Understanding dermal drug disposition using TCAT - a novel PBPK model

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What is PBPK?
It is a modeling technique not a single model

Wikipedia:
- PBPK modeling is mathematical *modeling technique* for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species.
- PBPK models *strive to be mechanistic* by mathematically transcribing anatomical, physiological, physical, and chemical descriptions of the phenomena involved in the complex ADME processes.

PBPK is:
- **PBPK is a modeling technique**
- **PBPK is striving to be mechanistic**
- **PBPK is attempting to separate physiology from drug related parameters**
- **PBPK is applicable to all routes of administration**
- **PBPK is increasingly accepted by regulatory**

PBPK is not:
- **PBPK is not a single model**
  Even though a Google image PBPK search reveal only variations of the same basic model
- **PBPK is not just for IV / oral**
  Detailed oral absorption models (e.g. ACAT/ADAM) coupled with simple compartmental PK are also PBPK models
- **PBPK is not just an alternative to allometry**
  PBPK can provide tissue concentration predictions, drug delivery predictions for various dosage routes and much more
- **PBPK is not just for small molecules**
The first documented application of PBPK by FDA was in 1990s for review and approval tretinoin topical cream interactions in humans [46]. Although employment of PBPK in academic pharmacology research was reported in the 70s [47], the first documented application by FDA was in the 1990s review and approval of the teratogenic topical ‘wrinkle cream’ active ingredient, tretinoin [48]. In consideration of the potential risk of fetal exposure and birth defects, FDA requested PBPK simulations to assess the risk of fetal exposure, from which FDA concluded that the risk is de minimus. To support approval for marketing, the FDA clinical pharmacology reviewer wrote in his official review: “The data obtained in the clinical studies, and those discussed in the nonclinical pharmacokinetic section [of this FDA review] were used to develop a physiologically based pharmacokinetic model. The model was used to estimate maternal and fetal plasma concentrations of tretinoin and its metabolites in a theoretical abuse situation, i.e. after excessive application to face, lower arms, chest and neck and assuming exaggerated absorption of 10%. This model demonstrated that the systemic concentrations of tretinoin and potentially toxic metabolites achieved under such conditions remained several orders of magnitude below endogenous concentration and minimally teratogenic dose of retinoic acid.” [49]

Is a simple skin absorption model sufficient?

Complex organ structure and complex formulation

Dose

Flux through skin

Dermis

Diffusion to systemic circulation

Systemic

Systemic clearance

Dermis

Epidermis

Dermis

Capillaries

Formulation

Receptor

Sweat gland
Site of action

- The TCAT™ model allows us to predict drug concentration in each skin sublayer.

Not all skin is the same

SC Thickness (µm)

VE Thickness (µm)

DE Thickness (µm)

Blood Flow Rate

mL/min/100g skin
In vitro testing - cumulative amount over 24 h

Dissolution, supersaturation and precipitation are very important events

Compound A:
- Expected behavior

Solution 1.0%
Solution 0.45%
Solution 0.045%

Compound B:
- Unexpectedly low penetration at high dose
- Precipitation at higher dose
- Dissolution, supersaturation and precipitation are very important events

Solution 2.2%
Solution 0.5%
Solution 0.05%
FDA Classification of Transdermal Formulations

Transdermal Formulations

SOLUTION
- clear & homogenous

LOTION
- Emulsion

SUSPENSION
- solid dispersed in a liquid

Liquid formulations

Semi-solid formulations

GEL
- Solution of colloidal dispersion with a gelling agent
- >50% water and volatiles

CREAM
- CREAM
- <20-50% dispersed solids
- AND
- <50% of solids are waxes, PEGs, HCs
- OR
- >20% water and volatiles

OINTMENT
- <20-50% dispersed solids
- >50% of solids are waxes, PEGs, HCs

PASTE
- >20-50% dispersed solids
- <20% water and volatiles
Formulations from a modeling perspective

