

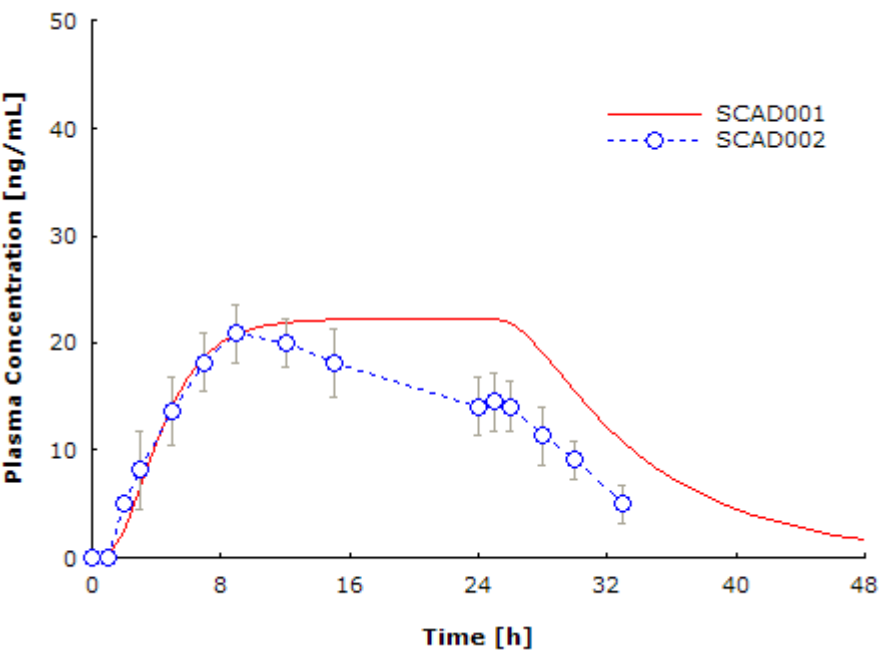
## **SKIN-CAD® Case Study**

## 1. Nicotine patch

【血中濃度予測】

Duration for Medication (Total Calculation Length) [h]	48
Duration of TTS Application [h]	24
TTS Size, $S_a$ [cm <sup>2</sup> ]	20
皮膚 2 層膜モデル	
Thickness of Stratum Corneum, $h$ [μm]	18.2 (文献 1)
Distance to Dermal Microcirculation, $H$ [μm]	200 (文献 2)
(ヘアレスマウス皮膚を用いた <i>in vitro</i> 透過試験より拡散係数, 分配係数を決定)	
Diffusion Coefficient in Stratum Corneum, $D_{sc}$ [cm <sup>2</sup> /s]	$6.21 \times 10^{-11}$
Diffusion Coefficient in Viable Skin, $D_{vs}$ [cm <sup>2</sup> /s]	$6.34 \times 10^{-7}$
Stratum Corneum/Viable Skin Partition Coefficient, $K_{sc/vs}$ [-]	207
Skin Surface Concentration, $C_s$ [μg/mL]	$7.49 \times 10^5$
体内動態 2-コンパートメントモデル (文献 3)	
Volume of Distribution, $V_1$ [L]	58
Volume of Distribution, $V_2$ [L]	138
Elimination Rate Constant, $k_{10}$ [min <sup>-1</sup> ]	0.0197
Transfer Rate Constant, $k_{12}$ [min <sup>-1</sup> ]	0.0216
Transfer Rate Constant, $k_{21}$ [min <sup>-1</sup> ]	0.00906

