

Is flip-flop kinetics a myth?



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INTRODUCTION/OBJECTIVES

Fip flop kinetics is being used in pharmacokinetics and pharmacometrics when following oral dosing the absorption half-life is larger than the elimination half-life [1-3] assuming first-order kinetics for drug absorption and elimination. According to the finite absorption time (F.A.T.) concept developed recently [4-6], the gastrointestinal absorption of drugs follows zero-order (single or multiple) kinetics because of the passive drug absorption under sink conditions caused by the high blood flow rate 20-40 cm/s in the portal vein; therefore, flip flop kinetics cannot be substantiated in the gastrointestinal absorption. In this work, we re-analyze pharmacokinetic data which have been reported to follow flip flop kinetics in gastrointestinal absorption or after intramuscular administration of long acting formulations [7,8].

METHODS

The concentration (C) and time (t)^(λ-1) data of the plots in [7,8] were digitized by transferring the published figures to the Windows utility MS Paint, reading off the coordinates of axis ranges and data points, and performing linear interpolation to recover the data shown in the published papers. They were then analyzed using physiologically based finite time pharmacokinetic (PBFTPK) models. The least-squares method was implemented within the programming environment of Igor Pro 9 by WaveMetrics for the PBFTPK model fittings. We also fitted the fractal kinetics [9,10] model, $dC/dt = kt^{(-λ)} - k_{el}C$, where k is a rate coefficient with concentration (time)^(λ-1) units and kel is the elimination rate constant, to the data; $E_1(λ, x)$ is Exponential Integral function. The analytical solution of the differential equation was used in the fitting exercise. The ODEs and their analytical solutions are shown in Table 1.

