CNS [4]. Notably, elacridar is not one of the first generation of P-gp and BCRP inhibitors developed: it is discovered and developed after two rounds of previous experimentation. Before elacridar was discovered, verapamil and cyclosporine-A were tested as potential efflux transporter inhibitors; however verapamil and cyclosporine-A unsatisfactory potency gave rise to preclinical tests of subsequent generation of drugs such as valsopodar [4]. Following the finding of valsopodar's inhibition on cytochrome P450, the third generation of efflux inhibitor – elacridar – was discovered [5]. Currently, elacridar shows potential to effectively inhibit the activity of the two BBB transporters. However, despite the promise of elacridar, the clinical pharmacokinetics (PK) of elacridar remains largely unoptimized and therefore a better understanding of its PK profile is essential to realizing its potential in improving brain penetration for treating CNS disorders.

PK is the study of drug movement in body systems, and is considered an important pillar of drug discovery for its revelation to scientists and clinicians of one drug's movement and concentration changes in the body [6]. Pharmacodynamics (PD), a field harvesting equally fundamental information to aid drug discovery, studies the extent and duration of action that a drug can trigger in test models [7]. The two fields complement with observations and the monitoring of ADME (absorption, distribution, metabolism, and excretion), a quartet narrating how a drug enters an organism's systems, gets distributed to all parts of the body by systemic flow (usually the bloodstream), becomes metabolized by different organs and gets eventually removed from the body together with its metabolites.

Pharmacokinetic-pharmacodynamic modeling (PK/PD modeling) is a mathematical and statistical approach used to describe and quantify the relationship between the concentration of a drug (pharmacokinetics) and its effect on the body (pharmacodynamics) [8]. PK/PD modeling is a valuable tool in drug development and clinical pharmacology for understanding and predicting drug response based on drug concentrations. For instance, PK/PD modeling could enable scientists to develop and refine designs for drug delivery to optimize the therapeutic regimen.

Herein, we used PK/PD modeling to explore the brain penetrating potential of elacridar.

2. PK Parameters and Concepts

The study of PK includes constructing a function that illustrates the time course of drug concentration in plasma. Such modeling of drug concentration requires examination and consideration of various parameters, such as dose (D), dosing interval (τ), bioavailability (F), clearance (CL), volume of distribution (V_d), elimination and absorption rate constants (k_a , k_e) and half-life ($t_{1/2}$). The meaning of these parameters is illustrated below:

Bioavailability (F) is the fraction that enters systemic circulation, elucidating how much of the drug can be absorbed into the blood plasma and delivered to its intended target organs or tissues. The bioavailability of a drug depends on its route of administration: for instance, if a drug is injected intravenously to the patient, it is considered 100% bioavailable as it is directly delivered to the systemic circulation; on the other hand, if the drug is orally administered in the form of tablets, it would have a lower bioavailability value because only a fraction of the dose can be absorbed and is subject to gut and hepatic metabolism, also known as first pass effect (Figure 1):

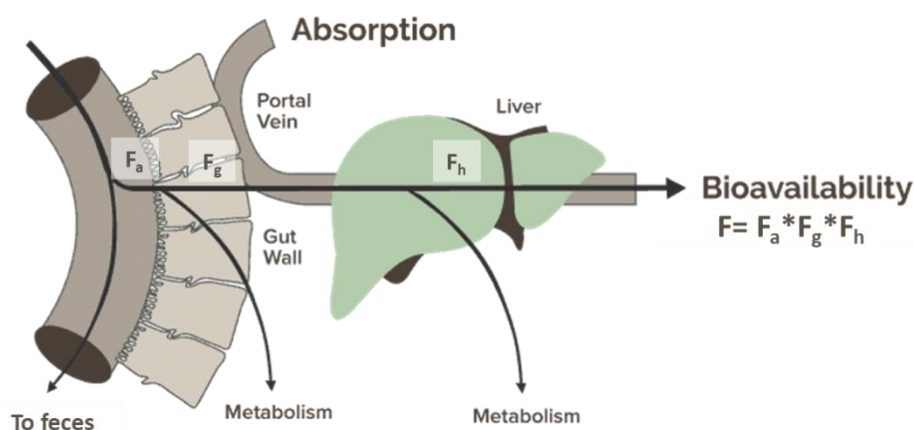


Figure 1. First pass effect, also known as first-pass metabolism, refers to the phenomenon where a portion of an orally administered drug is metabolized before reaching systemic circulation. $F = F_a \times F_g \times F_h$, where F_a is the fraction absorbed; F_g is the fraction escaping gut metabolism, and F_h is the fraction escaping hepatic metabolism

