biocom systems

Simulator for Skin Pharmacokinetics

SKIN-CAD®

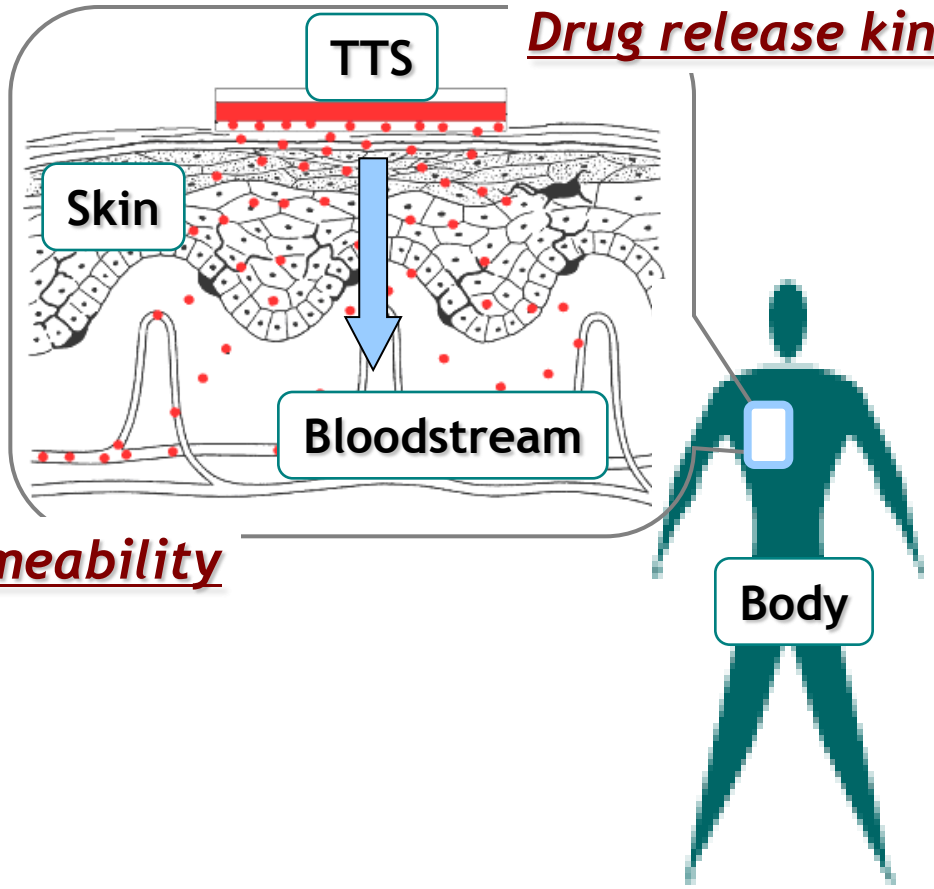
Version 6.0

Biocom Systems, Inc.

Simulator for Skin Pharmacokinetics

SKIN-CAD®

- Simulation software of pharmacokinetics following transdermal drug delivery
- Editor: Prof. K. Tojo (Kyushu Institute of Technology)
- Distribution from the year 2000
- 16 Japanese, US and UK users: pharmaceutical and chemical companies, and university labs (as of Aug., 2010)