- **SOLUTION**
  - CP: Liquid vehicle
  - DP: missing

- **LOTION**
  - CP: Liquid vehicle
  - DP: (oil) Droplet

- **SUSPENSION**
  - CP: Liquid vehicle
  - DP: Particle

- **GEL**
  - CP: Gel vehicle (slower diffusion)
  - DP: missing

- **CREAM**
  - CP: semisolid vehicle (slower diffusion)
  - DP: droplet

- **OINTMENT**
  - CP: semisolid vehicle (slower diffusion)
  - DP: droplet/particle

- **PASTE**
  - CP: semisolid vehicle (slower diffusion)
  - DP: particle
A “simple” solution formulation

Volatile Fast Evaporation (e.g. alcohol)

- Fast evaporation excipients disappear quickly (few min)
- They may leave a super saturated solution
- Huge concentration gradient can drive drug into skin but can also cause precipitation

Volatile Slower Evaporation (e.g. water)

- Water would evaporate in about 15 min – (perhaps longer in a gel formulation)
- There will be a residual level of non-volatile oils that would eventually be absorbed in the skin

Non-volatile (e.g. oils)

These stages are modeled explicitly
A likely concentration profile in vehicle

- **Fast evaporation excipient is completely gone**
- **Drug concentration in formulation**
- **Drug solubility in slow evaporating excipient**
- **Drug solubility in non volatile excipient**

**For many drugs the absorption window can be quite small (e.g. 15min)**

- **No re-dissolution of precipitated drug**
- **Precipitation brings concentration back close to solubility in non-volatile excipient**
- **Huge concentration increase as the slow evaporating excipient is almost vanished.**

**Concentration in Vehicle**

**time**
Transdermal Drug Disposition: Key processes

Vehicle

Absorption

Release/Dissolution

Evaporation

Precipitation/Redissolution

Partitioning Binding

Stratum corneum

Binding

Metabolism

Viable epidermis

Binding

Systemic Uptake

Dermis

Thanks to Siladitya Ray Chaudhuri and Simulations Plus
Modeling dermal formulations

- **Surface area of skin**
- **Surface area of follicles**
- **Surface area of hair**

**Drug and vCP absorption into SC**

**Drug, vCP, and vDP diffusion and partitioning**

**Drug absorption**

**Dermis**

**Viable epidermis**

**Stratum Corneum**

**Coalesce of disperse phase**

**Evaporation**

**Release**

**Disperse phase (DP)**

**Continuous phase (CP)**

**Film phase (FP)**

**Rest of skin**

**Systemic**

**Hair lipid outside**

**Hair core outside**

**Hair lipid**

**Hair core**

**Sebum**
Drug Dependent Input Parameters in SC

**Diffusion and partition**

**Potts-Guy**

\[ D^{SC} = 10^{0.5 \log(0.05) - 6.3 - 0.006 \text{MW}} \]

\[ K^{SC/w} = 10^{0.7 \log P} \]

**Robinson**

\[ \frac{1}{P^{SC} (\text{cm/h})} = \frac{1}{P^{lip} + P^{pol}} = 10^{(-1.326 + 0.6097 \log P - 0.1786 \text{MW}^{0.5})} + 0.0001519 \times \text{MW}^{-0.5} \]

\[ K^{SC/w} = 1 \]

\[ D^{SC} = \frac{P^{SC} h_{SC}}{K^{SC/w}} \]

---

**Table 4. Summary of Model Equations for Partially Hydrated SC**

<table>
<thead>
<tr>
<th>Lipid-phase properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula for ( D_{lip} ) is the same as in Table 3</td>
</tr>
<tr>
<td>( D_{lip} = (1.24 \times 10^{-7} \text{cm}^2/\text{s}) (100 \text{MW})^{0.42} + (2.34 \times 10^{-9} \text{cm}^2/\text{s})/H_{int} )</td>
</tr>
<tr>
<td>Model 1: ( \log_{10} (K_{trans}^{lip}/\text{cm/s}) = \frac{-0.970 - 0.840 \text{MW}^{0.3}}{\log_{10} H_{trans}} )</td>
</tr>
<tr>
<td>Model 2: ( \log_{10} (K_{trans}^{lip}/\text{cm/s}) = \frac{-0.725 - 0.792 \text{MW}^{0.3}}{\log_{10} H_{trans}} )</td>
</tr>
</tbody>
</table>