Clearance (CL), measured in L/hr or mL/min, is defined as the volume from which a drug is completely removed per unit time. CL reflects how quickly the body eliminates a drug. The major routes of clearance include: 1) hepatic clearance where drugs are broken down by specific enzymes in the liver; 2) renal clearance through which unchanged drugs are excreted into urine, and 3) biliary clearance where the drugs are excreted into bile.

Volume of distribution (V_d) is the total volume of body fluid that the drug circulates in its ADME process. Volume can be calculated by dividing the total amount of the drug by the concentration of a drug at a given time. V_d is used to assess how extensively a drug is distributed throughout the body.

Elimination rate constant (k_e) is defined as $k_e = CL/V$. k_e is a PK parameter used to describe the rate of drug removal from the body. It is an essential parameter in determining the drug's elimination half-life ($t_{1/2}$), which can be calculated using $t_{1/2} = \ln(2) / k_e$.

The starting concentration, $C(0)$, describes the initial concentration of the drug in the body immediately after its administration. It is calculated as D/V_d , dose divided by volume. In intravenous injections, the $C(0)$ equates to the C_{max} as the total drug is directly administered to systemic circulation.

Area under curve (AUC), namely, calculates the total area under the concentration-time function of the drug. It is a measure of total drug exposure over time, and is calculated by the equation of $D \cdot F / CL$, the total dose of drug entering systemic circulation divided by clearance.

To construct a PK model for elacridar, two routes of administration were considered – intravenous (IV) and extravascular dosing, in this paper considered the modeling for oral (PO) administration route. I have constructed four models to examine the relationship between different parameters and human PK profile of elacridar.

3. PK model building

PK modeling is a mathematical and statistical approach used to describe and predict the concentration-time profiles of drugs in the body based on various physiological and pharmacological parameters. The purpose of PK modeling is to predict the drug concentration time course under a certain dosing regimen. This prediction allows optimization of the dose and dosing interval based on the therapeutic window. This therapeutic window refers to the drug concentration within which a medication is effective while avoiding significant toxicity.

This project developed a PK model of elacridar based on four classic PK models: 1) single-dose intravenous model, 2) multiple-dose intravenous model, 3) single-dose extravascular model, and 4) multiple-dose extravascular model. All above models assume one-compartment distribution kinetics. The therapeutic window of elacridar is determined by the IC_{50} using various probe substrates (lower bound) and preclinical in vivo studies that showed no toxicity (upper bound).

3.1. Single-dose IV model

Single-dose IV model describes the time course of a drug when it is directly administered into the bloodstream as a single-dose. A typical IV model is shown in Figure 2. When a drug is administered intravenously, the entire amount enters systemic circulation, and therefore no absorption is involved in this route of administration and the bioavailability is considered 100%. Under such circumstances, there are only three input and four output parameters:

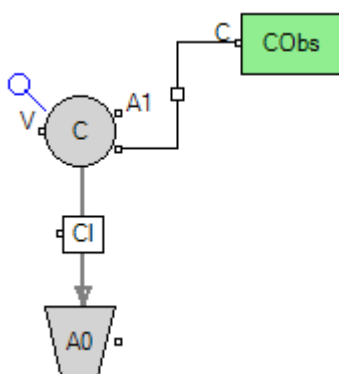


Figure 2. A typical intravenous PK model

Input parameters:

D (mg)
 CL (L/hr)
 V (L)

Output parameters:

$C(0)$ (mg/L)
 k_e (/hr)
 $t_{1/2}$ (hr)
 AUC_{inf} (mg*hr/L)

