Theoretical Considerations for the Design and Development of a Drug: Influence of Pharmacokinetics and Dosage Regimen on Receptor Interactions

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INTRODUCTION

In the preliminary evaluation process for a drug that manifests its activity only while bound to its receptor, one must determine how the receptor interactions (i.e., the association and dissociation constants) and the pharmacokinetics (i.e., the elimination rate constant) affect the residence time of the drug at its site of action. To address this issue, a new term, the efficiency factor, is introduced. This factor is a hybrid quantity that is based on drug–receptor affinity, pharmacokinetics, and dosage regimen. The goal is to maximize the efficiency factor, that is, to get the maximum clinical effect for the least amount of drug. In some instances, changes in the dosage regimen alone are sufficient for optimizing efficacy; in other instances, extensive molecular modifications may be necessary to change the activity. If the latter approach is taken, one must decide what is the best parameter to modify, e.g., the receptor interactions or the pharmacokinetics. In the following example, we show how the construction of a theoretical model helps in the solution of this problem.

METHODS

We construct our theoretical model using G4120, an antiplatelet drug that blocks the interaction of fibrinogen with the platelet membrane receptor glycoprotein IIb/IIIa (gpIIb/IIIa) (1,2). G4120 inhibits platelet aggregation only while bound to this receptor. We have conducted our analysis under the following assumptions.

- The activity of the drug is proportional to the residence time of the complex formed by the drug with its receptor.
- The complex is formed at a rate proportional to the concentration of the free receptors and of the free drug, and it dissociates at a rate proportional to its concentration.
- The free drug concentration in plasma represents the drug available to the receptors; this is true when the receptors are in the blood or in a well-perfused organ.
- The total number of receptors is constant.
- There is no cooperativity.
- The unbound drug is eliminated from the plasma at a rate proportional to its concentration.
- The elimination rate of the complex is negligible.
- Molecular modifications that change the dissociation constant, K_d, do not affect the pharmacokinetics, and vice versa.

To answer the question "Should a drug bind tighter to the receptor or be eliminated more slowly to increase its efficacy?" we need to determine the residence time of the complex as a function of these parameters as well as its dosage regimen. Since receptor interactions and dosage regimens can vary, we present numerical approximations for fast and slow receptor equilibration and consider the influence of bolus dosing and continuous infusion, including steady-state conditions, on the conclusions.

SLOW EQUILIBRATION

Call X the free ligand, Y the unoccupied receptor, and Z the ligand–receptor complex, and consider the reaction

$$\boxed{X} + \boxed{Y} \rightleftarrows \boxed{Z}$$

If x, y, and z are the concentrations of X, Y, and Z, respectively, we can write the equations,

$$\frac{dx}{dt} = -k_1 x\, y + k_2 z - k_3 x, \qquad x(0) = D/V \tag{1}$$

$$\frac{dy}{dt} = -k_1 x\, y + k_2 z, \qquad y(0) = R/V \tag{2}$$

$$\frac{dz}{dt} = +k_1 x\, y - k_2 z, \qquad z(0) = 0 \tag{3}$$

$$y + z = R/V \tag{4}$$

where k_1 is the formation rate constant and k_2 the dissociation rate constant of the complex, k_3 the elimination rate constant of the free ligand from the plasma, D/V the total concentration of the ligand at the beginning of the experiment, R/V the total concentration of the receptor (free and bound), and V the volume of the plasma. Equation (2) is redundant. Equation (4) can be substituted into Eqs. (1) and (3),

$$\frac{dx}{dt} = -k_1 x\,(R/V - z) + k_2 z - k_3 x \tag{5}$$

$$\frac{dz}{dt} = +k_1 x\,(R/V - z) - k_2 z \tag{6}$$

Divide both sides of Eqs. (5) and (6) by $k_2 \cdot R/V$,

$$\frac{1}{k_2}\frac{d}{dt}\frac{x}{R/V} = -\frac{k_1 R/V}{k_2}\frac{x}{R/V}\left(1 - \frac{z}{R/V}\right) + \frac{z}{R/V} - \frac{k_3}{k_2}\frac{x}{R/V} \tag{7}$$

$$\frac{1}{k_2}\frac{d}{dt}\frac{z}{R/V} = +\frac{k_1 R/V}{k_2}\frac{x}{R/V}\left(1 - \frac{z}{R/V}\right) - \frac{z}{R/V} \tag{8}$$

