Formulations in Flux: Simulating the Effect of Dynamic Formulation Composition Changes Following Application of Complex Topical Drug Products

AAPS Topical and Transdermal Community Webinar

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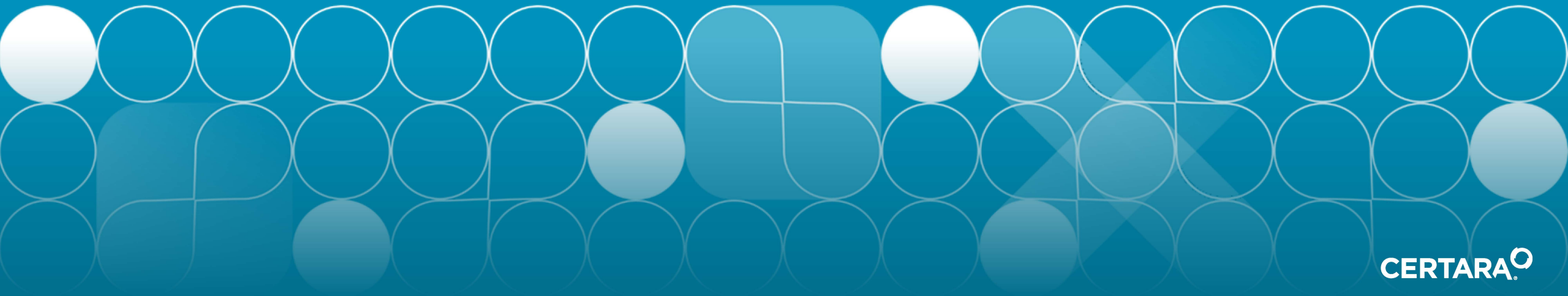
Certara Predictive Technologies

25TH JULY 2025

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD007954 totaling $750,000 with 100 percent funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.



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Contents

Aim: Demonstrate the process of building a robust formulation model

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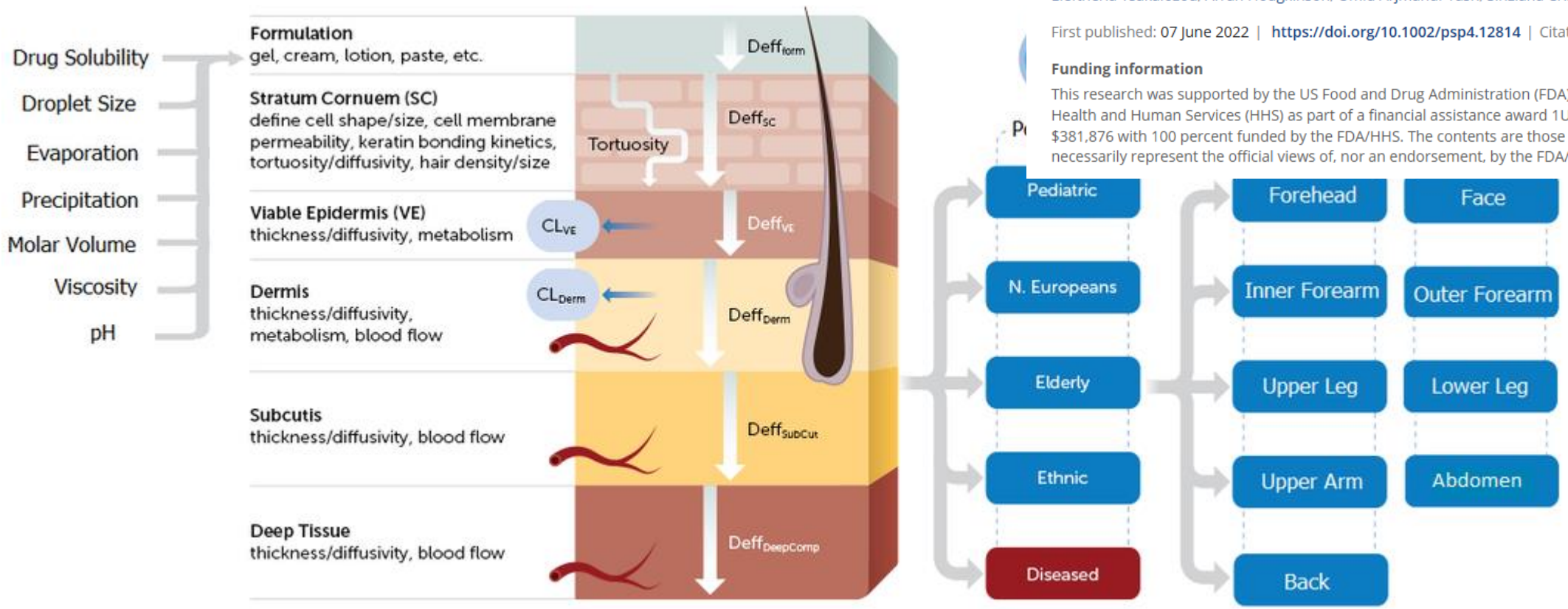
Dermal PBPK Modelling – MPML MechDermA