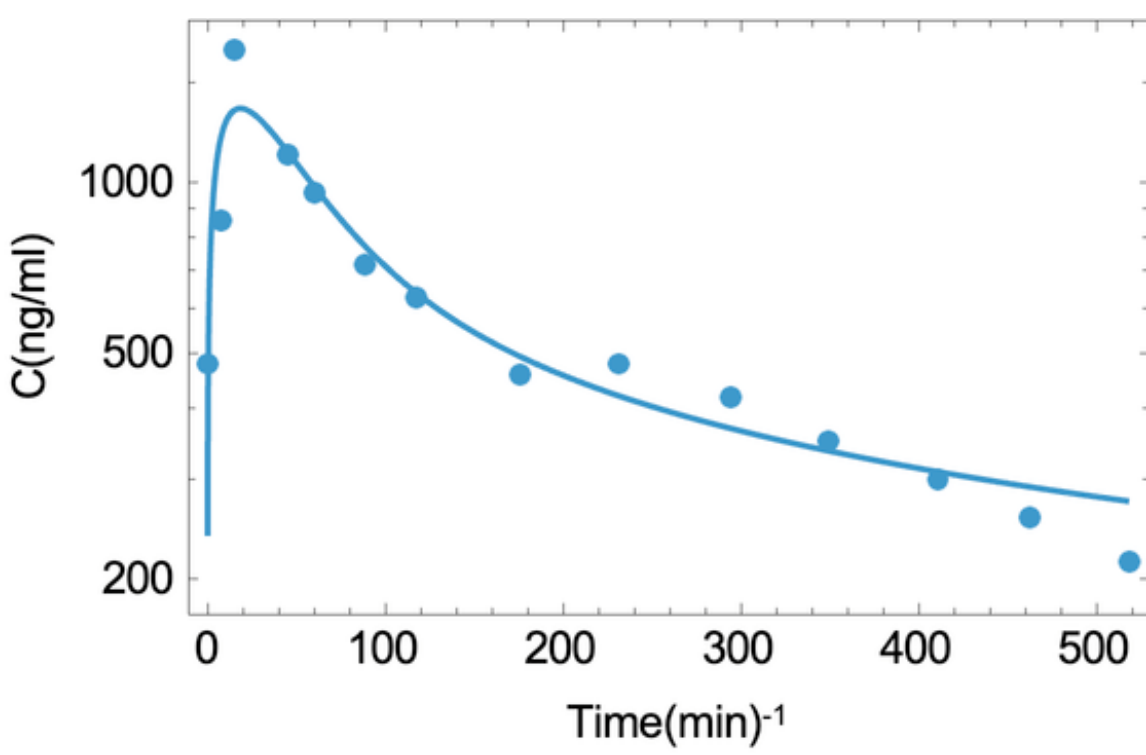
EQUATIONS

Graph	ODE Model	Best fit
1	$\frac{dC}{dt} = kt^{-λ} - k_{el}C$	$k = 229.01 \text{ (}^{109}/\text{mL)min}^{-0.514}$ $k_{el} = 0.04 \text{ min}^{-1}$
	$C(t) = e^{(-k_{el}t)}t^{-λ}(n_0t^λ - ktE_1(λ, -k_{el}t))$	$n_0 = 146.715 \text{ (}^{109}/\text{mL)min}^{0.486}$ $λ = 0.486$
2	$\frac{dC}{dt} = kt^{-λ} - k_{el}C$	$k = 14.36 \text{ (}^{109}/\text{mL)min}^{-0.56}$ $k_{el} = 0.17 \text{ min}^{-1}$
	$C(t) = e^{(-k_{el}t)}t^{-λ}(n_0t^λ - ktE_1(λ, -k_{el}t))$	$n_0 = 43.05 \text{ (}^{109}/\text{mL)min}^{0.44}$ $λ = 0.44$
3	$\frac{dC}{dt} = kt^{-λ} + kt^{-μ} - k_{el}C$	$k_1 = 5.13 \text{ (}^{109}/\text{mL)min}^{-0.553}$ $k_2 = 42 \text{ (}^{109}/\text{mL)min}^{-2.73}$ $k_{el} = 0.06 \text{ min}^{-1}$
		$n_0 = 8.02 \text{ (}^{109}/\text{mL)min}^{2.897}$
	$C(t) = e^{-k_{el}t}t^{-(λ+μ)}(n_0t^{(λ+μ)} - t(K_1t^λE_1(λ, -k_{el}t) + K_2t^μE_1(μ, -k_{el}t)))$	$λ = 0.447$ $μ = 2.25$

Table 1.

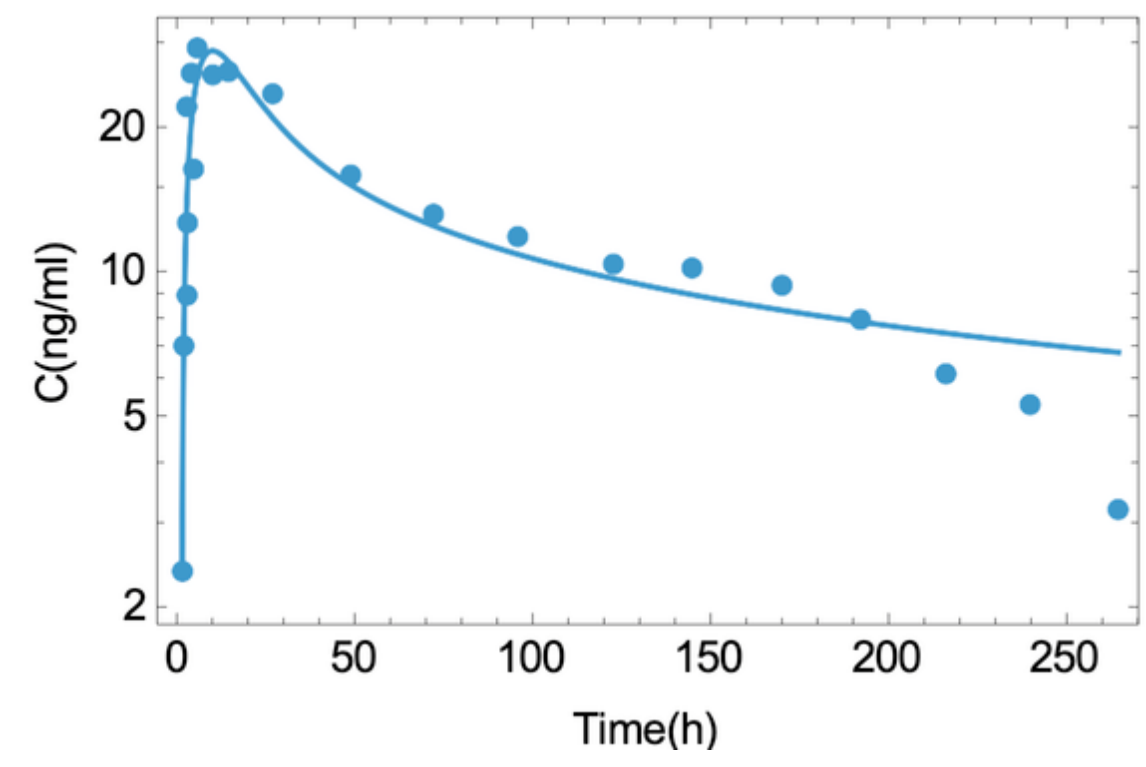
RESULTS

The doxycycline [7] data were nicely described with a PBFTPK model with one input stage, absorption duration 0.44±0.06 h, input rate 3.5±0.07(μg/mL)/h, elimination rate constant 0.073±0.09h⁻¹ correlation coefficient R²=0.985 and one compartment model disposition Since the input rate for the doxycycline data is described by zero-order kinetics (input rate 3.5±0.07 (μg/mL)/h, the comparison with the elimination rate constant (0.073±0.09 h⁻¹) can not be made.