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Define the dimensionless variables

$$\rho = \frac{x}{R/V}, \qquad \sigma = \frac{z}{R/V}, \qquad \tau = k_2 t$$

and the dimensionless parameters

$$\alpha = \frac{k_1 R/V}{k_2}, \qquad \beta = \frac{k_3}{k_2}, \qquad \gamma = \frac{D}{R}$$

Some typical values of these parameters for a 10-kg dog are

$$D/V \cong \frac{3 \text{ mg}}{0.7 \text{ L}} \cong \frac{4.3 \times 10^{-3}}{668} M \cong 6.4 \times 10^{-6} M$$

$$R/V \cong 5 \times 10^4 \cdot 3 \times 10^5 \, \mu\text{L}^{-1} = \frac{1.5 \times 10^{16}}{6 \times 10^{23}} M$$

$$\cong 2.5 \times 10^{-8} M$$

$$k_1/k_2 \cong 2.5 \times 10^8 M^{-1}$$

$$k_2 \cong 10^{-5} \text{ to } 10^3 \text{ sec}^{-1} \cong 2.78 \times 10^{-9} \text{ to } 2.78 \times 10^{-1} \text{ hr}^{-1}$$

$$k_3 \cong 2.7 \text{ hr}^{-1}$$

Therefore

$$\alpha = \frac{k_1 R/V}{k_2} \cong 6.25$$

$$\beta = \frac{k_3}{k_2} \cong 9.7 \times 10^8 \text{ to } 9.7$$

$$\gamma = \frac{D}{R} \cong 2.56 \times 10^2$$

Equations (7) and (8) in dimensionless form become

$$\frac{d\rho}{d\tau} = -\alpha\rho(1 - \sigma) + \sigma - \beta\rho, \qquad \rho(0) = \gamma \tag{9}$$

$$\frac{d\sigma}{d\tau} = +\alpha\rho(1 - \sigma) - \sigma, \qquad \sigma(0) = 0 \tag{10}$$

To the two equations above we add equation

$$\frac{d\Sigma}{d\tau} = \sigma(\tau), \qquad \Sigma(0) = 0 \tag{11}$$

By numerical integration we get the values of $\Sigma(\infty)$ shown in Table I. We now define the coefficient Θ such that

$$\Sigma(\infty) = \frac{\alpha \cdot \gamma}{\beta} \cdot \Theta \tag{12}$$

and Table II shows the values of this coefficient for different values of α, β, and γ. It is evident from those tables that the approximation

$$\Sigma(\infty) \cong \frac{\alpha \cdot \gamma}{\beta}$$

can be used for all values of α, β, and γ such that $\Theta \cong 1$.

The residence time T_z of the ligand in the complex is given by

$$T_z = \frac{1}{D/V} \int_0^\infty z \, dt = \frac{1}{D/V} \int_0^\infty R/V \cdot \sigma \, d(\tau/k_2)$$

$$= \frac{R}{k_2 D} \int_0^\infty \sigma \, d\tau = \frac{R}{k_2 D} \Sigma(\infty)$$

Using definition (12) we get

$$T_z = \frac{R}{k_2 D} \cdot \frac{\alpha\gamma}{\beta} \cdot \Theta$$

$$= \frac{k_1 R/V}{k_2 k_3} \cdot \Theta$$

As Table II shows, Θ is close to 1 when both ligand and receptors are at low concentrations, the elimination rate of the ligand is fast, and the formation rate of the complex is slow. The closer Θ is to one, the more nearly linear the system; in this case, the residence time T_z is close to $(k_1 R/V)/(k_2 k_3)$, i.e., it is proportional to the total concentration of receptors and to the formation rate of the complex, and inversely proportional to the dissociation rate of the complex and the elimination rate of the free ligand, as expected. This approximation is not valid when Θ is smaller than one; thus, Θ can be seen as an efficiency factor relating efficacy to the parameters.

FAST EQUILIBRATION

If the equilibration $X + Y \leftrightarrow Z$ is fast, Eqs. (1), (2), (3), and (4) become

$$K_d \, z = x \cdot y \tag{13}$$

$$y + z = R/V \tag{14}$$

$$\frac{d(x + z)}{dt} = -k_3 x \tag{15}$$

where $K_d = k_2/k_1$ is the dissociation constant of the complex, R/V the total concentration of the receptors (free and bound), and k_3 the elimination rate of the ligand.