臨床値（文献 4）との比較



## 2. Fentanyl patch

【血中濃度予測】【体内動態パラメータ個人差の影響】

Duration for Medication (Total Calculation Length) [h]	96
Duration of TTS Application [h]	72
TTS Size, $S_a$ [cm <sup>2</sup> ]	40
皮膚 2 層膜モデル	
Thickness of Stratum Corneum, $h$ [μm]	18.2 (文献 1)
Distance to Dermal Microcirculation, $H$ [μm]	200 (文献 2)
(物性値より拡散係数, 分配係数を決定)	
Molecular Weight	336.5 (文献 5)
Octanol/Water Partition Coefficient	860 (文献 5)
<i>In vitro</i> flux [μg/cm <sup>2</sup> /h]	2.5 (文献 6)
Diffusion Coefficient in Stratum Corneum, $D_{sc}$ [cm <sup>2</sup> /s]	$2.16 \times 10^{-11}$
Diffusion Coefficient in Viable Skin, $D_{vs}$ [cm <sup>2</sup> /s]	$2.16 \times 10^{-7}$
Stratum Corneum/Viable Skin Partition Coefficient, $K_{sc/vs}$ [-]	11.8
Skin Surface Concentration, $C_s$ [μg/mL]	$5.92 \times 10^4$
体内動態 3-コンパートメントモデル (文献 7)	
Volume of Distribution, $V_1$ [L]	26.8
Volume of Distribution, $V_2$ [L]	48.2
Volume of Distribution, $V_3$ [L]	189
Elimination Rate Constant, $k_{10}$ [min <sup>-1</sup> ]	0.0410
Transfer Rate Constant, $k_{12}$ [min <sup>-1</sup> ]	0.185
Transfer Rate Constant, $k_{21}$ [min <sup>-1</sup> ]	0.103
Transfer Rate Constant, $k_{13}$ [min <sup>-1</sup> ]	0.141
Transfer Rate Constant, $k_{31}$ [min <sup>-1</sup> ]	0.0200

拡散係数, 分配係数, 皮膚表面濃度算出方法 (文献 8)

$$D_{sc} = 2.089 \times 10^{-3} \times \text{M.W.}^{-3.16} = 2.089 \times 10^{-3} \times 336.5^{-3.16} = 2.16 \times 10^{-11} \text{ cm}^2/\text{s}$$

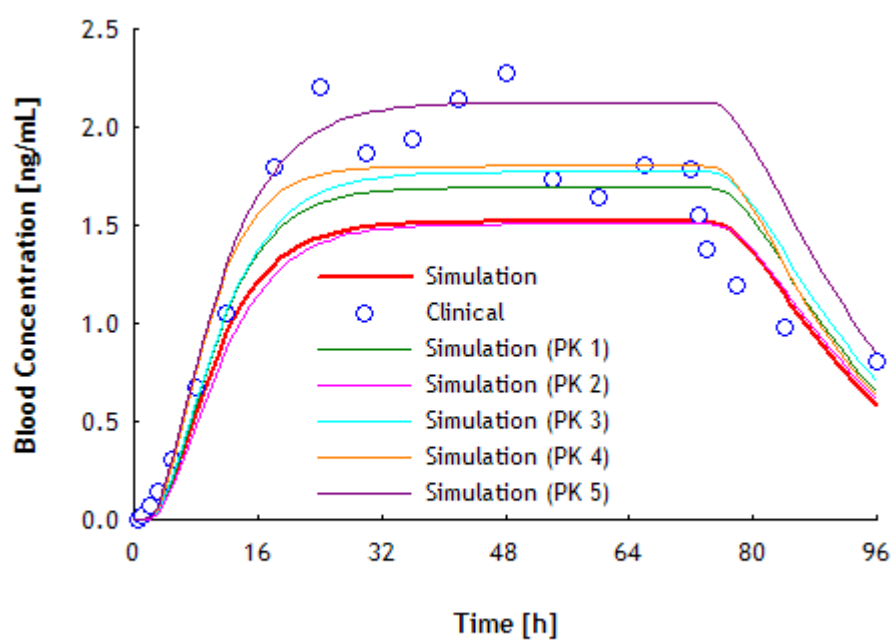
$$D_{vs} = 10000 D_{sc} \text{ と仮定}$$

$$K_{sc/vs} = 0.460 \times K_{o/w}^{0.480} = 0.460 \times 860^{0.480} = 11.8$$

$$J = 2.5 \text{ μg/cm}^2/\text{h} \rightarrow C_s = J \left\{ \frac{h}{D_{sc}} + \frac{(H-h)K_{sc/vs}}{D_{vs}} \right\}$$

No.	1	2	3	4	5	<i>mean</i>
$V_1$ [L]	39.4	39.5	17.1	25.7	12.8	26.8
$V_2$ [L]	90.4	63.7	27.0	33.4	32.7	48.2
$V_3$ [L]	111	217	208	209	159	189
$k_{10}$ [ $\text{min}^{-1}$ ]	0.0250	0.0280	0.0550	0.0360	0.0612	0.0410
$k_{12}$ [ $\text{min}^{-1}$ ]	0.188	0.187	0.204	0.139	0.207	0.185
$k_{21}$ [ $\text{min}^{-1}$ ]	0.0822	0.116	0.129	0.107	0.0810	0.103
$k_{13}$ [ $\text{min}^{-1}$ ]	0.0870	0.132	0.243	0.130	0.112	0.141
$k_{31}$ [ $\text{min}^{-1}$ ]	0.0310	0.0240	0.0200	0.0360	0.00900	0.0200

臨床値（文献 6）との比較



Blood concentration following 72-h application of fentanyl patch.