As one of the simplest PK model, an IV elacridar model can be constructed using the following equation:

$$C(A) = C(0) \times e^{-k_e \cdot t} \quad (1)$$

Where $C(A)$ refers to the concentration of drug A in the body at a given time. As the dose is directly delivered to systemic circulation, the aforementioned starting concentration, $C(0)$, can be simple represented as:

$$C(0) = D/V \quad (2)$$

Of which D and V are inputs into the model. Given the simulation of concentration change, a new intermediate parameter dAA can be conceived that illustrates how much the amount of the drug is cleared from systemic circulation due to elimination processes. As this variable involves the clearance

of a drug, or the speed of eliminating a drug from systemic circulation, it can be described using the following equation:

$$dAA = \Delta t \times C(A) \times CL \quad (3)$$

Where the $C(A)$ is the drug concentration derived from the previous moment. Herein, the total amount of drug entering systemic circulation during the time interval, AA , can then be computed using the following equation:

$$AA_{\text{last}} = AA_{\text{previous}} - dAA \quad (4)$$

The two intermediate variables are not essential for this model due to its simple requirements. However, they will play a more significant role in latter models that are more complex to construct and manipulate.

A typical single-dose IV bolus PK profile is shown in Figure 3, with exponential decay shown in linear and logarithmic scale.

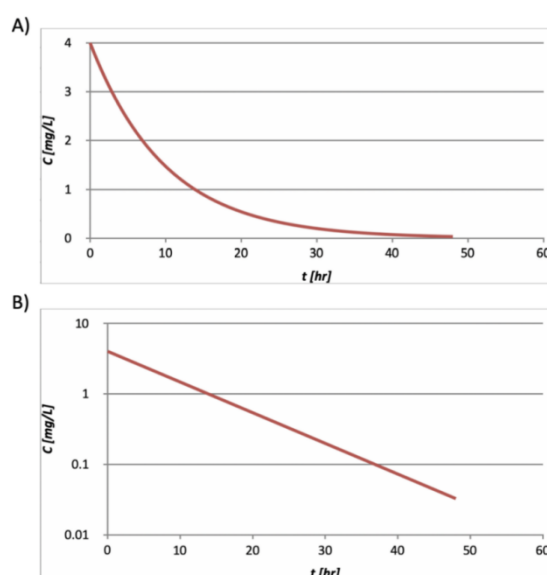


Figure 3. The PK function of a single-dose, intravenous dosed drug with plasma concentration in A) linear scale, and B) logarithmic scale.

3.2. Multiple-dose IV model

Similar to the single-dose IV model, the multiple-dose IV model describes the time course of an intravenously administered drug; the difference is that this model concerns repeat dose. Upon repeat dose, accumulation may occur, which eventually leads to a steady state in which the rate of drug administration equals the rate of drug elimination. At steady state, the drug concentration in the body remains relatively constant over time, and the overall drug exposure becomes predictable. Compared to single-dose IV model, multiple-dose model has two additional input parameters – τ (dosing interval) and N (number of doses). As repeat dose leads to a steady state, output parameters are obtained such as $C_{ss,max}$ (steady-state maximal concentration), $C_{ss,min}$ (steady-state minimal concentration) and AUC_{ss} (steady-state area under curve).

The formulation for starting $C(0)$ and intermediate variable dAA is calculated as expressed in the single-dose IV model; however, a difference exists in the setting of time. As a new dose of the drug will be administered every τ hours after the previous one, the concentration cannot be calculated using the aforementioned equation as it neglects the accumulation of added dose. In this case, two additional

intermediate variables can be created: NA , describing the total number of doses the drug is administered at a given time, and $InputA$, the total dose amount administered.

As an integer, NA can be formulated as:

$$NA = Int(t/\tau) + 1 \quad (5)$$

And hence, if the model detects that the value NA changes by one unit, $InputA$ will be added. Hereby, AA acts as an efficient intermediate variable to conveniently calculate the concentration:

$$AA_{last} = AA_{previous} - dAA + InputA$$

$$C(0) = AA/V \quad (6)$$

A typical multiple-dose IV PK profile is illustrated as in Figure 4.