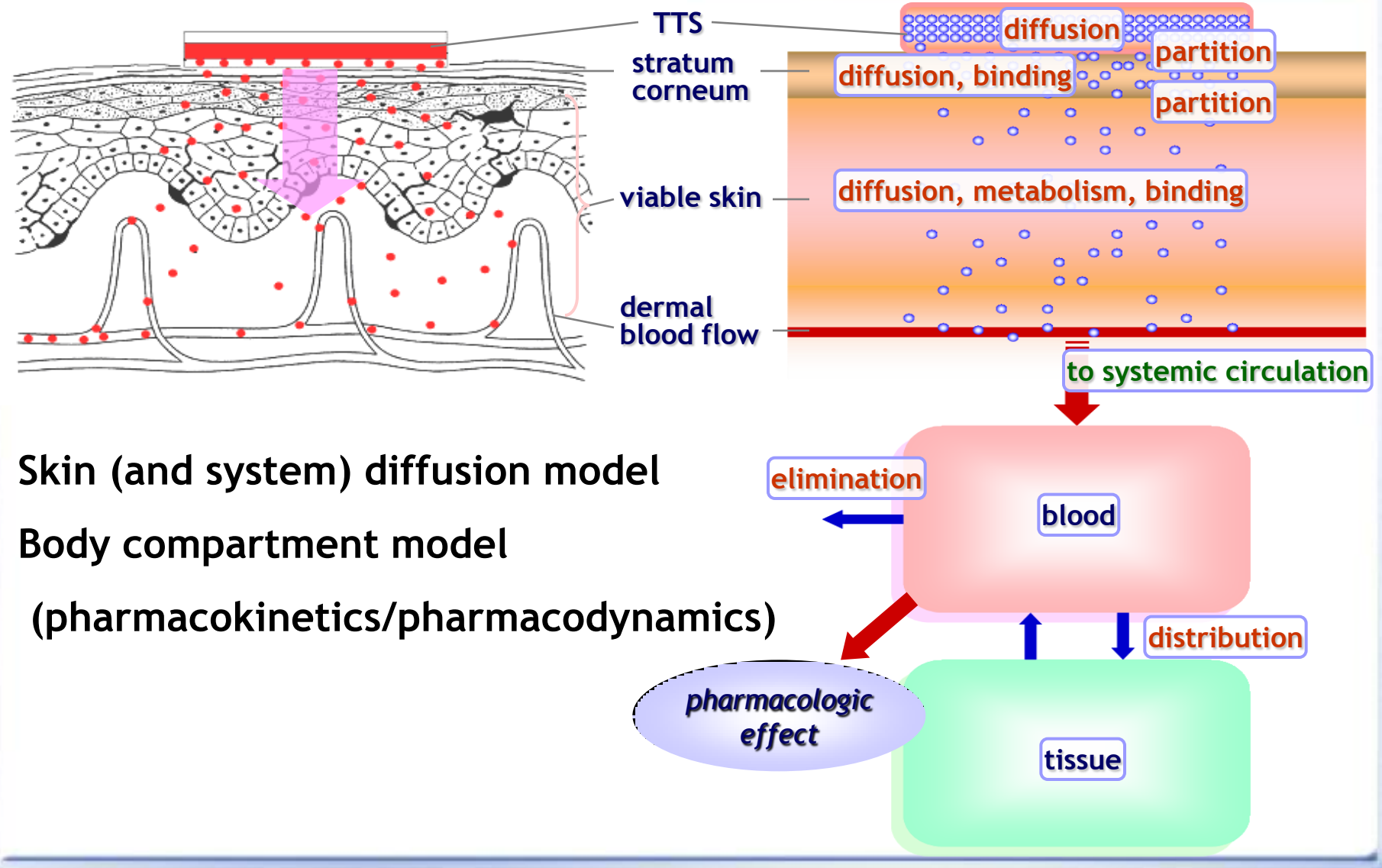


Drug release kinetics

Skin permeability

Distribution & elimination

TTS patches: Nicotine, Fentanyl, Nitroglycerin, Estradiol, etc.



Skin (and system) diffusion model

Body compartment model

(pharmacokinetics/pharmacodynamics)

Release kinetic parameters

(*In vitro* drug release data from TTS)

Skin permeation parameters

(*In vitro* permeation data through the skin)