## 3. Fentanyl E-TRANS®

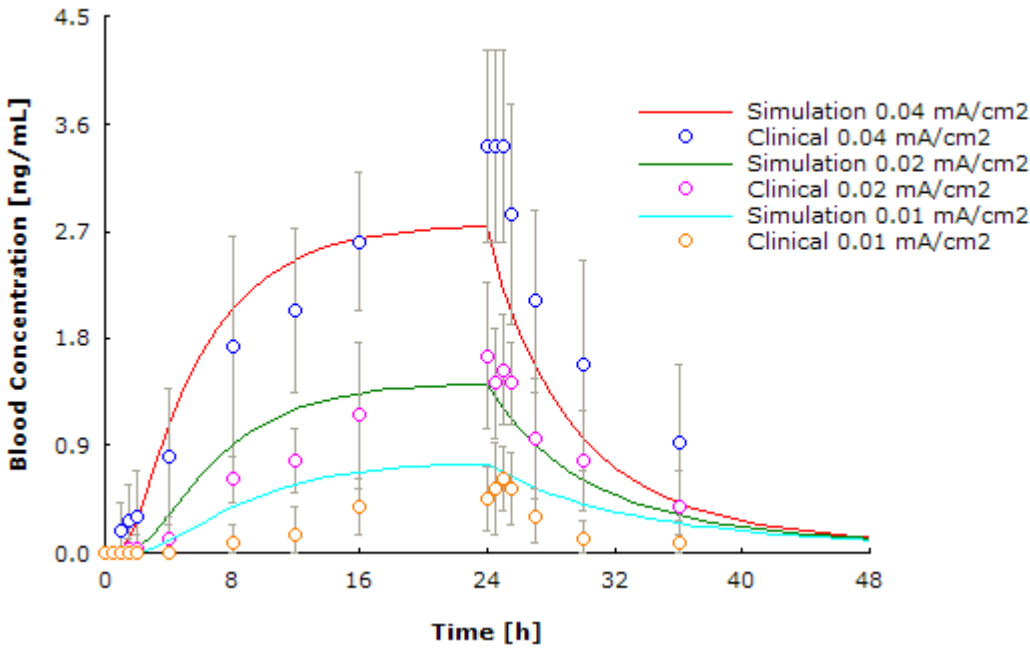
【血中濃度予測】【電流密度の影響】

Duration for Medication (Total Calculation Length) [h]	48
Duration of TTS Application [h]	24
TTS Size, $S_a$ [cm <sup>2</sup> ]	5
皮膚 2 層膜モデル	
Thickness of Stratum Corneum, $h$ [μm]	18.2 (文献 1)
Distance to Dermal Microcirculation, $H$ [μm]	200 (文献 2)
(物性値より拡散係数, 分配係数を決定)	
Molecular Weight	336.5 (文献 5)
Octanol/Water Partition Coefficient	860 (文献 5)
<i>In vitro</i> flux [μg/cm <sup>2</sup> /h]	2.5 (文献 6)
Diffusion Coefficient in Stratum Corneum, $D_{sc}$ [cm <sup>2</sup> /s]	$2.16 \times 10^{-11}$
Diffusion Coefficient in Viable Skin, $D_{vs}$ [cm <sup>2</sup> /s]	$2.16 \times 10^{-7}$
Stratum Corneum/Viable Skin Partition Coefficient, $K_{sc/vs}$ [-]	11.8
Skin Surface Concentration, $C_s$ [μg/mL]	$5.92 \times 10^4$
体内動態 : 3-コンパートメントモデル (文献 7)	
Volume of Distribution, $V_1$ [L]	26.8
Volume of Distribution, $V_2$ [L]	48.2
Volume of Distribution, $V_3$ [L]	189
Elimination Rate Constant, $k_{10}$ [min <sup>-1</sup> ]	0.0410
Transfer Rate Constant, $k_{12}$ [min <sup>-1</sup> ]	0.185
Transfer Rate Constant, $k_{21}$ [min <sup>-1</sup> ]	0.103
Transfer Rate Constant, $k_{13}$ [min <sup>-1</sup> ]	0.141
Transfer Rate Constant, $k_{31}$ [min <sup>-1</sup> ]	0.0200
イオントフォレシス適用条件パラメータ (文献 8, 文献 9)	
Duration of Iontophoretic Application, $t_a$ [h]	24
Periodic Cycle of Iontophoretic Application, $t_b$ [h]	24
Electric Potential, $E$ [V]	0.076
Drug Charge, $z$ [-]	1
Peclet Number of Convective Flow, $Pe$ [-] ( $Pe_{sc} = Pe_{vs}$ )	13.5