**Nominal values (to be revised by future study):** \( H_{int} = 3, H_{trans} = 3 \)

**Corneocyte-phase properties**

\[ (K_{cor/w})_{free} = 1 - \psi_f \]

\[ \psi_f = (0.6044)(1 + \lambda)^2 \]

\[ (D_{cor})_{free} = D_{eq}(1 - \psi_f)(1.0001 - 2.4497 \lambda + 1.141 \lambda^2 + 0.5432 \lambda^3) \]

Formulas for \( \lambda, \alpha_w \), and \( D_{eq} \) are the same as in Table 3

**Dimensionless groups**

\[ R = H_{trans}/(0.14196 \text{cm}^{-1}) \times D_{lip} \]

**Formula for \( R \) is the same as in Table 3**

**Model 1:** \( (P_{SC/w})^{comp} = 1/(0.8979 \sigma + 5.536 \times 10^5 /R) + 2.935 \times 10^{-4} \)

**Model 2:** \( (P_{SC/w})^{comp} = 1/(0.8979 \sigma + 5.536 \times 10^5 /R) \) for \( R > 100 \)

**Model 1:** \( (P_{SC/w})^{comp} \) for \( R < 100 \) should be computed from Eq. (6) with coefficients listed in 6th column of Table 1, or Fortran code (available upon request)

**Dimensional SC permeability**

\[ (P_{SC/w})^{comp} = (P_{SC/w})^{comp}D_{lip}K_{lip/w}/(0.0013365 \text{cm}) \] or, equivalently,

\[ Model 1: \frac{(P_{SC/w})^{comp}}{1/(105/(K_{trans}K_{lip/w}) + (0.0012/cm)/[(D_{cor})_{free}(K_{cor/w})_{free}]) + (D_{lip}K_{lip/w})/(4.553 \text{cm})} \]

**Model 2:** \( (P_{SC/w})^{comp} = 1/(105/(K_{trans}K_{lip/w}) + (0.0012/cm)/[(D_{cor})_{free}(K_{cor/w})_{free}]) \) for \( R > 100 \)

**Effective (average) SC partition coefficient**

\[ K_{SC/w} = 0.040 (K_{lip/w})^{0.81} + 0.359 + 4.057 (K_{cor/w})^{0.97} \]

**Effective (average) SC diffusion coefficient**

\[ D_{SC} = (P_{SC/w})^{comp}/(0.0013365 \text{cm}) \]

---

Drug Dependent Parameters in Epidermis and Dermis

Diffusion and partition

**Sebum**

Valiveti

\[
\log K_{SBM/w} = 0.4894 \log P + 1.3329
\]

\[
\log P^{SBM} (\mu m / s) = 0.7856 \log P - 0.0047 MW + 0.28
\]

\[
D^{SBM} = \frac{0.008 P^{SBM}}{K_{SBM/w}}
\]

**Viable epidermis and Dermis**

**Kretsos**

\[
K^{VE/SC} = \frac{K^{VE/w}}{K^{SC/w}}
\]

\[
\log D^{VE} (cm^2 / s) = -4.15 - 0.655 \log MW
\]

\[
K^{VE/w} = \frac{\phi_{aq}}{f_{non}}; \phi_{aq} = 0.7
\]

**Bunge-Cleek**

\[
\log D^{VE} (cm^2 / s) = -5.15 - 0.5 \log MW
\]

\[
K^{VE/w} = 1
\]

**Robinson**

\[
K^{VE/w} = 1
\]

\[
\log P^{VE} (cm / s) = -3.16 - 0.5 \log MW
\]

\[
D^{VE} = \frac{P^{VE} h_{VE}}{K^{VE/SC}}
\]
Systemic absorption rate in Dermis

**Diffusion and partition**

**First order**

\[ \text{SysRate}_j = k_j^{\text{sys}} \times (C_{j,\text{DE}} - C_{\text{free}}^{\text{sys}}) \]