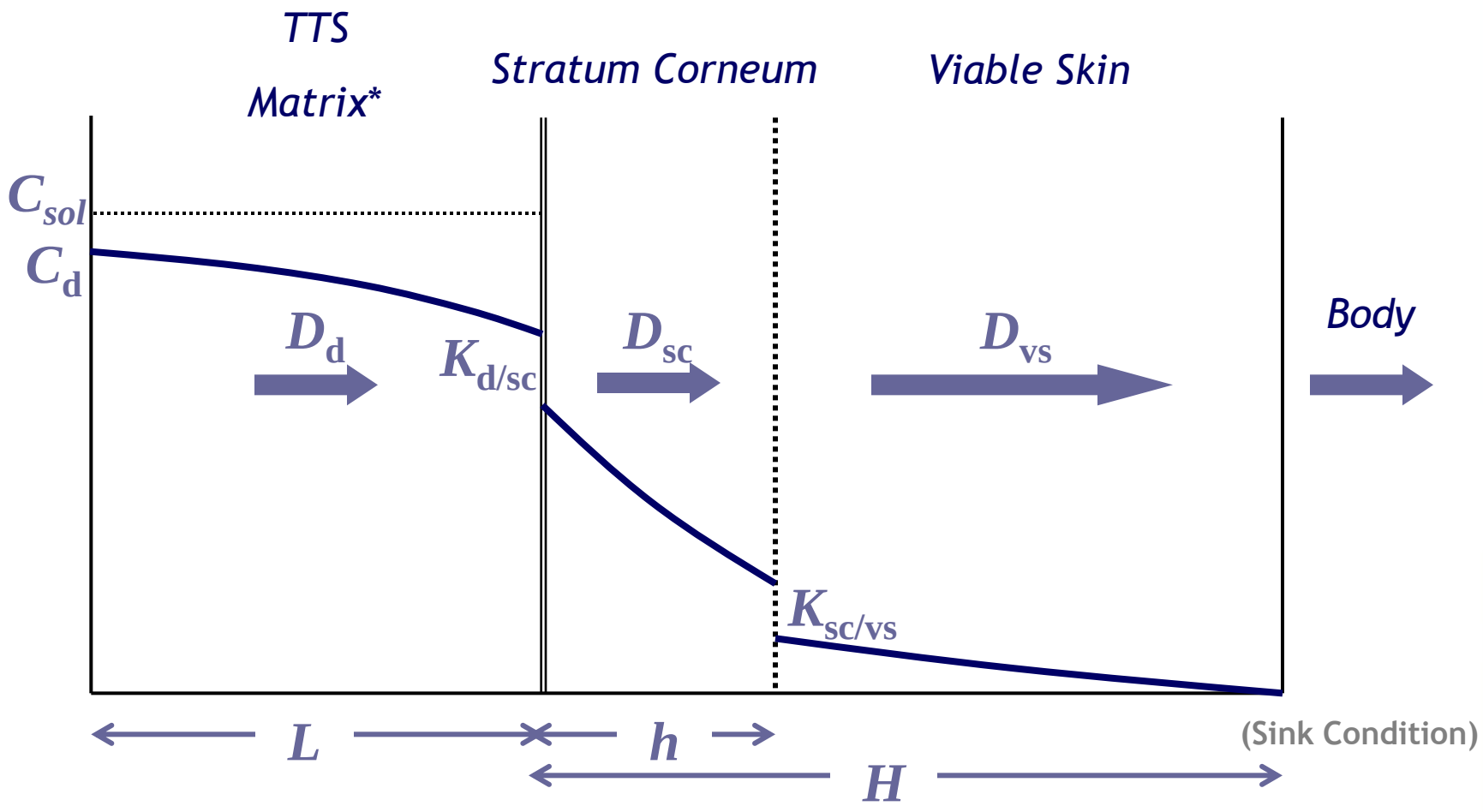
Body pharmacokinetic parameters

(Intravenous or oral administration data)

Under various conditions (application time, system size,…)

SKIN-CAD®

Simulate drug concentration in blood following transdermal delivery



*matrix: drug-adhesive composite layer

$$\{1+\mathrm{B}(C_{sc})\}\frac{\partial C_{sc}}{\partial t}=D_{sc}\frac{\partial^2 C_{sc}}{\partial x^2}+\mathrm{ER}(C_{sc})+\mathrm{EO}(C_{sc})$$