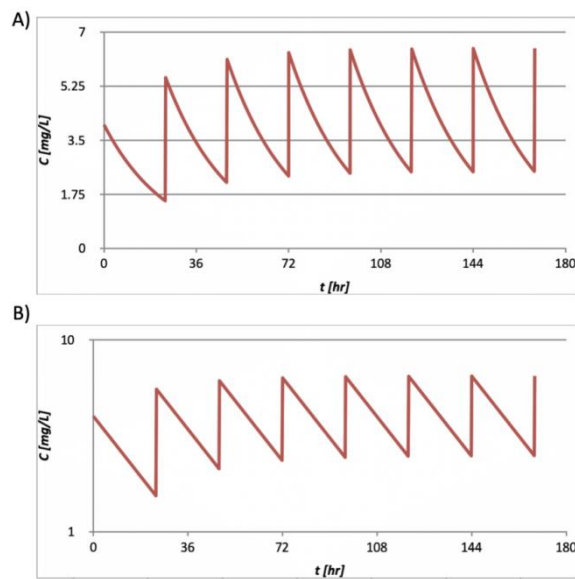


Figure 4. The PK function of a multiple-dose, intravenous dosed drug with plasma concentration in A) linear scale, and B) logarithmic scale.

3.3. Single-dose extravascular model

Single-dose extravascular model describes the time course of a drug upon single-dose by routes other than intravenous injection, typically through oral administration. A typical extravascular model is shown in Figure 5. Compared to the IV model previously described, the oral model includes considerations of bioavailability (F) and absorption rate constant (k_a). It is important to note, without F , CL and V cannot be calculated because the amount entering systemic circulation is unknown. In case F is not determined, the CL and V are expressed as CL/F and V/F to incorporate the F term. Additionally, as oral administration involves the absorption process, the concentration rises over time until reaches C_{max} and gradually declines afterwards.

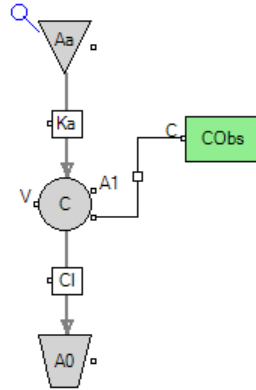


Figure 5. A typical extravascular model

The intermediate variables and data that needs to be calculated additionally includes “Amount to be absorbed” (*AaA*) using the following equation:

$$AaA = F \times D \times e^{-k_a \times t} \quad (7)$$

With this consideration, the calculation of the amount change (*dAA*) can be represented as below:

$$dAA = \Delta t \times (CL \times C(A) - AaA \times ka) \quad (8)$$

where Δt refers to the change of time, $C(A)$ represents the concentration of the drug in the body at the previous moment, and *AaA* represents the aforementioned ‘amount to be absorbed’ by the target organs from the systemic circulation.

With *dAA*, the total amount of drugs present in the body (*AA*) could be calculated as the *AaA* subtract *dAA* at the previous unit time, just as formulated in the two previous models.

A typical PK profile of the single-dose, extravascular model is illustrated in Figure 6. A absorption phase can be identified from the models (the yellow curve before C_{max}).

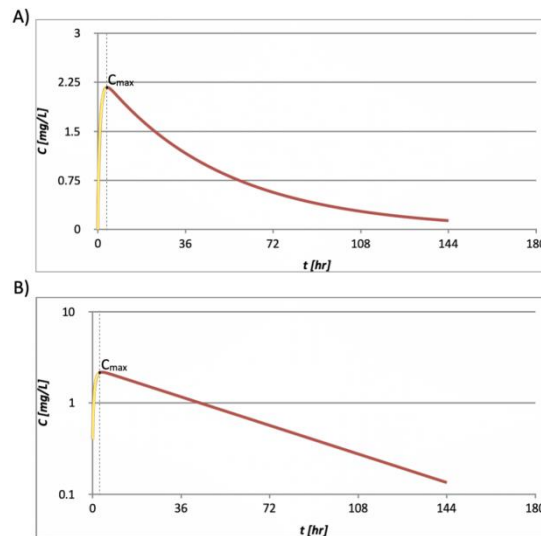


Figure 6. The PK function of a single-dose, extravascular dosed drug with plasma concentration in A) linear scale, and B) logarithmic scale. The absorption phase before C_{max} is highlighted in yellow.