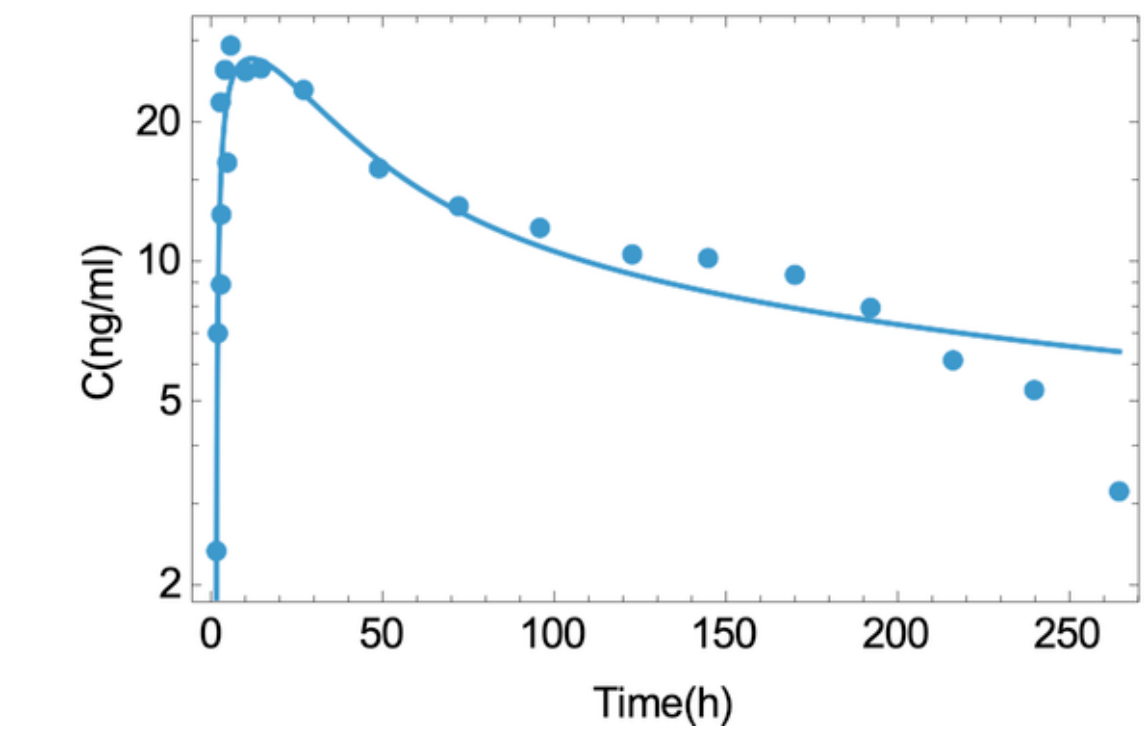
Graph 1. Doxycycline

The two sets of data in [8] were best described with a model having input rate driven by a time-dependent coefficient and one compartment model disposition. For the data set of methylprednisolone sodium succinate (MPS) which is a hydrosoluble pro-drug of methylprednisolone (MP), administered intravenously and transformed to MP, the time dependent coefficient was equal to 229.1 (ng/mL)h^{-0.52}, λ=0.48, the elimination rate constant was found 0.041 h⁻¹ and R²=0.964.



Graph 2. Methylprednisolone sodium

For methylprednisolone acetate, a non-hydrosoluble pro-drug of MP administered intramuscularly at the same dose rate of 4 mg/kg (as MP), the time dependent coefficient was equal to 14.36 (ng/mL)h^{-0.56}, λ=0.44, the elimination rate constant was found 0.179 h⁻¹ and R²=0.958. The time-dependent character of the absorption process of MP in both data sets examined does not allow a comparison with the elimination characteristics of MP; this is so since a half-life for MP's absorption, which follows fractal kinetics cannot be defined [11].



Graph 3. Methylprednisolone acetate

CONCLUSION

For all data sets examined the fittings were superior using PBFTPK and fractal kinetics models to the flip-flop kinetics models.

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