for stratum corneum, $0 < x < h$

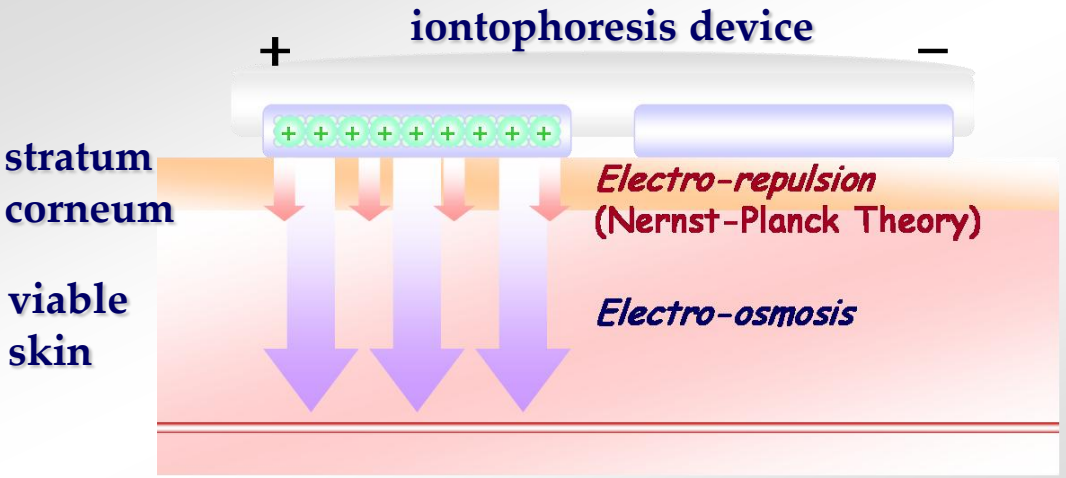
$$\{1+\mathrm{B}(C_{vs})\}\frac{\partial C_{vs}}{\partial t}=D_{vs}\frac{\partial^2 C_{vs}}{\partial x^2}-\mathrm{M}(C_{vs})+\mathrm{EO}(C_{vs})$$

for viable skin, $h < x < H$

- Skin binding, B(*C*): Langmuir-type or Freundlich-type scheme
- Skin metabolism, M(*C*): Michaelis-Menten or First-order kinetics
- Iontophoretic enhancement

ER(*C*): electro-repulsion

EO(*C*): electro-osmosis



- 1-, 2- or 3-compartment model (pharmacokinetics, PK)

$$V_1 \frac{dC_1}{dt} = \left(\frac{dQ}{dt}\right) S_a - (k_{10} + k_{12} + k_{13}) C_1 V_1 + k_{21} C_2 V_2 + k_{31} C_3 V_3$$

$$V_2 \frac{dC_2}{dt} = k_{12} C_1 V_1 - k_{21} C_2 V_2$$

$$V_3 \frac{dC_3}{dt} = k_{13} C_1 V_1 - k_{31} C_3 V_3$$

V: distribution volume [mL], k_{10}: elimination rate constant [s^{-1}],

k: transfer rate constant [s^{-1}], S_a: system size [cm^2],

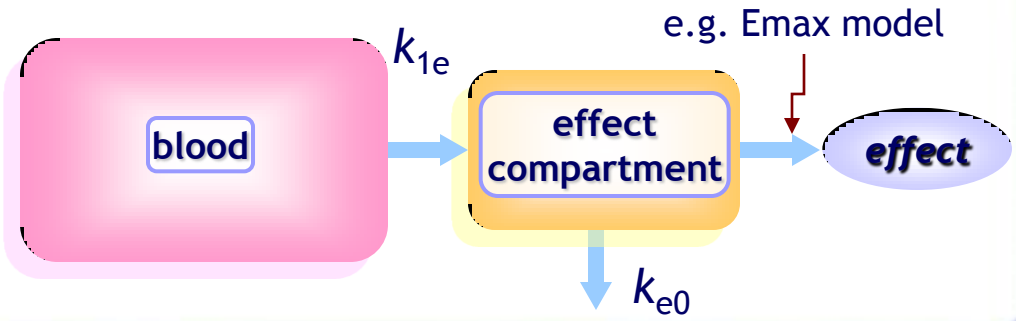
dQ/dt: skin permeation flux [$mg/cm^2/s$]