3.4. Multiple-dose extravascular model

Multiple-dose extravascular model describes the time course of a drug administered through an extravascular route upon repeat dose. Due to repeat dose, a steady state can be reached after a certain number of doses. The intermediate variables NA and $InputA$ are set similarly in the multiple-dose intravenous model with regard to repeat dosing.

A typical multiple-dose extravascular PK model is shown in Figure 7. A steady state is achieved after a few doses.

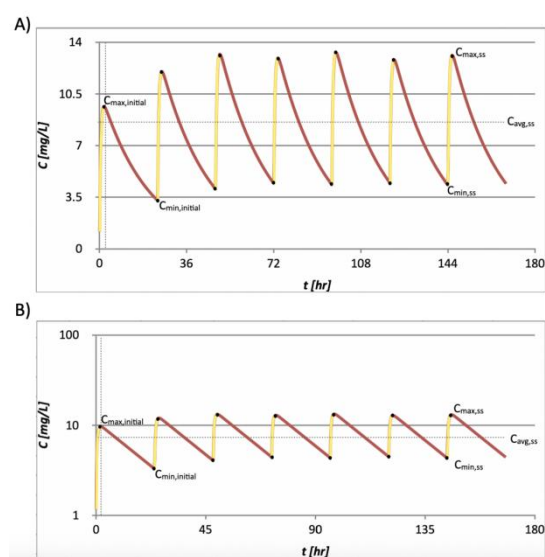


Figure 7. The PK function of a multiple-dose, extravascular dosed drug with plasma concentration in A) linear scale, and B) logarithmic scale. C_{max} , C_{min} at different stages (initial and steady-state) are noted.

These above PK models can be used to describe linear PK, where the relationship between drug dose and its resulting blood concentration is proportional. In other words, when a drug exhibits linear PK, doubling the dose will approximately double the drug concentration, and halving the dose will result in approximately half the blood concentration. In linear PK models, CL , V , k_a , and F remain constant.

4. Elacridar PK model

With the four general PK models on hand, we set out to construct the PK model for elacridar.

Firstly, to build a PK model for elacridar, we used the reported human single-dose clinical PK at 25, 250, and 1000 mg doses.[9] This modeling process is carried out by fitting the reported clinical data using input PK parameters within the model. Having plotted these different values on the chart, the value of the parameters of the classical oral, single-dose PK function can be changed and adjusted so that it best fits these observed data.

Based on the clinical data at oral 25, 250, and 1000 mg, three sets of PK input parameters were obtained, shown in Figure 4 and Table 1. The CL/F and V/F appear relatively constant between 25 and 250 mg; in contrast, 1000 mg dose showed significantly decreased CL/F and much slower k_a , which indicates saturation in the absorption and elimination processes. Saturation leads to nonlinear PK, which can no longer be predicted by the linear PK models set forth. Therefore, 1000 mg PK parameters were not used for elacridar PK model building. The final PK parameters were determined as $CL/F = 138$ (L/hr) and $V/F = 2250$ (L).