- A mechanistic dermal absorption model that simulates drug diffusion
- Implemented in the Simcyp Simulator.

- Utilises a Graphical User Interface to make modelling accessible to nc



CPT: Pharmacometrics & Systems Pharmacology

ARTICLE | Open Access

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDermA) model to predict local and systemic exposure of drug products applied on skin

Nikunjkumar Patel, James F. Clarke, Farzaneh Salem, Tariq Abdulla, Frederico Martins, Sumit Arora, Eleftheria Tsakalozou, Arran Hodgkinson, Omid Arjmandi-Tash, Sinziana Cristea ... See all authors

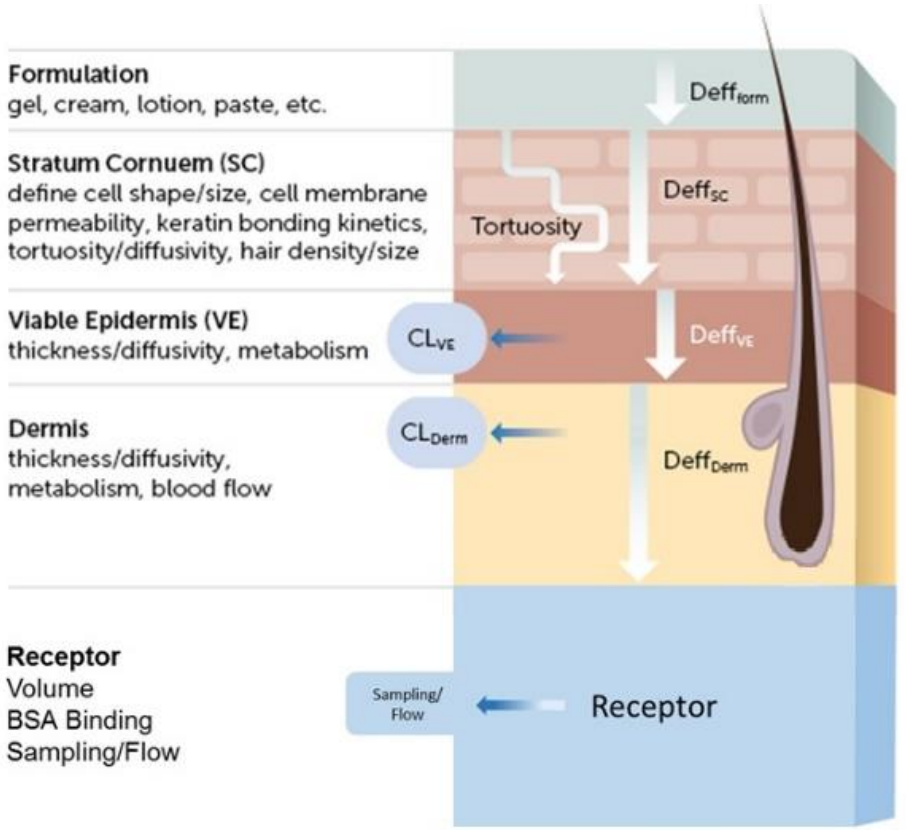
First published: 07 June 2022 | https://doi.org/10.1002/psp4.12814 | Citations: 8