Current density [mA/cm <sup>2</sup> ]	<i>E</i> [V]	Linear velocity of convective flow <i>u</i> [cm/s]	<i>Pe</i> [-]*
0.04	0.076	1.60×10 <sup>-7</sup>	13.5
0.02	0.038	8.01×10 <sup>-8</sup>	6.75
0.01	0.019	4.01×10 <sup>-8</sup>	3.38

\*  $Pe = uh/D_{sc}$

臨床値（文献 9）との比較



#### 4. Drug Dissolved Matrix

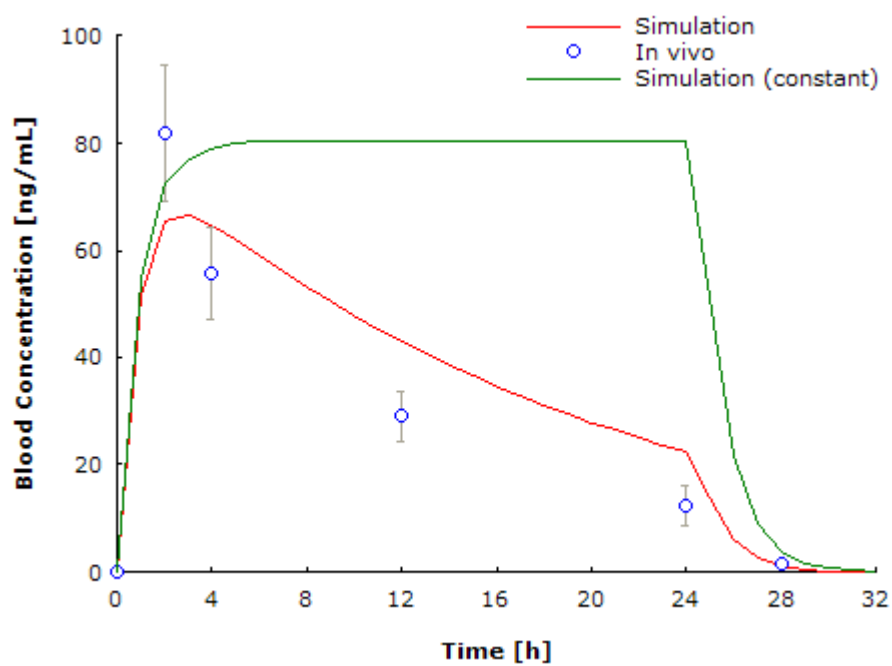
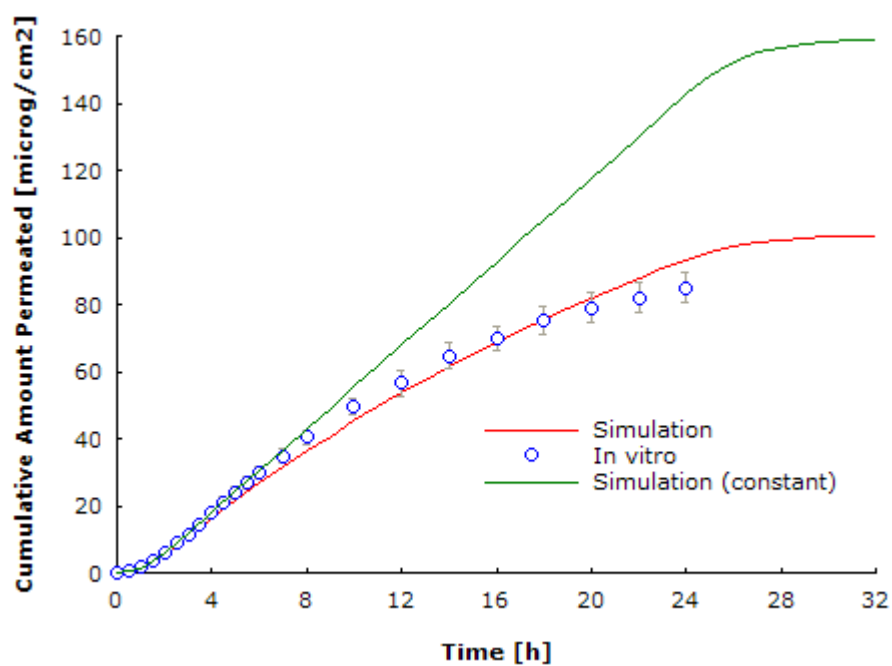
【GTS-21 製剤のヘアレスラット in vitro-in vivo 相関】（文献 10, 文献 11）

