

Suppl. Fig. 1 Model approach diagram.

Suppl. Fig. 2 Four preliminary screening TK models.

(A) 1compk.for. (B) 1lagk.for. (C) 2compk.for. (D) 2lagk.for.

For the primary selection model establishment, the following four possible TK models were established: (1) MOD I <1compk.for>, a one-compartment linear model; (2) Mod II <1lagk.for>, a one-compartment linear model with an absorption delay; (3) Mod III <2compk.for>, a two-compartment linear model; (4) Mod IV <2lagk.for>, a two-compartment linear model with an absorption delay.

Suppl. Fig. 3 Convergence equation of different dosages by MATLAB.

(A) Time vs. concentration at 0.36 g/kg. (B) Time vs. concentration at 0.42 g/kg. (C) Time vs. concentration at 0.49 g/kg. HA, MA and AC (from left to right).

Note: The fitting data were analyzed by MATLAB to obtain the TK output equation at different dosages:

$$f(x_1) = (0.3814x_1 - 0.000412)/(x_1^3 + 3.057x_1^2 + 2.987x_1 + 5.701) \quad (1)$$

$$f(x_2) = (0.4797x_2 - 0.002287)/(x_2^3 + 12.33x_2^2 - 2.626x_2 + 14.16) \quad (2)$$

$$f(x_3) = (0.2285x_3 - 0.0002068)/(x_3^3 + 2.286x_3^2 + 6.32x_3 + 4.894) \quad (3)$$

$$f(x_4) = (0.7929x_4 - 0.001222)/(x_4^3 + 8.944x_4^2 - 0.6063x_4 + 11) \quad (4)$$

$$f(x_5) = (0.8297x_5 - 0.00399)/(x_5^3 + 20.23x_5^2 - 12.36x_5 + 21.67) \quad (5)$$

$$f(x_6) = (0.4507x_6 - 0.000955)/(x_6^3 + 9.513x_6^2 - 0.8772x_6 + 11.29) \quad (6)$$

$$f(x_7) = (0.8674x_7 - 0.001103)/(x_7^3 + 6.733x_7^2 - 0.1482x_7 + 9.784) \quad (7)$$

$$f(x_8) = (0.5946x_8 - 0.0009964)/(x_8^3 + 9.28x_8^2 - 4.549x_8 + 11.7) \quad (8)$$

$$f(x_9) = (0.7215x_9 - 0.002338)/(x_9^3 + 15.75x_9^2 - 8.618x_9 + 18.5) \quad (9)$$

Equations (1), (2), and (3) were expressions of HA, MA and AC, at 0.36 g/kg; (4), (5), and (6) were at 0.42 g/kg; and (7), (8), and (9) were at 0.49 g/kg.

Since the sample distribution type was approximately the normal distribution, the Maximum Likelihood (ML) estimation was preferred for the data fitting. Generally, smaller error would result in higher precision, and the sample size must be at least 100. Therefore, before analysis, the data were converged and extended with the MATLAB Software. First create M file myfun1.m: function Y = myfun1 (x), and enter in the command window:

```
PLOT(X,Y,S)
```

```
x=linspace(0,25*pi,3); y=sin(x); z=cos(x); plot(x,y,'r',x,z,'g0')
```

```
plot(x,z,:)
```

```
hold on
```

```
Plot(x,y)
```

The character string and the like may be converted into a character string according to a specified format.

Suppl. Fig. 4 T-RC of HR and QT interval changes induced by different dosages of RAK.

The Biophase TD model, also known as Effect compartment model, has the following characteristics. The amount of drug in the biological phase is very small and does not affect the overall dynamic behavior. The delay time does not change with the dose. The Jusko's Indirect Response (IDR) PD model also applies when Emax lags Cmax, and Tmax increases with increasing dose. Therefore, by observing the TD index data, a suitable TD model can be initially determined.

Suppl. Fig. 5 The Biophase TD model and the Jusko's Indirect Response (IDR) PD model were described with mathematical models.

1. Use mechanism analysis to establish the necessary simplified assumptions:

$$\frac{d\beta}{dt} = \eta \cdot \alpha - \zeta \cdot \gamma$$

2. The preliminary processing of the data according to the T-CC and T-RC curves, and the modeling operation in combination with the developed model:

$$\frac{d\beta}{dt} = CLt \cdot \alpha - Ke0 \cdot (\gamma - \beta) \quad (1)$$

Integral operation of the Equation (1):

$$C_{SSS} = \frac{b \cdot CLt}{(Ke0 - CLd)} (e^{-CLd \cdot t} + e^{Ke0 \cdot t}) \quad (2)$$

$$E_{HR} = \frac{E_{max} \cdot C_{SS}}{EC_{50} + C_{SS}} \quad (3)$$

3. The equations 2 and 3 are transformed by Laplace transform to obtain the differential equations and input equations required by ADAPT 5:

$$\frac{d\gamma_{HR}}{dt} = Ke0 \cdot \left(\frac{\alpha}{V} C_{SS} - \gamma_{HR} \right)$$

$$XP(1) = PS(1) * X(1)/Y(1) - Y(2)$$

For the same reason, the following equations can be obtained:

$$\frac{dC_{SS}}{dt} = CLt \cdot C + K_{in} \cdot C\beta - C\gamma$$

$$C_{SS} = \frac{bCLt}{(CLd - K_{in})} (e^{CLd \cdot t} - e^{(-K_{in} \cdot K_{out})t})$$

$$E_{QT'} = \frac{I_{max} \cdot C_{SS}}{IC_{50} + C_{SS}} - K_{out}$$

$$\frac{d\lambda_{QT'}}{dt} = K_{in} \cdot \left(1 - \frac{C_{SS}}{IC_{50} + C_{SS}} \right) - K_{out} \cdot \gamma_{QT'}$$

Modeling Approach

**Step 1:
T-CC and T-RC
curve analyses**

**Step 2:
Establishment of
TK model**

Four possible TK model
were established

Converge and extend
data

Select the optimal TK
model

TK model description

**Step 3:
Establishment of
TD model**

Indirect response
TD model

TD model
description

TD model output
and fitting

**Step 4:
Establishment of
TK-TD model**

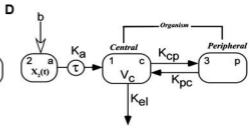
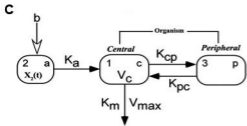
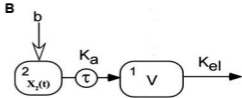
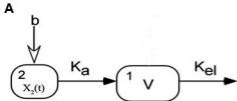
Structural
model

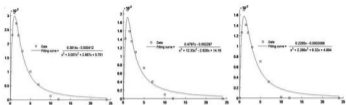
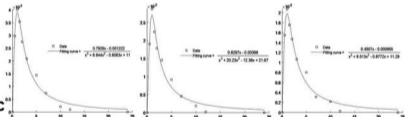
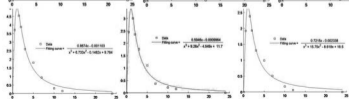
Three-
dimensional fit
map

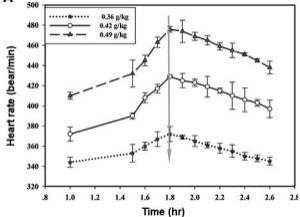
**Step 5:
Model Validation**

Simulation

AMOS
analysis



A**B****C**

A**B**