The additional hypothesis made here is only that the reaction $X + Y \leftrightarrow Z$ is always at equilibrium.

Eliminate y between Eq. (13) and Eq. (14)

$$K_d \, z = x \, (R/V - z) \tag{16}$$

Define the dimensionless variables

$$\frac{x}{R/V} = \rho$$

$$\frac{z}{R/V} = \sigma$$

$$k_3 \cdot t = \tau$$

and the dimensionless parameter

$$\frac{R/V}{K_d} = \alpha$$

Equations (15) and (16) become

$$\frac{d\rho}{d\tau} + \frac{d\sigma}{d\tau} = -\rho \tag{17}$$

$$\sigma = \alpha \cdot \rho(1 - \sigma) \tag{18}$$

then eliminating ρ,

$$\frac{d\sigma}{d\tau} = \frac{-\sigma(1 - \sigma)}{1 + \alpha \cdot (1 - \sigma)^2} \tag{19}$$

Table I. Value of $\Sigma(\infty)$

		γ					
α	β	0.01	0.1	1	10	100	1000
0.1	0.001	0.9995	9.955	95.70	705.5	2440	4665
	0.01	0.09995	0.9955	9.573	70.65	244.3	466.9
	0.1	0.009996	0.09959	0.9602	7.173	24.82	47.15
	1	0.0009998	0.009976	0.09767	0.8034	2.925	5.236
	10	0.0001	0.0009995	0.009955	0.09563	0.6624	1.268
1	0.001	9.975	97.54	790.3	2808	5106	7408
	0.01	0.9975	9.755	79.10	281.2	511.1	741.3
	0.1	0.09976	0.9766	7.980	28.54	51.61	74.64
	1	0.009983	0.09835	0.8502	3.314	5.711	8.023
	10	0.0009996	0.009958	0.09594	0.6777	1.315	1.555
10	0.001	99.55	954.8	5944	9512	11900	14210
	0.01	9.955	95.49	594.7	951.9	1191	1422
	0.1	0.9955	9.552	59.80	95.82	119.7	142.8
	1	0.09958	0.9586	6.280	10.24	12.64	14.95
	10	0.009976	0.09764	0.7842	1.775	2.026	2.258
100	0.001	995	9505	51900	56800	59200	61510
	0.01	99.5	950.5	5191	5681	5921	6152
	0.1	9.951	95.06	519.7	568.9	592.9	616
	1	0.9951	9.510	52.56	57.68	60.08	62.39
	10	0.09955	0.9552	5.758	6.579	6.820	7.051

This equation must be completed by appropriate initial conditions. From Eq. (18),

$$\sigma(0) = \alpha \cdot \rho(0) \cdot [1 - \sigma(0)] \tag{20}$$

we can also write

$$x(0) + z(0) = D/V$$

which, defining the dimensionless parameter

$$\gamma = D/R$$

becomes

$$\rho(0) + \sigma(0) = \gamma \tag{21}$$

Eliminating $\rho(0)$ between (20) and (21),

$$\sigma(0) = \tfrac{1}{2} \cdot [1/\alpha + \gamma + 1 - \sqrt{(1/\alpha + \gamma + 1)^2 - 4 \cdot \gamma}] \tag{22}$$

The values of $\sigma(0)$ for different values of α and γ are shown in Table III.

To Eq. (19) with initial condition (22), we can add the equation

$$\frac{d\Sigma}{d\tau} = \sigma(\tau), \qquad \Sigma(0) = 0 \tag{23}$$

By numerical integration we get the values of $\Sigma(\infty)$ shown in Table IV.

If we now define the coefficient Ψ such that

$$\Sigma(\infty) = \alpha\gamma\Psi \tag{24}$$

Table V shows the values of this coefficient for different values of α and of γ. From that table it is evident that making

$$\Sigma(\infty) \cong \alpha \cdot \gamma \tag{25}$$

the error is less than 5% for a large range of values of α and γ.

The residence time T_z of the ligand in the complex is given by

$$T_z = \frac{1}{D/V}\int_0^\infty z\,dt = \frac{1}{D/V}\int_0^\infty R/V \cdot \sigma\, d(\tau/k_3)$$

$$= \frac{R}{k_3 D}\int_0^\infty \sigma\, d\tau = \frac{R}{k_3 D}\Sigma(\infty)$$

Using definition (24) we get

$$T_z = \frac{R}{k_3 D}\alpha\gamma\Psi = \frac{R/V}{k_3 K_d}\Psi$$

i.e., the residence time, in the range of α and γ indicated, is proportional to the total concentration of receptors and inversely proportional to the dissociation constant of the complex and to the elimination rate of the free ligand, as expected. Ψ is an efficiency factor, like Θ, relating efficacy to the parameters. The closer Ψ is to 1, the more efficient the system.