- Pharmacokinetic (PK) – pharmacodynamic (PD) model

Direct response model

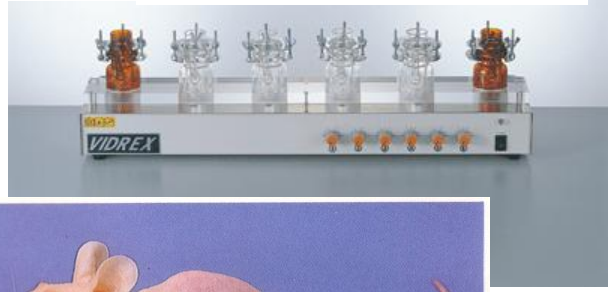
Effect compartment model

Indirect response model



In vitro matrix release and skin permeation studies

Diffusion cell system



Hairless mouse

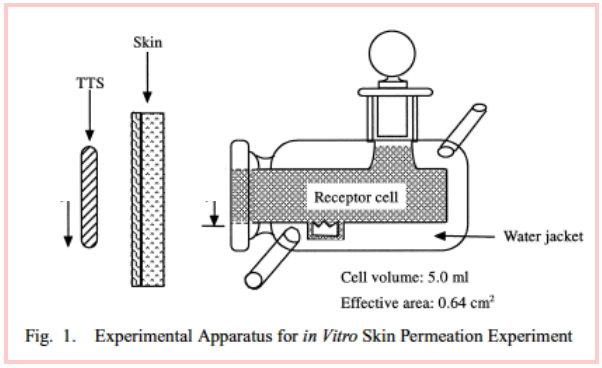
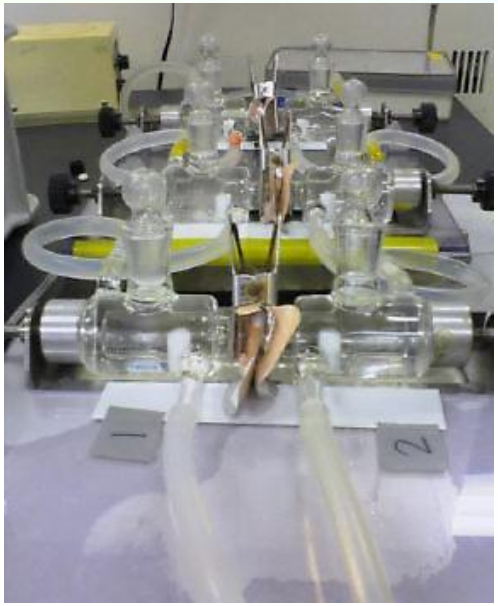
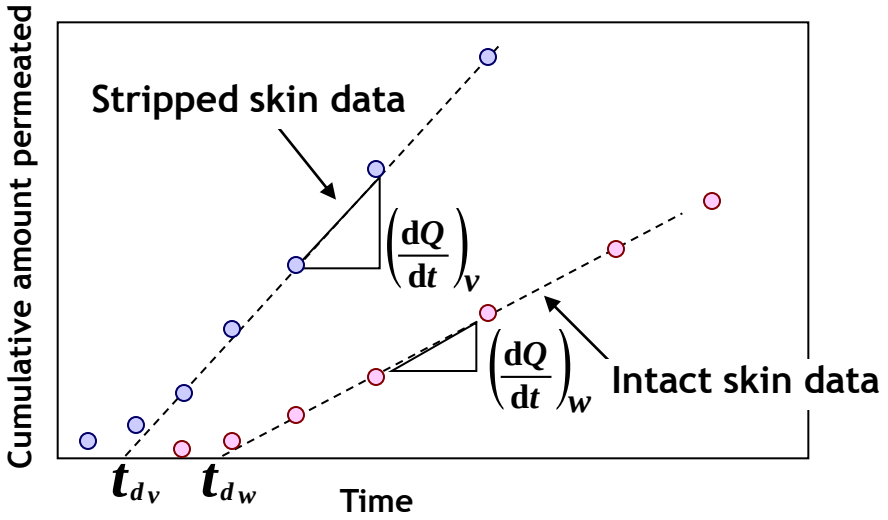