**IBRAHIM**

\[
\frac{1}{k_j^{\text{sys}}} = \frac{C_u^{\text{sys}}}{\text{VolRate}} + \frac{1}{\bar{Q}}
\]

- \( J_{Vs} = \alpha_s L_{cp}^{\text{tot}} S (\Delta P - \sigma_s \Delta \pi) \)
- \( J_{VL} = \alpha_L L_{cp}^{\text{tot}} S (\Delta P - \sigma_L \Delta \pi) \)
- \( P_{e_s} = \frac{J_{Vs} (1 - \sigma_s)}{P_{\text{slit-s}} \times S} \)
- \( P_{e_L} = \frac{J_{VL} (1 - \sigma_L)}{P_{\text{slit-L}} \times S} \)
- \( \alpha_s = 1 - \alpha_L \)
- \( \alpha_L = n_L \left( \frac{W_L}{W_s} \right)^3 = \frac{A_L}{A_s} \left( \frac{W_L}{W_s} \right)^2 \)
- \( P_{\text{slit}} = f \cdot W_L \times D_{\text{slit}} \times \frac{\Phi_i}{\Delta x} \)
- \( D_{\text{slit}} = D_w \times \left( 1 + \frac{9}{16} \lambda_i \ln \lambda_i - 1.19358 \lambda_i + 0.4285 \lambda_i^2 ight. \)
- \( -0.3192 \lambda_i^4 + 0.08428 \lambda_i^5 \)
- \( \lambda_i = \frac{r_{\text{sys}}}{W_i/2} \)

Permeability and Diffusion in Stratum Corneum

As a function of MW

- Wang-Kasting-Nitsche model 1 for partially hydrated skin
- Wang-Kasting-Nitsche model 2 for partially hydrated skin
- Potts&Guy
- Wang-Kasting-Nitsche model 1 for fully hydrated skin
- Wang-Kasting-Nitsche model 2 for fully hydrated skin

**Permeability cm/sec (logP=2.0)***

**Diff Coeff cm²/sec (logP=2.0)***

- minutes
- hours
- days
Permeability and Diffusion in Stratum Corneum

As a function of $K_{OW}$

- **Wang-Kasting-Nitsche model 1 for partially hydrated skin**
- **Wang-Kasting-Nitsche model 2 for partially hydrated skin**
- **Potts&Guy**

**MW=250, Perm cm/sec**

**MW=250, Diff Coeff cm²/sec**

- minutes
- hours
- days

**MW=250, KP**

- hours
Partition - skin capacity to absorb drug
Assuming no metabolism, no excipient effects, no protein/melanin binding

- Most drugs can partition into sebum (SB) however sebum volume is low
- For small logP Dermis would have the capacity to hold most drug
- Extremely lipophilic compounds would partition preferentially in SC
- Sebum partitioning is most significant for compounds with logP around 5
Permeability in various skin layers

Assuming no metabolism, no excipient effects, no protein/melanin binding

- Stratum corneum is the key diffusion barrier for most compounds (not surprising)
- For most compounds of interest Sebum permeability is quite high
- Metabolism, binding and systemic uptake can make the dermis a more significant barrier
Three dimensional finite element skin model

Attempting to model the 3D skin complex structure

thanks Sumeet Thete
Sample simulation

3D finite element model (2D axial symmetry)

$MW = 250, \ logP = 5, \ no \ vehicle \ partitioning, \ high \ systemic \ absorption$
LogP effect

MW = 250, no vehicle partitioning, high systemic absorption

**LogP = 5**

Less lipophylic

**LogP = 2**

**LogP = 8**

More lipophylic
Making the PBPK dermal model available
Additional Dosage Routes Modules in GastroPlus

- Oral absorption - ACAT model

Input parameters
PBPK model
Output

Additional Dosage Routes Modules
- Transdermal
- Pulmonary
- Ocular
In-vitro to Human - Model Based Translation

**Principle**

**Scaling Approach**

Which factors to use?  
Is it predictive?  
Does it translate?