Funding information

This research was supported by the US Food and Drug Administration (FDA) of the US Department of Health and Human Services (HHS) as part of a financial assistance award 1U01FD006521 totaling $381,876 with 100 percent funded by the FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by the FDA/HHS, or the US Government

IVPT Modelling

- The IVPT model is identical to the in vivo model in terms of physiology.
- The blood flow and deeper layers are removed and replaced with receptor solution
- The model can account for different cell setups such as:
  - *Isolated Epidermis, Dermatome, Full Thickness*
  - *Flow Through or Static Cells*
  - *Sampling procedure and/or Flow Rate*
  - *The effect of LLOQ*
  - *Receptor Solubility*



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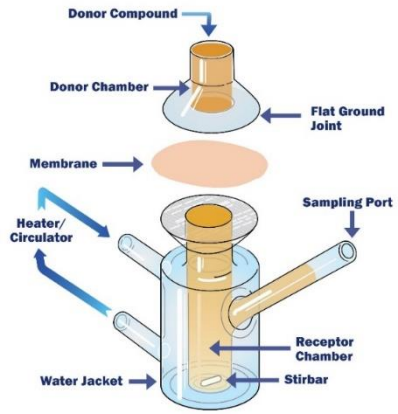
Dermal *In Vitro* - *In Vivo* Extrapolation (IVIVE) with MPML MechDermA

Input



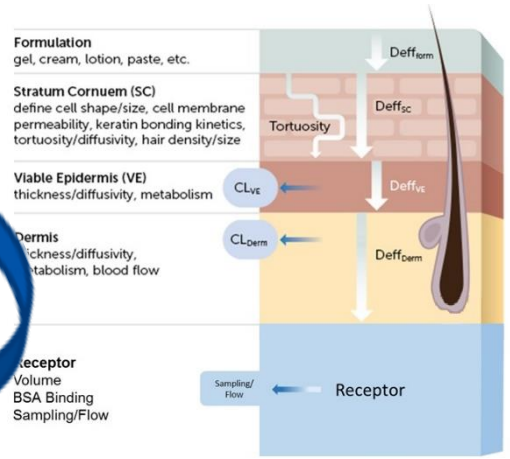
***In vitro* Release/Permeation Studies**

Confirm & Learn Approach

Understanding Q1, Q2 and Q3 properties of topical products

- Composition
- Drug Solubility in various phases
- Drying Rate (evaporation – weight loss)
- Specific gravity
- Particle size (solid particles/droplets)
- Rheology
- Precipitation characterization
- Excipients penetration

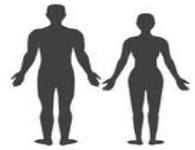
Validate



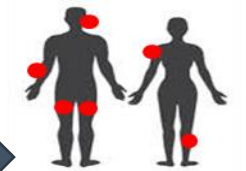
Mechanistic Dermal Absorption Model

- Confirm key drug/formulation parameters: partition and diffusion coefficients
- Verify model performance with challenge formulations (different strengths, non-Q1, Q2, Q3 formulation)

Extrapolate



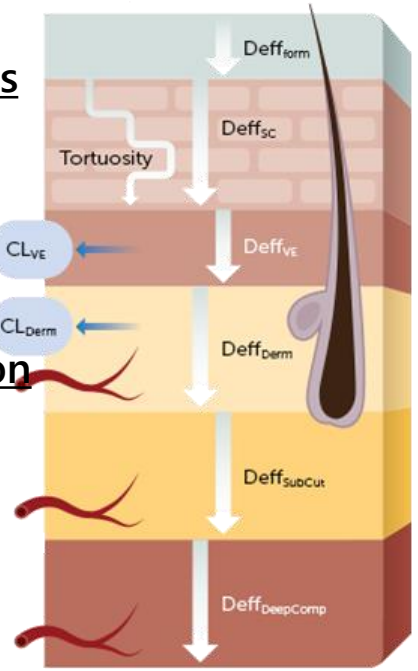
Healthy Volunteers



Diseased Population

Elderly Subjects

Paediatric Population



Q1 – Qualitative Sameness Q2 – Quantitative Sameness Q3 – Microstructure sameness