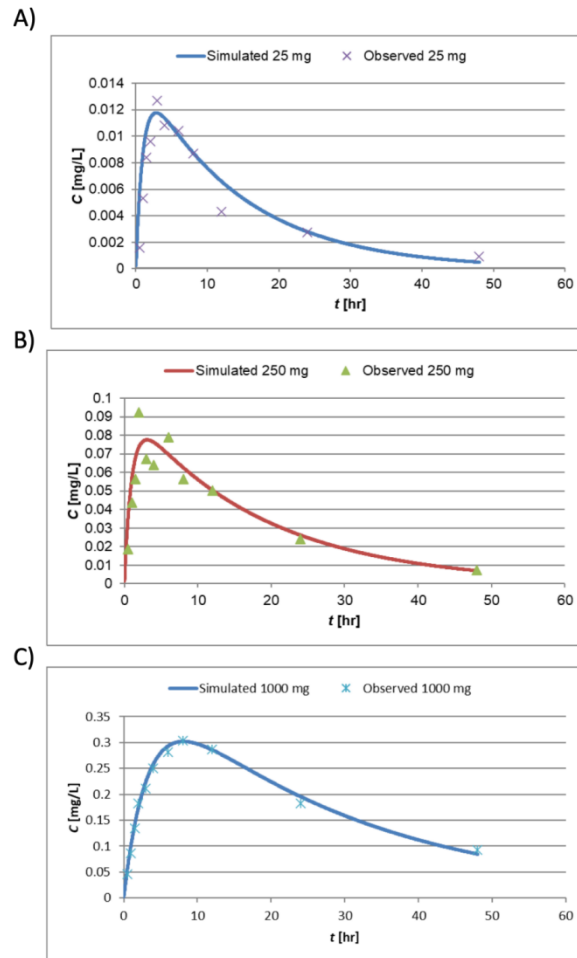


Figure 8. Curve fitting using input PK parameters listed in Table 1. Simulated PK curve overlaid with observed data for A) 25 mg, B) 250 mg, and C) 1000 mg.

Table 1. Input PK parameters used in curve fitting to generate Figure 4.

Input	Average of 25 and 250 mg PK input			
<i>Dose</i> (mg)	25	250	1000	<1000
<i>CL/F</i> (L/hr)	125	150	87.5	138
<i>V/F</i> (L)	1750	2750	2500	2250
<i>k_a</i> (hr ⁻¹)	1	1	0.3	1

The upper and lower bound of drug is important in that it provides information on concentrations at which the drug becomes toxic or ineffective. Upper bound is often determined by preclinical safety studies, and lower bound is often determined by IC_{50} (half maximal inhibitory concentration), an indicator of the inhibitory potency of a substance. The determination of upper and lower bound is discussed below.

Firstly, literature reported IC₅₀ values were used to estimate the lower bound for drug efficacy.[10] These IC₅₀ values were obtained using different probe substrates that elacridar exerts effect on. The literature reported IC₅₀ values of five probe substrates are listed in Table 2. The probe substrates are calcein, digoxin, vinblastine, colchicine, and prazosin. The values displayed in the first row in are considered as naked IC₅₀ as they are measured in the absence of plasma protein; the reported IC₅₀ values in μM were converted to mg/L to match the concentration unit used in the PK model. Displayed in the third row is the protein adjusted IC₅₀ (paIC₅₀), accounted for plasma protein binding; paIC₅₀ is calculated by dividing the naked IC₅₀ over the fraction unbound (fu) of the drug. Adjusting for plasma protein binding is necessary because, based on free drug hypothesis, only the unbound fraction of a drug in the bloodstream is available to interact with its target and exert its therapeutic effects.[11]

As these IC₅₀ values measure the ability of elacridar to effectively inhibit P-gp and allow the passage of these substances, the highest value should be chosen to calculate the lower bound to ensure elacridar's inhibitory potency. Therefore, the IC₅₀ values obtained in the calcein assay, with a value of 0.0569 mg/L, was used to calculate the lower bound. The paIC₅₀ is calculated to be 0.34 mg/L after dividing 0.0569 by the unbound fraction of 0.168.[12] With this lower bound, the fold coverage is then calculated based on the predicted steady state minimum concentration (C_{ss,min}), which is discussed in detail later.

Table 2. The IC₅₀ values of different probe substrates when co-dosed with elacridar. * values are calculated using PK output parameters obtained from the final model.

	Calcein	Digoxin	Vinblastine	Cochicine	Prazosin
Reported IC₅₀ (μM)	0.101	0.055	0.043	0.027	0.025
Converted IC₅₀ (mg/L)	0.057	0.031	0.024	0.015	0.014
Calculated paIC₅₀ (mg/L)	0.34	0.18	0.14	0.09	0.08
Fold coverage*	1.2	2.1	2.7	4.3	4.7

Next, the upper bound concentration describes the maximal concentration of elacridar within the body without causing toxicity and subsequently, harm. This is determined by elacridar exposure in preclinical safety studies reported from the literature, summarized in Table 3.[13] Elacridar was dosed at 300 mg/kg in mouse and rat, and at 30 mg/kg in dog and monkey. The reported exposure, AUC in μg*min/mL was converted to mg*hr/L, and C_{max} in ng/mL to mg/L, to match the units used in the PK model. Margin is calculated by comparing the highest exposure level at which no adverse effects are observed in animal studies with the expected human exposure level. The margin calculation is discussed later when predicted human steady state exposure is determined.