Duration for Medication (Total Calculation Length) [h]	32
Duration of TTS Application [h]	24
TTS Size, $S_a$ [cm <sup>2</sup> ]	10
製剤拡散モデル	
Thickness of Matrix, $L$ [μm]	60
Diffusion Coefficient in Matrix, $D_m$ [cm <sup>2</sup> /s]	$4.36 \times 10^{-7}$
Initial Drug Concentration in Matrix, $C_m^0$ [μg/mL]	$2.87 \times 10^4$
Matrix/Skin Partition Coefficient, $K_{m/s}$ [-] (= $C_m^0/C_s$ )	2.25
皮膚 2 層膜モデル	
Thickness of Stratum Corneum, $h$ [μm]	15
Thickness of Intact Skin, $H$ [μm] ( <i>in vitro</i> データ解析時)	354
Distance to Dermal Microcirculation, $H$ [μm] ( <i>in vivo</i> データ解析時)	47
( <i>In vitro</i> 皮膚透過データより拡散係数, 分配係数を決定)	
Steady-State Flux Across Intact Skin, $(dQ/dt)_w$ [μg/cm <sup>2</sup> /h]	6.18
Time Lag Across Intact Skin, $t_{dw}$ [h]	1.11
Steady-State Flux Across Stripped Skin, $(dQ/dt)_v$ [μg/cm <sup>2</sup> /h]	15.78
Time Lag Across Stripped Skin, $t_{dv}$ [h]	0.25
Diffusion Coefficient in Stratum Corneum, $D_{sc}$ [cm <sup>2</sup> /s]	$3.34 \times 10^{-10}$
Diffusion Coefficient in Viable Skin, $D_{vs}$ [cm <sup>2</sup> /s]	$2.13 \times 10^{-7}$
Stratum Corneum/Viable Skin Partition Coefficient, $K_{sc/vs}$ [-]	18.1
Skin Surface Concentration, $C_s$ [μg/mL]	$1.27 \times 10^4$
体内動態 2-コンパートメントモデル	
Volume of Distribution, $V_1$ [mL]	507.9
Volume of Distribution, $V_2$ [mL]	254.7
Elimination Rate Constant, $k_{10}$ [s <sup>-1</sup> ]	$6.55 \times 10^{-4}$
Transfer Rate Constant, $k_{12}$ [s <sup>-1</sup> ]	$1.60 \times 10^{-4}$
Transfer Rate Constant, $k_{21}$ [s <sup>-1</sup> ]	$3.19 \times 10^{-4}$