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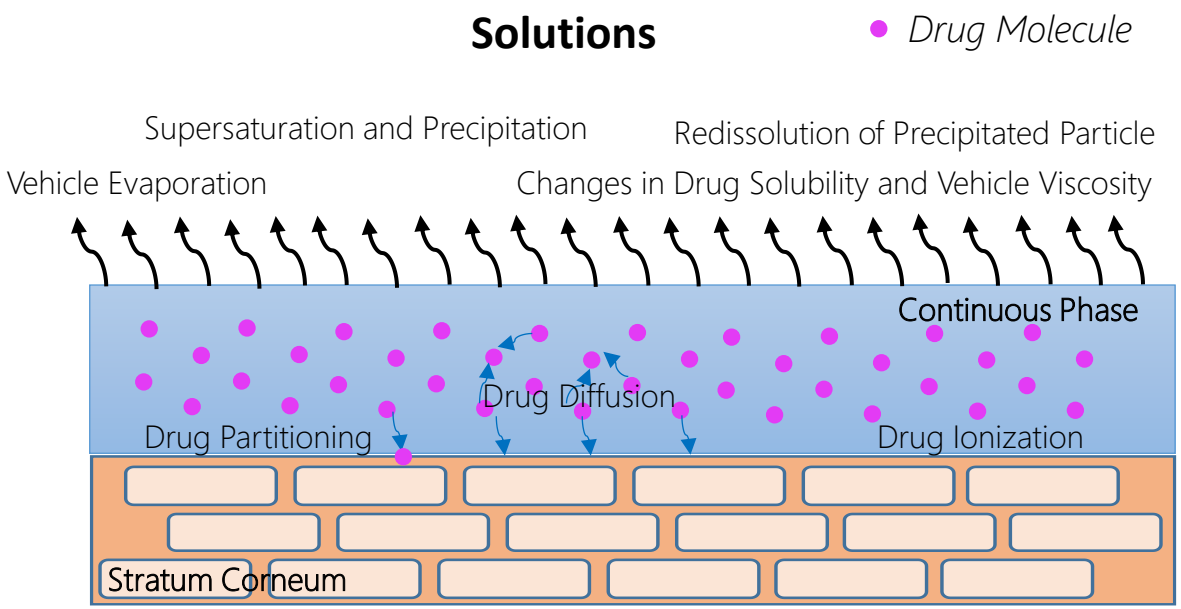
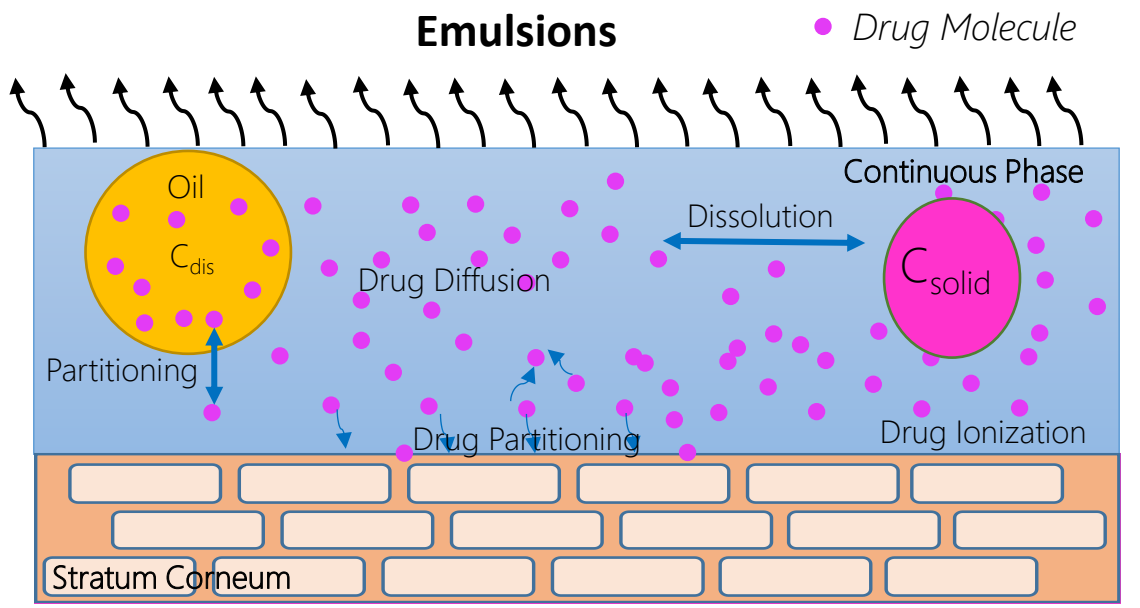