Table 3. Reported exposure in preclinical animal studies. * values are calculated using PK output parameters obtained from the final model

	Mouse (300 mg/kg)	Rat (300 mg/kg)	Dog (30 mg/kg)	Monkey (30 mg/kg)
AUC (μg*min/ml)	1151	107	202	187
AUC (mg*hr/L)	19.2	1.8	3.4	3.1
AUC human margin (fold)*	2.94	0.27	0.52	0.48
C_{max} (ng/mL)	962	100	219	179
C_{max} (mg/L)	0.962	0.1	0.219	0.179
C_{max} human margin (fold)*	1.42	0.15	0.32	0.26

The human margin C_{\max} can be calculated by dividing the C_{\max} of tested animals over the steady-state C_{\max} output in the PK model (0.676 mg/L). As the C_{\max} human margin needs be greater than 1, the C_{\max} provided by mouse PK (1.42 mg/L) is selected as the upper bound for elacridar to be considered safe.

Now with PK parameters CL/F of 138 L/hr, V/F of 2250 L, and the therapeutic window set (upper bound = 1.42 mg/ml and lower bound = 0.34 mg/L), the PK model can be configured to find the optimal value of the two remaining input parameters, dose (D) and dosing interval (τ). Notably, as mentioned previously, a dose greater than 1000 mg leads to nonlinear PK and therefore this model cannot be applied at such high dose. On the other hand, short dose interval would be considered inconvenient which can lead to poor patient adherence.

To find the optimal value of the two input parameters (D and τ), the critical criteria is that the PK function should be controlled to fit within the upper and lower bounds. This means that the peaks and troughs of the function should be maintained within therapeutic window. At the same time, the less frequent dosing can improve patient adherence. For instance, a patient would prefer a drug that is administered once per day, rather than every hour.

After exploration of several combinations, we have obtained a dose size of 900 mg and dosing interval of 12 hours (BID) as values that give the best PK profile of elacridar, shown in Figure 5. In addition, combination of dose 500 mg and a dosing interval of 6 hrs (QID, quarter in die) is also attempted and proven plausible, but due to considerations of convenience, the BID dose can be concluded to be the optimal dosing regimen.

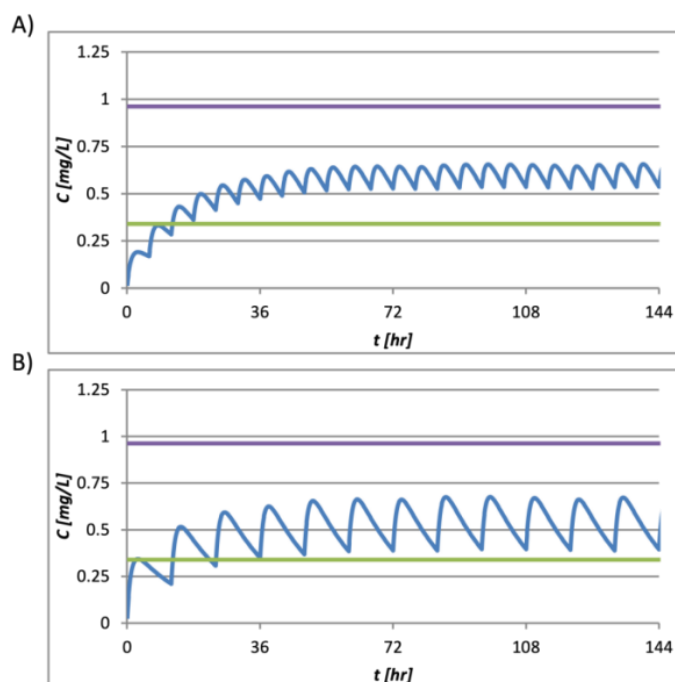


Figure 9. Predicted A) 900 mg BID and B) 500 mg QID PK profiles.

