Pharmacokinetics Model Formulation

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1 Fundamentals of Pharmacokinetics

Pharmacokinetics is the study of how drugs move through the body, including absorption, distribution, metabolism, and excretion. Plasma concentration (the amount of drug in the bloodstream at a given time) serves as a key measure of a medication's presence and activity in the body. For optimal therapeutic outcomes, many medications require plasma concentrations within a specific range:

- **Below minimum effective concentration (MEC)**: Insufficient therapeutic effect
- **Within therapeutic window**: Optimal clinical effect
- **Above maximum tolerated concentration**: Increased risk of adverse effects

Different drug formulations (immediate release, sustained release, extended release) are designed to achieve specific plasma concentration profiles to optimize therapeutic benefit.

2 Modeling using Bateman Function

The Bateman function provides a mathematical model for describing drug concentration in plasma over time following oral administration. This first-order kinetic model balances two competing processes, absorption phase and elimination phase:

$$C(t) = A \cdot (e^{-K_e \cdot t} - e^{-K_a \cdot t})$$

Where:

- $C(t)$ = Plasma concentration at time t
- A = Coefficient based on dose and distribution volume
- K_e = Elimination rate constant (related to $T_{1/2}$)
- K_a =Absorption rate constant
- t = Time since dose administration

3 Solving the Bateman Function

The pharmacokinetic model is characterized by three key parameters, which are properties of the medication typically determined through clinical trials or medical studies.

- T_{max}: Time to maximum concentration (hours)
- C_{max}: Peak plasma concentration (ng/ml)
- $T_{1/2}$: Elimination half-life (hours)

To apply the Bateman function in practice, we need to determine the function parameters from known pharmacokinetic values:

1. **Elimination rate constant** (K_e): Calculated from $T_{1/2}$, since drug elimination follows exponential decay model:

$$C(t) = C_0 \cdot e^{-K_e \cdot t}$$

   At $t = T_{1/2}$, $C(t) = \frac{C_0}{2}$, leading to:

$$\frac{C_0}{2} = C_0 \cdot e^{-K_e \cdot T_{1/2}}$$

$$K_e = \frac{\ln(2)}{T_{1/2}}$$

2. **Absorption rate constant** (K_a): Calculated from T_{max} and K_e, since at peak concentration ($t = T_{max}$), the derivative of the concentration function is zero:

$$\left.\frac{dC(t)}{dt}\right|_{t=T_{max}} = 0$$

$$\frac{K_a e^{-K_a T_{max}} - K_e e^{-K_e T_{max}}}{e^{-K_e T_{max}} - e^{-K_a T_{max}}} = 0$$

   Solving for K_a:

$$\frac{\ln(K_a) - \ln(K_e)}{K_a - K_e} = T_{max}$$

3. **Coefficient** (A): Once K_a and K_e are known, A is determined using C_{max} and T_{max}:

$$A = \frac{C_{max}}{e^{-K_e T_{max}} - e^{-K_a T_{max}}}$$

4 Extended Implementation with Metabolic Factor

This implementation extends the basic Bateman model by incorporating several advanced features:

1. **Metabolic Factor**: An adjustment parameter that accounts for individual variations in drug metabolism, affecting how quickly the drug is absorbed and eliminated
    - Adjusted $T_{max} = T_{max}/\text{Metabolic Factor}$
    - Adjusted $C_{max} = C_{max}/\sqrt{\text{Metabolic Factor}}$
    - Adjusted $K_e = K_e \times \text{Metabolic Factor}$
2. **Multiple-dose regimens**: Simulating realistic medication schedules with varying frequency
3. **Flexible dosing patterns**:
    - Variable dosing frequency and interval throughout the day
    - Skip-day dosing patterns
    - Customizable initial dose timing
4. **Advanced metrics**:
    - Area Under the Curve (AUC) calculations for total drug exposure
    - Average concentration measurements
    - End-of-day concentration tracking

5 Collected Sample Data

Table 1: Sample A Simulation Result

Metabolic Factor	**Adj. C_{max}** (ng/ml)	**Adj. T_{max}** (h)	**Adj. $T_{1/2}$** (h)	**EoD Conc.** (ng/ml)	**AUC/d** (ng·h/ml)
1.0	2000	1.0	5.0	522	12787
0.75	2309	1.33	6.67	883	16994
1.25	1789	0.8	3.0	319	10005

[1] Estimated properties of 100mg caffeine from coffee drinks at metabolic factor = 1.0

[2] Simulation of 1 day, one light roasted coffee drink (12g beans) at 13:00

[3] EoD Conc. represent concentration at end of day

Table 2: Sample B Simulation Result

Dosing	**C_{max}** (ng/ml)	**T_{max}** (h)	**$T_{1/2}$** (h)	**Max** (ng/ml)	**EoD Avg.** (ng/ml)	**Avg.** (ng/ml)	**AUC/d** (ng·h/ml)
2/d, q.8h	40	2	21	192	152	146	3504
2/d, q.8h	55	2	21	264	209	201	4818
1/d	80	2	21	209	137	148	3552
2/d, q.8h	80	2	21	384	305	292	7008
1/d	85	3	21	224	152	162	3895
1/d	130	3	21	342	233	248	5957
1/d	120	5	21	324	236	244	5854
1/2d	120	5	21	203	121	126	3035
2/3d	120	5	21	261	145	155	3725
3/4d	120	5	21	295	184	190	4551

[1] Metabolic factor = 0.75

[2] Simulation over 14 days, daily initial dose at 08:00

[3] EoD Avg. represent average concentration at end of each day