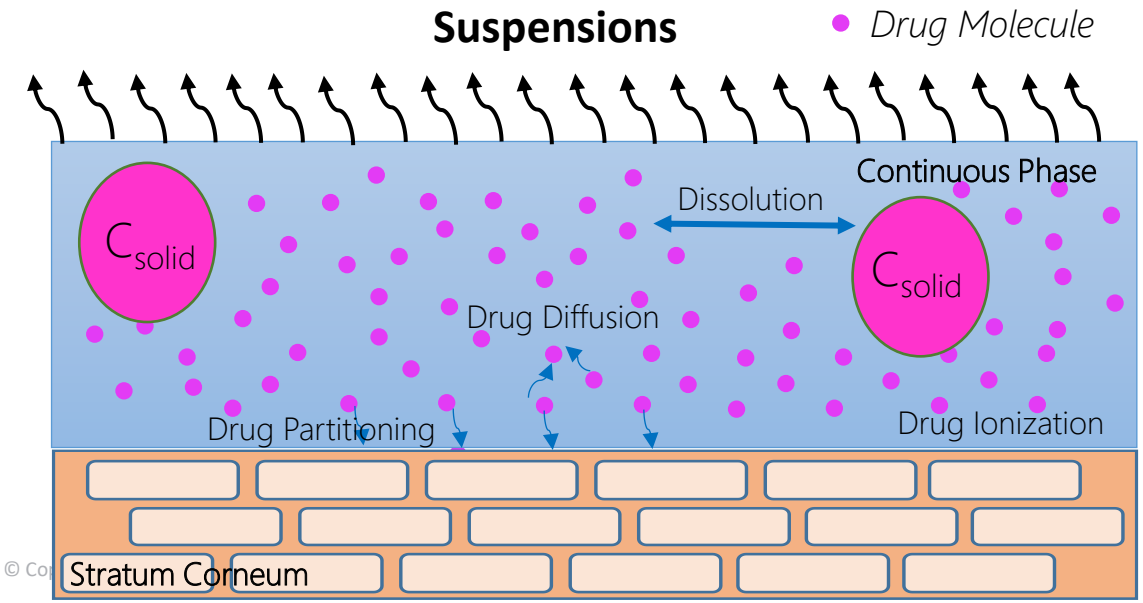
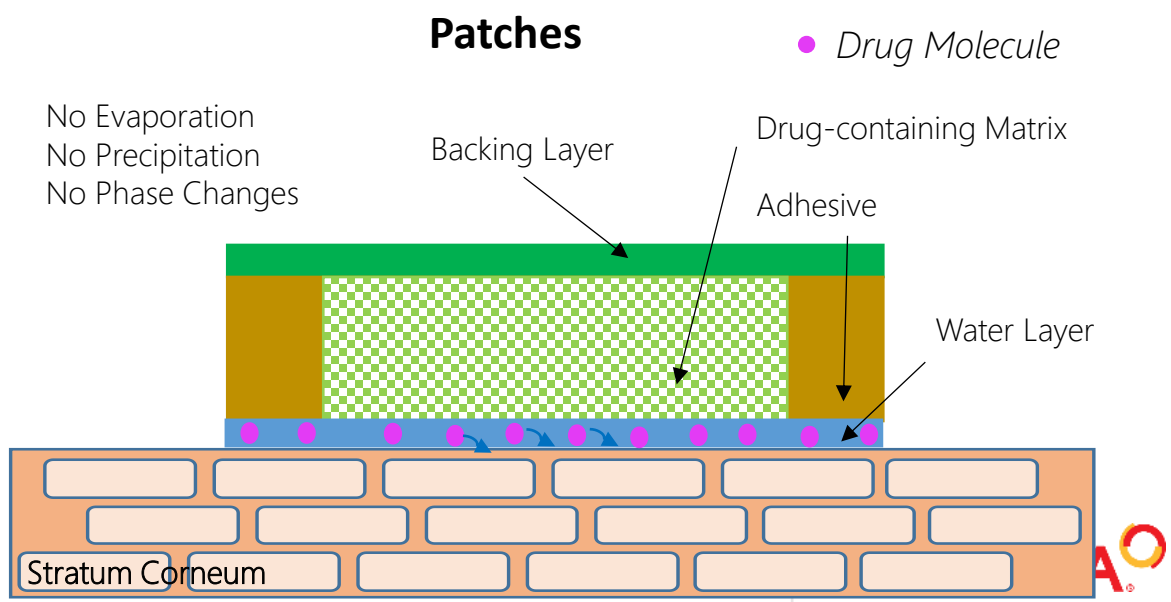
Modeling Topical/Transdermal Formulations