- In-vitro to in-vivo scaling factors
- PBPK model
- Human tissue PK predictions
- Human Physiology
- Trial Protocol

Predictions not accurate?  
Change the in-vitro conditions to be more relevant to the in-vivo situation

**Model Based Translation**

- In-vitro data
- In-vitro Protocol
- In-vitro "Physiology"

Use same PBPK model for both in-vitro and in-vivo
Using more fundamental drug parameters (e.g. diffusion, lipid bilayer permeability)

- Human Physiology
- Trial Protocol
- Human tissue PK predictions

Change model to capture more biological processes and use more fundamental drug parameters
“In–vitro” physiology
Using PBPK model to simulate in-vitro skin penetration

TCAT model
- Select “Human Abdomen” skin physiology
- Adjust Dermis thickness to match skin sample thickness (~450 microns)
- Remove sebum (set sebum partition to zero)
- Set high systemic absorption rate

“PK” parameters
- Match central compartment to receptor chamber
- No clearance (all compound accumulates in receptor fluid)

Instead of using in-vitro flux in PBPK

Validate diffusion and partition parameters using in-vitro data and use them in PBPK
Excipient effects

Vehicle
- Release/Dissolution
- Evaporation
- Precipitation/Redissolution
- Absorption
- Diffusion

Stratum corneum
- Shed/Rub/Wash off
- Partitioning
- Modified partitioning
- Penetration enhancement
- Metabolism
- Binding

Viable epidermis
- Absorption
- Diffusion
- Metabolism
- Binding

Dermis
- Systemic Uptake

DRUG

Excipients

Systemic Uptake
Penetration of co-solvent with drug in the tissue

Slower penetration of drug compared to solvent

Figure 3. Imaging the penetration of deuterated PG (upper panel) and ketoprofen (lower panel) across the stratum corneum. Images acquired at the depths indicated down the left-hand side of the figure and times indicated along the top show the penetration of cosolvent and drug into the tissue using SRS contrast at 2120 cm$^{-1}$ and 1599 cm$^{-1}$, respectively. Scale bar = 50 μm.

Figure 4. Integrated depth-profiling analysis of percutaneous penetration. (A) Depth profiles of deuterated PG as a function of time. (B) Comparison of the areas under the normalized SRS signal versus skin depth profiles (AUCs) of PG and ketoprofen at different times (26 and 104 min, and 34 and 134 min, respectively) postapplication of the formulation (left-hand y-axis). The ratios of the AUCs (right-hand y-axis) determined after the first and last measurements (at approximately 0.5 and 2 h) demonstrate the slower penetration rate of the drug compared to that of the cosolvent.

Topical Formulation Components

How can we represent this in the model?
Novel Skin PBPK model in Action: Clindamycin Modeling

Anu Shilpa Krishnatry
Clindamycin is a lincosamide antibiotic.

- It is usually used to treat infections with anaerobic bacteria.
- It is a common topical treatment for acne.
- Typical IV administration seems to be as clindamycin phosphate - phosphate is quickly converted to clindamycin in the plasma.

Available Clinical Data

- IV infusion: 600mg of clindamycin phosphate over 25 min
- PO capsule: 600mg of clindamycin hydrochloride (with 170 mL of water)
- Healthy males, average age 27 years, average body weight 73 kg

- 600mg of clindamycin phosphate infused over 30 min every 6 h
- 1200mg of clindamycin phosphate was infused over 1h every 12h
- Healthy males, average age 29 years, average body weight 73 kg

- **Dalacin T solution**: 5 mg single application
- **Duac Gel**: 10 mg single application
- **Clindagel**: 40 mg QD repeat application
- **Evoclin foam**: 40 mg QD repeat application

Test if TCAT model can predict exposure differences with different formulations
What All information needed for the TCAT model?
What All information needed to build a TCAT model?