Fig. 1. Experimental Apparatus for *in Vitro* Skin Permeation Experiment





Simulation of blood concentration under human clinical condition

- Model: Matrix/skin 2-layer diffusion model
- Matrix release parameters

Application period: 72 h

D_m: Determined by *in vitro* matrix release study

System size, thickness, and initial drug content

- Skin permeation parameters

Thickness of stratum corneum, h = 20 μm

Distance to dermal microcirculation, H = 200 μm

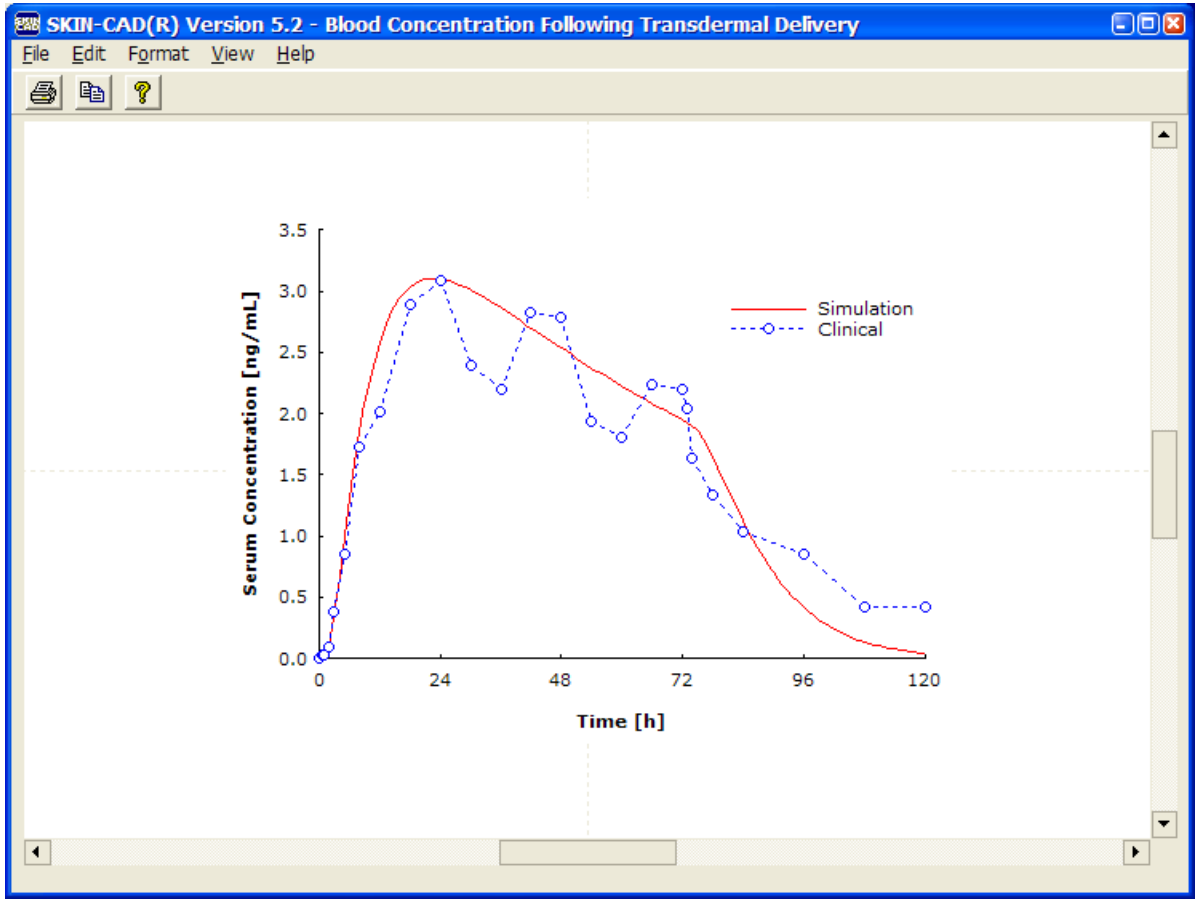
D_{sc}, D_{vs}, $K_{sc/vs}$, C_s:

Determined by *in vitro* skin permeation study using hairless mouse skin

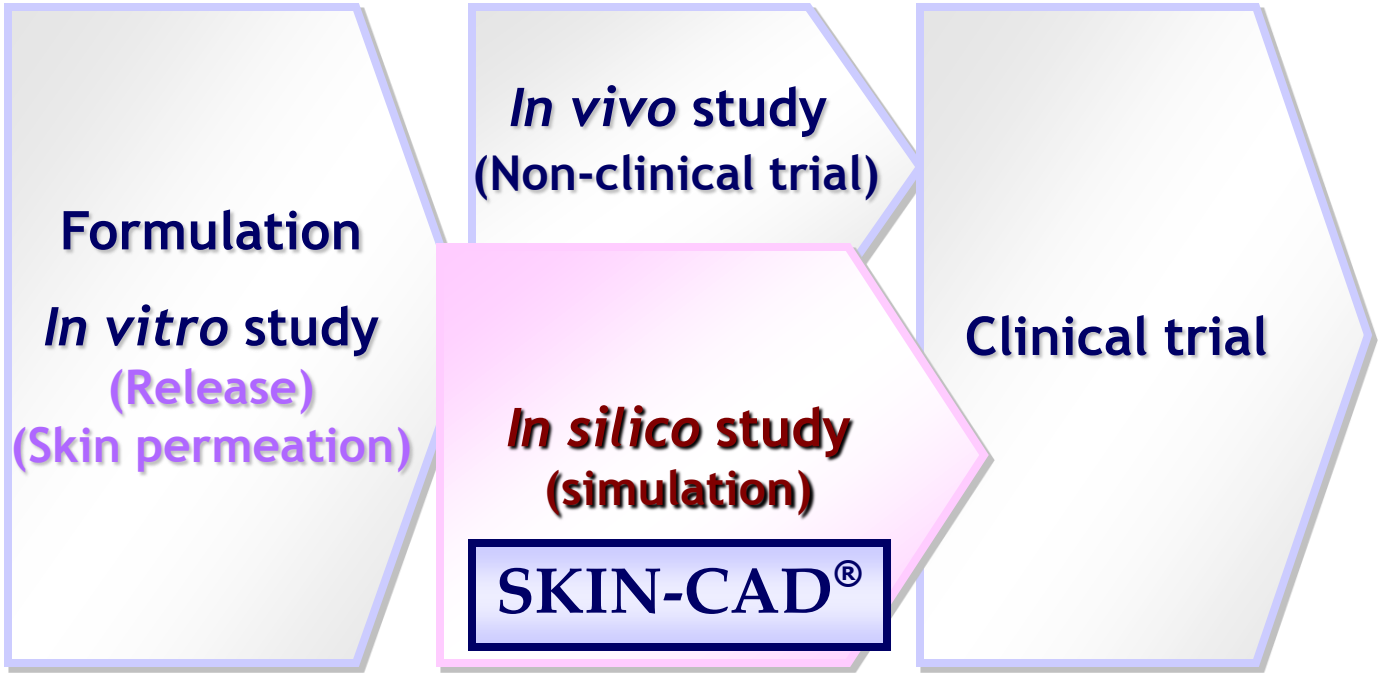
- 3-Compartmental PK parameters (obtained from ref.: Bentley et al., 1982)

V_1 = 18.3 L, V_2 = 51.9 L, V_3 = 214 L

k_{10} = 2.76 h^{-1}, k_{12} = 19.1 h^{-1}, k_{21} = 6.73 h^{-1}, k_{13} = 7.90 h^{-1}, k_{31} = 0.674 h^{-1}



Comparison between simulated and clinical data



- Prediction of clinical performance based on *in vitro* data
- Optimal design and evaluation of TTS at early stage
- R&D at a lower cost and in a shorter period