CONTINUOUS INFUSION

Consider now the administration of the same dose D as a continuous infusion into the plasma at rate f for a time interval D/f; Eq. (15) becomes

$$\frac{d(x + z)}{dt} = -k_3 x + f/V \qquad \text{for} \qquad 0 \leq t \leq D/f$$

$$= -k_3 x \qquad \text{for} \qquad t > D/f$$

Table II. Value of Θ

α	β	γ 0.01	0.1	1	10	100	1000
0.1	0.001	0.9995	0.9955	0.9570	0.7055	0.2440	0.04665
	0.01	0.9995	0.9955	0.9573	0.7065	0.2443	0.04669
	0.1	0.9996	0.9959	0.9602	0.7173	0.2482	0.04715
	1	0.9998	0.9976	0.9767	0.8034	0.2925	0.05236
	10	1.0000	0.9995	0.9955	0.9563	0.6624	0.1268
1	0.001	0.9975	0.9754	0.7903	0.2808	0.05106	0.007408
	0.01	0.9975	0.9755	0.7910	0.2812	0.05111	0.007413
	0.1	0.9976	0.9766	0.7980	0.2854	0.05161	0.007464
	1	0.9983	0.9835	0.8502	0.3314	0.05711	0.008023
	10	0.9996	0.9958	0.9594	0.6777	0.1315	0.01555
10	0.001	0.9955	0.9548	0.5944	0.09512	0.01190	0.0014210
	0.01	0.9955	0.9549	0.5947	0.09519	0.01191	0.001422
	0.1	0.9955	0.9552	0.5980	0.09582	0.01197	0.001428
	1	0.9958	0.9586	0.6280	0.1024	0.01264	0.001495
	10	0.9976	0.9764	0.7842	0.1775	0.02026	0.002258
100	0.001	0.995	0.9505	0.5190	0.05680	0.00592	0.0006151
	0.01	0.995	0.9505	0.5191	0.05681	0.005921	0.0006152
	0.1	0.9951	0.9506	0.5197	0.05689	0.005929	0.000616
	1	0.9951	0.9510	0.5256	0.05768	0.006008	0.0006239
	10	0.9955	0.9551	0.5758	0.06579	0.00682	0.0007051

with initial condition

$$x + y = 0$$

Equations (13) and (14) do not change. Proceeding as in the previous section, we obtain

$$\sigma = \alpha\rho(1 - \sigma)$$

$$\frac{d\rho}{d\tau} + \frac{d\sigma}{d\tau} = -\rho + \gamma\delta \quad \text{for} \quad 0 \leq \tau \leq \delta$$

$$= -\rho \quad \text{for} \quad \tau > \delta$$

where

$$\delta = k_3 D/f$$

The initial conditions are

$$\rho(0) = 0, \qquad \sigma(0) = 0$$

Eliminating ρ we obtain

$$\frac{d\sigma}{d\tau} = \frac{1 - \sigma}{1 + \alpha(1 - \sigma)^2}\left(\frac{\alpha\gamma}{\delta}(1 - \sigma) - \sigma\right) \quad \text{for} \quad 0 \leq \tau \leq \delta$$

$$= \frac{-\sigma(1 - \sigma)}{1 + \alpha(1 - \sigma)^2} \quad \text{for} \quad \tau > \delta$$

This equation can be solved together with Eq. (23).

Table VI shows the values of $\Psi = (\Sigma(\infty))/(\alpha\gamma)$ for different values of α, γ, and δ. Even with $\delta = 100$, corresponding to an infusion lasting a hundred times the turnover time, the increase in efficiency is noticeable only for extreme values of α and of γ, i.e., for large doses and small dissociation constants.