## 実験データ（文献 10）との比較

（製剤貼付時に薬物が枯渇していくと仮定した場合と薬物が一定供給されると仮定した場合）

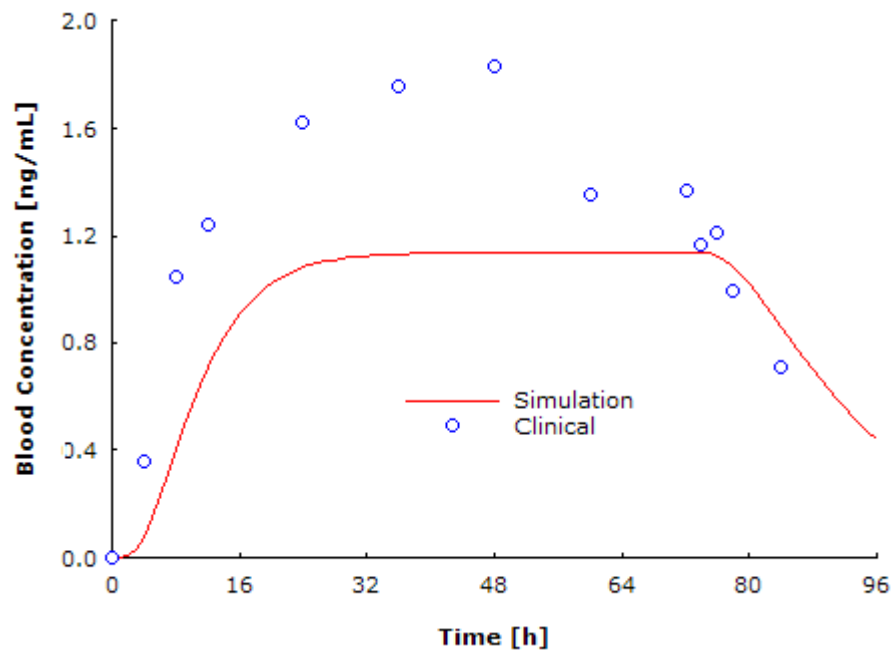


## 5. Fentanyl patch

【薬物動態（PK）-薬力学（PD）解析】

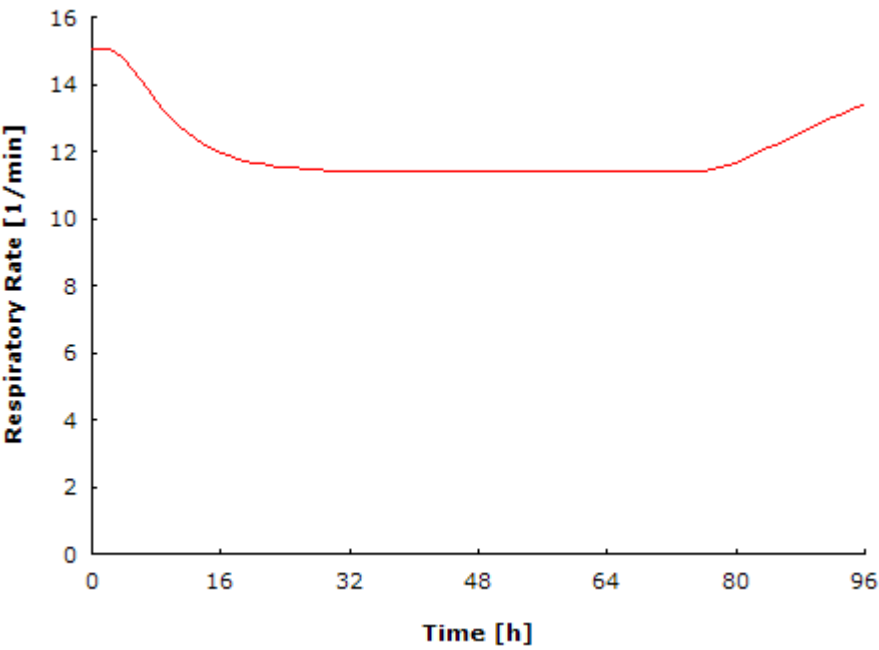
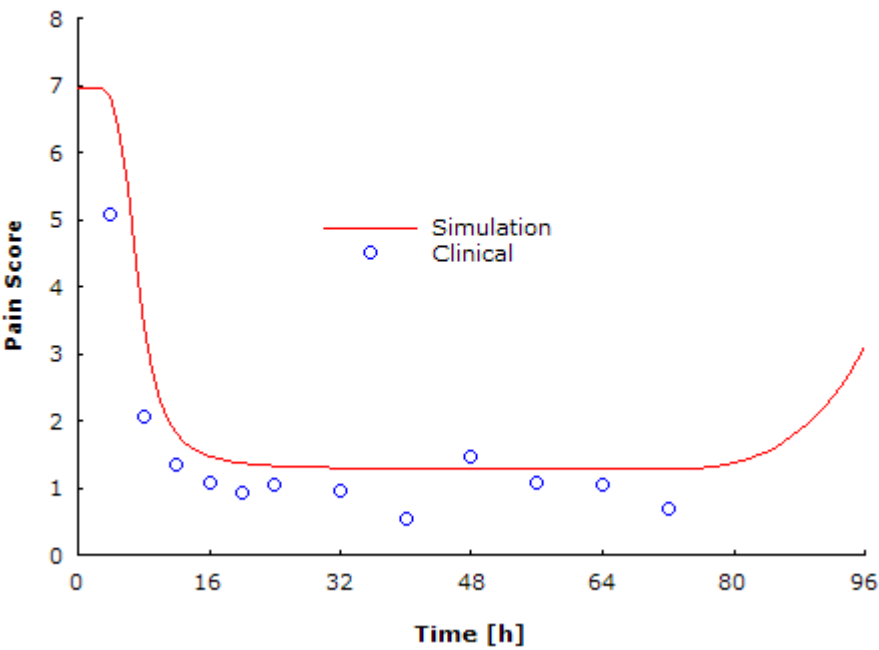
Duration for Medication (Total Calculation Length) [h]	96
Duration of TTS Application [h]	72
TTS Size, $S_a$ [cm <sup>2</sup> ]	30
皮膚 2 層膜モデル	
Thickness of Stratum Corneum, $h$ [μm]	18.2（文献 1）
Distance to Dermal Microcirculation, $H$ [μm]	200（文献 2）
（物性値より拡散係数，分配係数を決定）	
Molecular Weight	336.5（文献 5）
Octanol/Water Partition Coefficient	860（文献 5）
<i>In vitro</i> flux [μg/cm <sup>2</sup> /h]	2.5（文献 6）
Diffusion Coefficient in Stratum Corneum, $D_{sc}$ [cm <sup>2</sup> /s]	$2.16 \times 10^{-11}$
Diffusion Coefficient in Viable Skin, $D_{vs}$ [cm <sup>2</sup> /s]	$2.16 \times 10^{-7}$
Stratum Corneum/Viable Skin Partition Coefficient, $K_{sc/vs}$ [-]	11.8
Skin Surface Concentration, $C_s$ [μg/mL]	$5.92 \times 10^4$
体内動態 3-コンパートメントモデル（文献 7）	
Volume of Distribution, $V_1$ [L]	26.8
Volume of Distribution, $V_2$ [L]	48.2
Volume of Distribution, $V_3$ [L]	189