- **Compound details**
  - Log P, pKa
  - Solubility at various pH, biorelevant media, solvent
  - Permeability
  - Protein binding and skin tissue binding
  - Blood cell association
  - Clearance

- **Formulation details**
  - Type (Solution, suspension, gel, ointment..)
  - Volatile components
  - Volume
  - Dose

- **Study Details**
  - Dosing region (face, arms, scalp, back, abdomen, legs)
  - Application surface area
  - Skin covered/not
  - Any Washing step performed
  - Any in vitro flux data
Building Clindamycin TCAT model

• Compound details
  • Log P, pKa
  • Solubility at various pH, biorelevant media, solvent
  • Permeability
  • Protein binding and skin tissue binding
  • Blood cell association
  • Clearance

Predicted / Experimental values were used for model building.
Systemic disposition was calibrated against plasma concentration-time profiles after intravenous administration from literature

• Formulation details
  • Type (Solution, suspension, gel, ointment..)
  • Volatile components, solvent evaporation rate
  • Volume
  • Dose
  • API solubility in Formulation

• Study Details
  • Dosing region (face, arms, scalp, back, abdomen, legs)
  • Application surface area and Time
  • Skin covered/not
  • Any Washing step performed
  • Any in vitro flux data
Building Clindamycin TCAT model

- Diffusivity and partition coefficients calculations:
  - In **Stratum Corneum** using Wang-Kasting Nitsche equation
  - In **Viable epidermis** using Krestos equation
  - In **Sebum** calculated according to the equation derived from Valiveti et al., data

- Sublayers (10, Uniform Grid)

Building Clindamycin TCAT model

- Optimized only 2 parameters after accounting for all compound, formulation and study specific details: Vehicle /Water partition coefficient and systemic uptake rate
Published Human data available

- IV infusion: 600mg of clindamycin phosphate over 25 min
- PO capsule: 600mg of clindamycin hydrochloride (with 170 mL of water)
- Healthy males, average age 27 years, average body weight 73 kg

- 600mg of clindamycin phosphate infused over 30 min every 6 h
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- Healthy males, average age 29 years, average body weight 73 kg

Data Captured using Digit It (Simulations Plus)
Building Clindamycin TCAT model
PK Characterization using Literature Data

Compartmental PK model fitted to match observed plasma concentration vs. time profile after 600 mg IV infusion for 25 mins of Clindamycin phosphate as in Gatti et al., 600 mg and 1200mg repeat IV infusions from Plaisance et al.

- Gatti 600 mg IV infusion - Plasma Concentration
- Plaisance 600 mg IV infusion - Plasma Concentration
- Plaisance 1200 mg IV infusion - Plasma Concentration

Simulating Systemic Exposures from Different Formulations

- In all cases, clindamycin phosphate is dosed and clindamycin is measured

- Single dose administration
  - Duac gel
  - Dalacin T solution

- Multiple dose administrations
  - Evoclin foam
  - Clindagel
Simulating Systemic Exposures from Different Formulations

Simulated Plasma concentration vs. time profile (solid line) and observed plasma concentrations (open squares with CV% as the bars, N=12)
Understanding exposures in various skin compartments
Simulating exposures in various skin compartments

Simulated concentration of Clindamycin in various skin compartments (VH: Vehicle, SC: Stratum Corneum; VE: Viable Epidermis and DE: Dermis) at 0, 1, 4, 8, and 24 hours following application of Dalacin T Solution.

Dissolved concentration of Clindamycin in dermis from different formulations of Clindamycin.

Dissolved concentration of Clindamycin in Sebum from different formulations of Clindamycin.
Clindamycin gets into sebum?

As early as 1 hour after application of CT Gel, clindamycin phosphate was diffusely distributed throughout the dermis with a clear accumulation of drug in and around the hair follicles, and some accumulation around the sebaceous glands.

4 hours after application of CT Gel, significantly more clindamycin phosphate was distributed diffusely throughout the dermis with a clear accumulation near hair follicles, and sebaceous glands.