STEADY-STATE INFUSION

If the infusion is protracted until a steady state is reached, Eqs. (1), (3), and (4) become

$$-k_1 x_{ss} y_{ss} + k_2 z_{ss} - k_3 x_{ss} + f/V = 0$$

$$+k_1 x_{ss} y_{ss} - k_2 z_{ss} = 0$$

$$y_{ss} + z_{ss} = R/V$$

where the subscript "ss" means the value at steady state. The solution of these ordinary equations is

$$x_{ss} = \frac{f/V}{k_3}$$

$$z_{ss} = \frac{k_1 R/V \cdot f/V}{k_2 k_3 + k_1 f/V}$$

The residence time of the ligand–receptor complex of course cannot be defined because the integral

$$\int_0^\infty z_{ss}(t)dt$$

does not converge, but we can define a *partial residence time* T_z^* by the ratio

$$T_z^* = \frac{\int_{t_1}^{t_2} V \cdot z(t)dt}{f \cdot (t_2 - t_1)}$$

where the numerator is the integral of the amount of material present over a given interval of time, and the denominator is the amount infused over the same interval. In our case,

$$\int_{t_1}^{t_2} V \cdot z(t)dt = V \cdot z_{ss}(t_2 - t_1)$$

Table III. $\sigma(0)$

	α			
α	0.1	1	10	100
0.01	$9.08 \cdot 10^{-4}$	$4.99 \cdot 10^{-3}$	$9.08 \cdot 10^{-3}$	$9.90 \cdot 10^{-3}$
0.02	$1.82 \cdot 10^{-3}$	$9.95 \cdot 10^{-3}$	$1.82 \cdot 10^{-2}$	$1.98 \cdot 10^{-2}$
0.05	$4.53 \cdot 10^{-3}$	$2.47 \cdot 10^{-2}$	$4.53 \cdot 10^{-2}$	$4.95 \cdot 10^{-2}$
0.1	$9.02 \cdot 10^{-3}$	$4.88 \cdot 10^{-2}$	$9.01 \cdot 10^{-2}$	$9.89 \cdot 10^{-2}$
0.2	$1.79 \cdot 10^{-2}$	$9.50 \cdot 10^{-2}$	$1.78 \cdot 10^{-1}$	$1.98 \cdot 10^{-1}$
0.5	$4.36 \cdot 10^{-2}$	$2.19 \cdot 10^{-1}$	$4.26 \cdot 10^{-1}$	$4.90 \cdot 10^{-1}$
1	$8.39 \cdot 10^{-2}$	$3.82 \cdot 10^{-1}$	$7.30 \cdot 10^{-1}$	$9.05 \cdot 10^{-1}$
10	$4.88 \cdot 10^{-1}$	$9.01 \cdot 10^{-1}$	$9.89 \cdot 10^{-1}$	$9.99 \cdot 10^{-1}$
100	$9.08 \cdot 10^{-1}$	$9.90 \cdot 10^{-1}$	$9.99 \cdot 10^{-1}$	1.00
1000	$9.90 \cdot 10^{-1}$	$9.99 \cdot 10^{-1}$	1.00	1.00

therefore

$$T_z^* = \frac{V \cdot z_{ss}}{f} = \frac{k_1}{k_2 k_3 + k_1 f/V} R/V$$

Thus the ratio between the effect that can be obtained in the interval Δt with a continuous infusion at rate f, and the total effect with the corresponding dose $D = f \cdot \Delta t$ given as a bolus, is

$$\frac{T_z(\text{bolus})}{T_z(\text{infusion})} = \frac{(k_1/k_2k_3) \cdot \Theta}{k_1/(k_2k_3 + k_1 \cdot f/V)} = \frac{k_2k_3 + k_1 \cdot f/V}{k_2k_3} \cdot \Theta = \left(1 + \frac{k_1 \cdot f/V}{k_2k_3}\right) \cdot \Theta$$

If the dose given as a bolus clears fast enough so that we can neglect the amount left in the body when the next dose is given, then the same amount of drug given in a steady-state infusion has a higher efficacy than given in repeated boli, if

$$\left(1 + \frac{k_1 \cdot f/V}{k_2k_3}\right) \cdot \Theta < 1$$

i.e., if

$$k_3 \Delta t > \alpha \cdot \gamma \frac{\Theta}{1 - \Theta}$$

Table IV. $\Sigma(\infty)$

	α			
γ	0.1	1	10	100
0.01	$9.992 \cdot 10^{-4}$	$9.980 \cdot 10^{-3}$	$9.951 \cdot 10^{-2}$	0.995
0.02	$2.003 \cdot 10^{-3}$	$1.990 \cdot 10^{-2}$	0.1987	1.980
0.05	$4.992 \cdot 10^{-3}$	$4.941 \cdot 10^{-2}$	0.4891	4.878
0.1	$9.959 \cdot 10^{-3}$	$9.764 \cdot 10^{-2}$	0.9548	9.505
0.2	$1.984 \cdot 10^{-2}$	0.1903	1.818	18.06
0.5	$4.884 \cdot 10^{-2}$	0.4422	3.908	37.67
1	$9.567 \cdot 10^{-2}$	0.7903	5.945	51.90
10	0.7063	2.808	9.509	56.90
100	2.436	5.105	11.91	—
1000	4.655	7.406	—	—