Elimination Rate Constant, $k_{10}$ [min <sup>-1</sup> ]	0.0410
Transfer Rate Constant, $k_{12}$ [min <sup>-1</sup> ]	0.185
Transfer Rate Constant, $k_{21}$ [min <sup>-1</sup> ]	0.103
Transfer Rate Constant, $k_{13}$ [min <sup>-1</sup> ]	0.141
Transfer Rate Constant, $k_{31}$ [min <sup>-1</sup> ]	0.0200

臨床値（文献 12）との比較



$E = E_0 - \frac{E_{\max} C_b^n}{EC_{50}^n + C_b^n}$	Pain score (文献 12)	Respiratory rate (文献 13)
Baseline, $E_0$	6.97	15.1 min <sup>-1</sup>
$E_{\max}$	5.93	15.1 min <sup>-1</sup>
$EC_{50}$ [μg/mL]	0.346	3.5
Sigmoidicity; Hill coefficient, $n$ [-]	2.62	1

臨床値（文献 12）との比較



臨床値：11 min<sup>-1</sup>（文献 14）

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前述の解析例以外で SKIN-CAD®解析結果を含む学術論文・学会発表・特許文書

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本資料につきまして、ご意見・ご質問等ございましたら下記までお問い合わせ下さい。



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株式会社バイオコム・システムズ

〒839-0864 福岡県久留米市百年公園 1 番 1 号

福岡バイオインキュベーションセンター201 号

TEL: 0942-27-6581, FAX: 0942-27-6582

E-mail: [skin-cad@biocom.co.jp](mailto:skin-cad@biocom.co.jp)

URL: <http://www.biocom.co.jp/>