Micro-autoradiographs of H³-Clindamycin in mouse skin after 1 hour (left) or 4 hours (right) of administration. Silver grains identify location of radioactive drug in skin

Jon Lenn, Stiefel
Poster at 2010 American Academy of Dermatology
### TABLE 1

**Serum, Tissue, and Fluid Antibiotic Levels of Subjects Receiving Various Doses of Clindamycin**

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>No. with positive values</th>
<th>Average serum value (micrograms/ml)</th>
<th>Average tissue value (micrograms/ml or mg)</th>
<th>Range (micrograms/ml)</th>
<th>Clindamycin regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper Respiratory Tract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonsils</td>
<td>9</td>
<td>2.4</td>
<td>5.1</td>
<td>0.9–12.7</td>
<td>75 mg q.i.d. for 7 doses</td>
<td></td>
</tr>
<tr>
<td>Adenoids</td>
<td>6</td>
<td>2.7</td>
<td>6.8</td>
<td>1.3–15.1</td>
<td>75 mg q.i.d. for 7 doses</td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td>12</td>
<td>3.5</td>
<td>0.43</td>
<td>0.25–0.92</td>
<td>150 mg q.i.d. for 7 doses</td>
<td></td>
</tr>
</tbody>
</table>

| **Lower Respiratory Tract** | | | | | |
| Bronchus              | 3               | 3                        | 13.3                                | 1.4                                        | 0.7–2.5               | 150 mg q.i.d. for 12 doses |
| Lung                  | 8               | 8                        | 10.1                                | 5.0                                        | 1.5–7.2               | 150 mg q.i.d. for 15 doses |
| Pleura                | 7               | 7                        | 12.2                                | 1.4                                        | 0.4–3.9               | 150 mg q.i.d. for 16 doses |
| Pleural fluid         | 3               | 3                        | 10.1                                | 9.3                                        | 1.3–22.1              | 150 mg q.i.d. for 14 doses |

| **Soft Tissue** | | | | | |
| Muscle             | 10              | 4                        | 2.9                                 | 0.7                                        | 0.3–1.07              | 150 mg q.i.d. for 12 doses |
| Sweat              | 9               | 9                        | 2.9                                 | 4.9                                        | 2.4–8.8               | 150 mg q.i.d. for 12 doses |
| **Sebum**          | 10              | 5                        | 2.9                                 | 45.0                                       | 8.8–124.3             | 150 mg q.i.d. for 12 doses |
| Pus                 | 1               | 1                        | 2.7                                 | 0.8                                        |                       | 150 mg q.i.d. for 9 doses |

| **Bone and Joint** | | | | | |
| Bone (hip)          | 7               | 4                        | —                                   | 0.62                                       | 0.32–1.11             | 150 mg q.i.d. for 8 doses |
| Synovial membrane   | 5               | 3                        | 3.6                                 | 5.0                                        | 1.5–10.0              | 150 mg q.i.d. for 5 doses |
| Synovial fluid      | 5               | 4                        | 3.2                                 | 2.2                                        | 0.7–3.7               | 150 mg q.i.d. for 5 doses |

| **Other** | | | | | |
| Semen           | 10              | 10                       | 2.9                                 | 2.6                                        | 0.7–7.2               | 150 mg q.i.d. for 12 doses |
| Prostate        | 5               | 5                        | 1.6                                 | 1.7                                        | 0.6–3.9               | 150 mg q.i.d. for 5 doses |
| White blood cells | 9               | 0                        | —                                   | —                                          |                       | 300 mg single dose       |

Clindamycin levels in various body tissues and fluids, Journal of Clinical Pharmacology, July 1972
Novel Skin PBPK Model in Action: Clindamycin and Tazarotene Modeling

INTRODUCTION

- Novel skin PBPK model
- Action on skin
- PBPK model
- Tazarotene modeling
- Antimicrobial
- Tazarotene

METHODS

- Novel skin PBPK model
- Tazarotene
- PBPK model
- Tazarotene

RESULTS

- Novel skin PBPK model
- Action on skin
- PBPK model
- Tazarotene

CONCLUSIONS

- Novel skin PBPK model
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REFERENCES
Conclusions

• Clindamycin model was able to appropriately characterize exposure differences with different formulations including a solution, gels, and foam.

• The TCAT model within GastroPlus is a novel model that will enable scientists to simulate the exposures from different topical formulations.

• Its applications span from candidate compound and formulation decisions to maximizing the potential for the right amount of drug to be delivered to the target tissues in the body.
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