Table V. Ψ with Bolus

	α			
γ	0.1	1	10	100
0.01	1.00	1.00	1.00	1.00
0.1	1.00	0.98	0.95	0.95
0.2	0.99	0.95	0.91	0.90
0.5	0.98	0.88	0.78	0.75
1	0.96	0.79	0.59	0.52
10	0.71	0.28	0.10	0.06
100	0.24	0.05	0.01	—
1000	0.05	0.01	—	—

For Θ close to 1 a bolus is always more effective than an infusion; the infusion becomes preferable only for Θ sufficiently small. For instance, for $\alpha = 10$, $\beta = 1$, $\gamma = 1$, from Table II we have $\Theta = 0.628$, thence the above condition becomes

$$k_3 \cdot \Delta t > 16.88$$

i.e., the steady-state infusion is more effective than the boli if the interval between them is larger than 16.88 times the elimination rate of the complex.

CONCLUSION

We have shown that for small values of the formation rate of the complex, and of the concentration and elimination rate of the free drug, the residence time of the complex is given approximately by

$$T_z = \frac{k_1 R/V}{k_2 k_3}$$

when the formation rate of the complex is slow, and by

$$T_z = \frac{R/V}{k_3 k_d}$$

Table VI. Ψ with Infusion

		γ				
α	δ	0.1	1	10	100	1000
0.1	1	1.00	0.97	0.75	0.28	0.05
	2	1.00	0.97	0.79	0.31	0.06
	10	1.00	0.99	0.92	0.54	0.11
	100	1.00	1.00	0.99	0.91	0.50
1	1	0.98	0.92	0.31	0.06	0.01
	2	0.98	0.84	0.34	0.06	0.01
	10	0.99	0.93	0.55	0.12	0.01
	100	1.00	0.99	0.91	0.51	0.09
10	1	0.96	0.61	0.10	0.01	—
	2	0.96	0.62	0.11	0.01	—
	10	0.97	0.71	0.16	0.02	—
	100	0.99	0.92	0.52	0.10	0.01
100	1	0.95	0.52	0.06	0.01	—
	2	0.95	0.52	0.06	0.01	—
	10	0.95	0.55	0.06	0.01	—
	100	0.96	0.68	0.14	0.02	—

when the formation rate is fast. Thus the effect of the drug increases in proportion to its dose and in inverse proportion to k_3 and to K_d or k_2/k_1, as long as the above approximation is valid, i.e., as long as the efficiency factor Θ, as given in Table II, or the efficiency factor Ψ, as given in Table V, is close to 1. The advantage resulting from any possible reduction of the elimination rate constant of the drug from the plasma, k_3, or of the dissociation constant of the complex, K_d, should be evaluated together with the consequent changes of the efficiency factors, Θ or Ψ.

GLOSSARY OF TERMS

Dimensionless parameter: A fixed quantity that determines the behavior of a function, but whose numerical value does not depend upon the unit of measurement.

Dimensionless variable: A variable whose numerical value does not depend upon the unit of measurement; if an equation is reduced to a relationship among a set of dimensionless quantities, it depends upon a minimum number of parameters.

Efficiency factor: The ratio between the actual residence time and the maximum residence time attainable with an appropriate choice of parameters.

G4120: An antiplatelet drug that blocks the interaction of fibrinogen with the platelet membrane receptor glycoprotein IIb/IIIa (gpIIb/IIIa).

Partial residence time: The ratio between the expected time spent by the drug in a compartment during a finite interval of time and the amount of drug administered during the same interval of time.

Residence time: The expected time spent in one compartment by the drug administered to another compartment; it is given by $(1/D_i)\int_0^\infty c_j(t)dt$, where D_i is the dose administered to compartment i, and $c_j(t)$ is the concentration measured in compartment j. When $i = j$, the residence time coincides with the permanence time.

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