Critical Quality Attributes

pH

Viscosity

Solubility in Continuous Phase

Globule Size Distribution

Solubility in Dispersed Phase

Solid Particle Size Distribution

Critical Quality Attributes

pH

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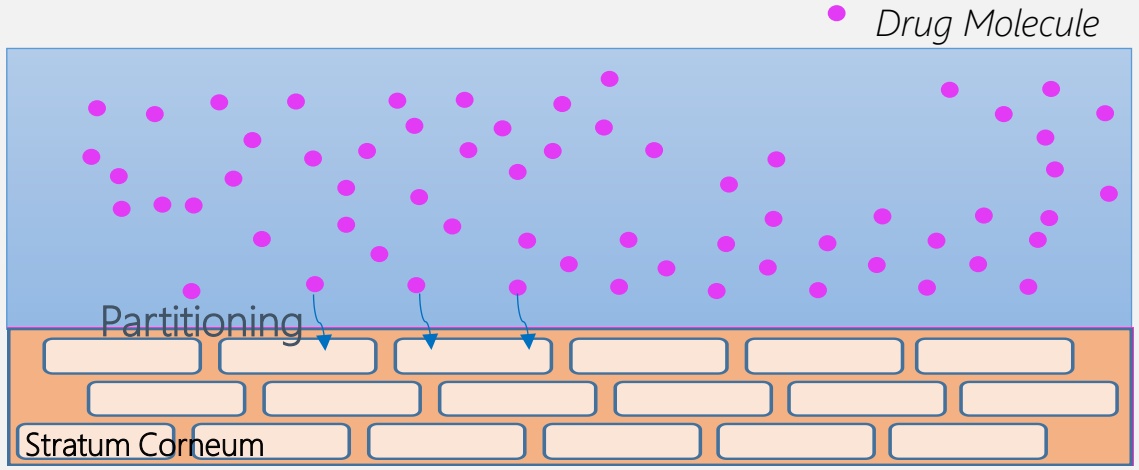
Solid Particle Size Distribution



$$\frac{dM_{SC,lip1}}{dt} = \left(\frac{D_{lip,1} * A_t}{L_{eff1}}\left(\left(\frac{K_{lip:1} f_{ni} M_{form,i}}{V_{form,i}}\right) - \left(\frac{M_{SC,lip1}}{V_{lip1}}\right)\right)\right) - \left(\frac{D_{lip,2} * A_t}{L_{eff2}}\left(\left(\frac{M_{SC,lip1}}{V_{lip1}}\right) - \left(\frac{M_{SC,lip2}}{V_{lip2}}\right)\right)\right)$$

- Ionized drug is (assumed) not absorbed
- Fraction non-ionized (f_{ni}) can be predicted for a certain pH using Henderson Hasselbach equations