Using the previously constructed multiple-dose extravascular model with 900 mg dose, and 12 hours dose interval as input, we can obtain the following output parameters shown in Table 4. Using the $C_{ss,\max}$ of 0.676 mg/L and $C_{ss,\min}$ of 0.392 mg/L, fold coverage can be calculated using predicted human $C_{ss,\min}$ divided by in vitro $paIC_{50}$ (listed in Table 2), as well as safety margin using preclinical C_{\max} divided by predicted human $C_{ss,\max}$ (listed in Table 3).

Table 4. Input and Output of the built PK model

Input		Output	
Dose (mg)	900	k_e (hr^{-1})	0.06
CL/F (L/hr)	138	$t_{1/2}$ (hr)	11.3
V/F (L)	2250	AUC _{ss} (mg*hr/L)	6.52
k_a (hr^{-1})	1	C _{ss,max} (mg/L)	0.676
τ (hr)	12	C _{ss,min} (mg/L)	0.392
		C _{ss,av} (mg/L)	0.543

5. Results

Existing preclinical and clinical data were utilized for the determination of elacridar's therapeutic windows. Through curve fitting with clinical data of varying dose, we are able to determine apparent clearance (CL/F) = 138L/hr and apparent volume of distribution (V/F) = 2250L and the therapeutic window, of which the upper bound = 1.42mg/L and lower bound = 0.34mg/L. With the given therapeutic limits, the multiple-dose extravascular PK model is then used to simulate for the drug orally dosed by patients to obtain an optimal dose regimen with dose of 900 mg with a dose interval of 12 hours (BID).

6. Discussion

6.1. Implications

This project uses modeling to obtain a PK function of elacridar with its parameters derived from preclinical as well as clinical studies. The PK model can clarify the PK properties of elacridar and can be utilized by clinicians to optimize the clinical dose regimen as the phase of the development of the drug transits from preclinical animal tests to clinical test on patients and volunteers. Moreover, the model also provides a tool for efficient calculations of elacridar's exposure at different regimens: for researchers to want to test elacridar potency while modulating the dose or dosing interval can again input them into the model and adjust them so to ensure that they fall within the therapeutic window. Hence, the results of this project provide valuable implications for researchers on the transition of elacridar development from a stage of preclinical experimentation to possessing more clarified information on elacridar's human PK profile. This elacridar model also enables researchers and clinicians to better design and conduct clinical studies of elacridar in the future.

6.2. Limitations and Future Directions

Despite the optimal dose regimen being obtained from the model, certain limitations remain in this project that requires further research. As could be noted from Table 3, the parameter of bioavailability is incorporated into other parameters (CL/F, V/F) instead of being listed as an independent parameter. This is because there is no sufficient information provided specifically on elacridar's bioavailability and it can vary significantly between preclinical animals (mice, rat, dog, monkey) and humans. Therefore, although the PK function and major parameters could be calculated from provided, existing research, future experiments and modeling should aim to clarify elacridar's bioavailability in humans through different administration routes.

Furthermore, a potential area of exploration is the administration of elacridar through different routes, such as cerebrospinal (CSF) injection and peritoneal injection. A deeper study on balancing convenience from the patient's perspective and potency on the clinician's perspective should be instigated, after having compared the PK and PD profiles of elacridar through different administration routes.

7. Conclusion

A series of four basic PK models with different modes of dosing and pathways of administration (single-dose IV, multiple-dose IV, single-dose extravascular, and multiple-dose extravascular) were constructed in this project and used to study the PK profile of elacridar. Existing clinical data were leveraged to determine two of elacridar's PK input parameters (CL/F and V/F) through curve fitting, and preclinical test results were used to determine elacridar's therapeutic window. The multiple-dose, extravascular elacridar PK model is subsequently constructed to simulate for the repeat oral administration of the drug to patients. After adjustment, an optimized dose regimen with the value a dose of 900 mg with a dose interval of 12 hours (BID) was obtained, which holds the potential to improve patient adherence and clinical outcome.

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