Critical Quality Attributes

pH

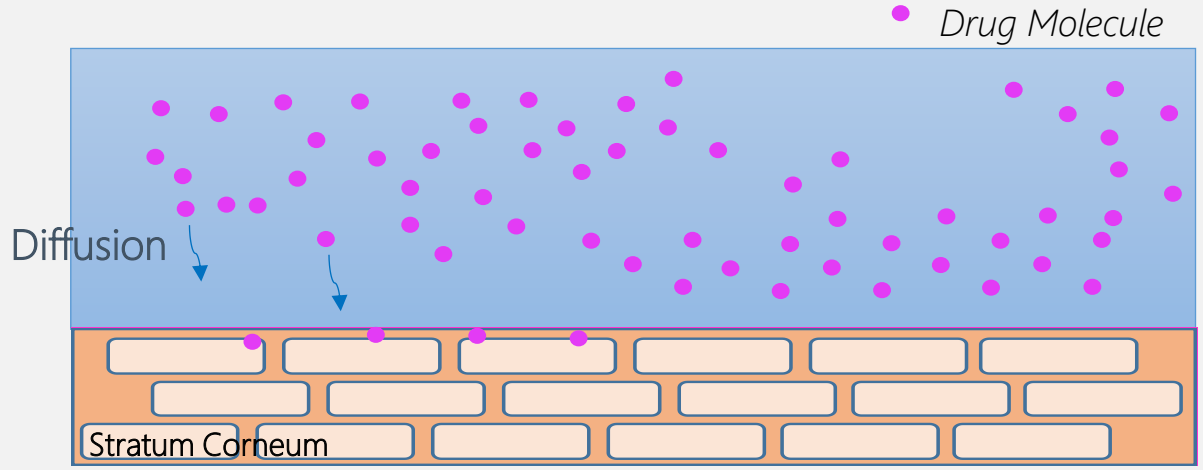
Viscosity

Solubility in Continuous Phase

Globule Size Distribution

Solubility in Dispersed Phase

Solid Particle Size Distribution



- Diffusivity in the vehicle is slower with higher viscosity
- Drug at the skin surface can become depleted if flux into the SC is faster than diffusion can replace drug.
- Solid drug dissolves slower into more viscous solutions

Critical Quality Attributes

pH

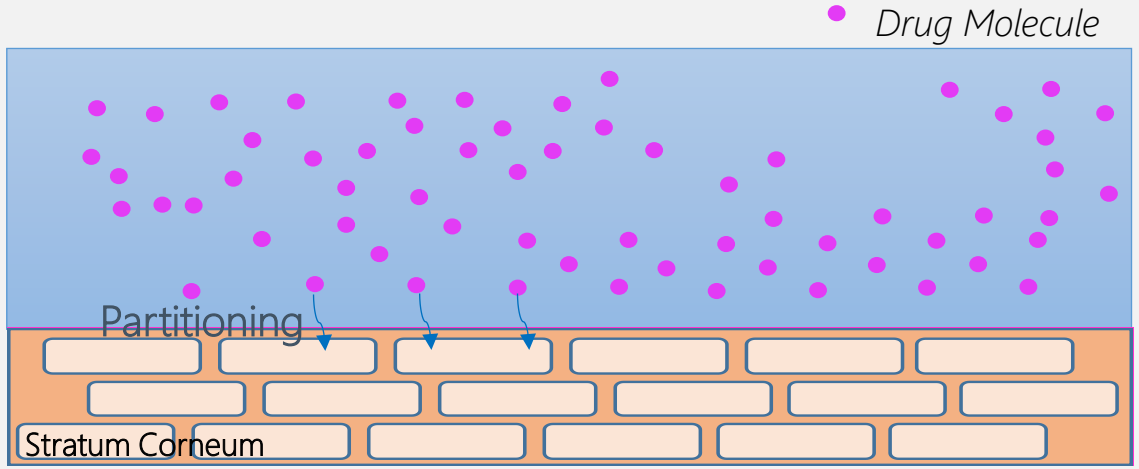
Viscosity

Solubility in Continuous Phase

Globule Size Distribution

Solubility in Dispersed Phase

Solid Particle Size Distribution



$$\frac{dM_{SC,lip1}}{dt} = \left(\frac{D_{lip,1} * A_t}{L_{eff1}}\left(\left(\frac{K_{lip:v} f_{ni} M_{form,i}}{V_{form,i}}\right) - \left(\frac{M_{SC,lip1}}{V_{lip1}}\right)\right)\right) - \left(\frac{D_{lip,2} * A_t}{L_{eff2}}\left(\left(\frac{M_{SC,lip1}}{V_{lip1}}\right) - \left(\frac{M_{SC,lip2}}{V_{lip2}}\right)\right)\right)$$

- $K_{lip:water}$ can be predicted from LogP with QSARs

$$K_{lip:vehicle} = K_{lip:water} * \frac{Solubility_{water}}{Solubility_{vehicle}}$$

- As solubility in the vehicle increases, partitioning into the SC decreases

Critical Quality Attributes

pH

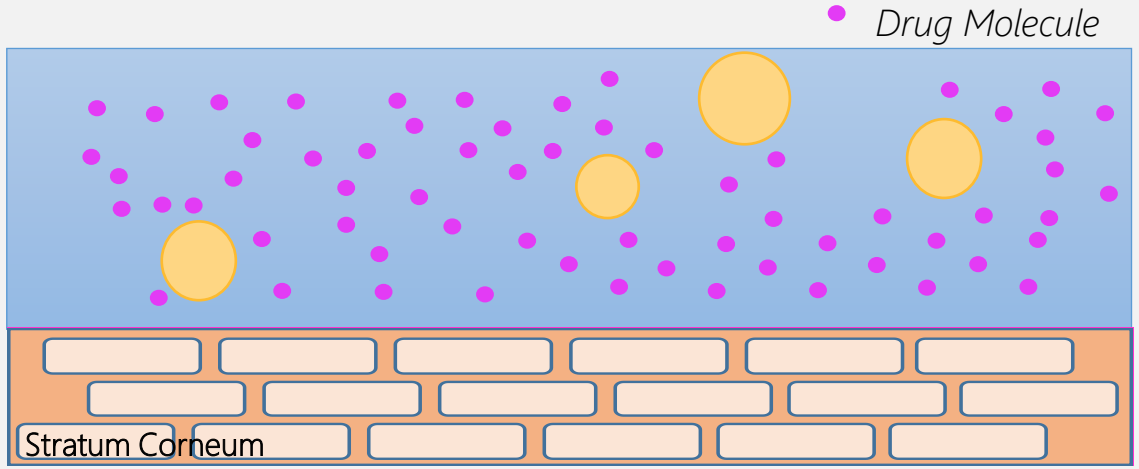
Viscosity

Solubility in Continuous Phase

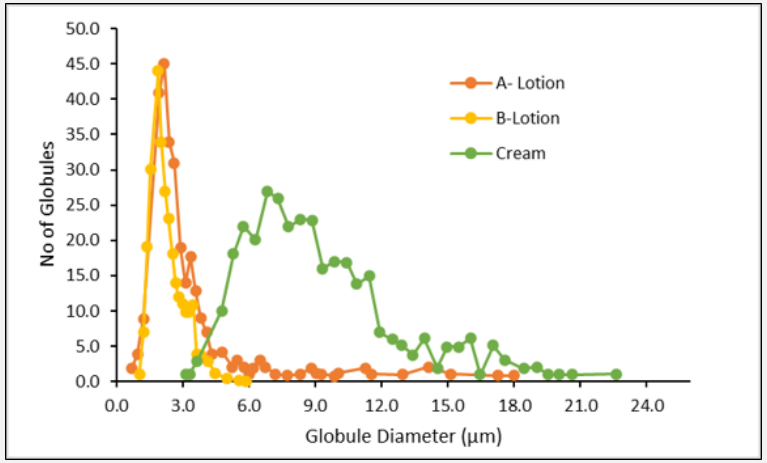
Globule Size Distribution

Solubility in Dispersed Phase

Solid Particle Size Distribution



- Dispersed phase volume affects the amount of drug available in the continuous phase.
- Globule size distribution affect the flux between the two phases,
- Smaller globules release drug faster due to their higher surface area to volume ratio



Critical Quality Attributes

pH

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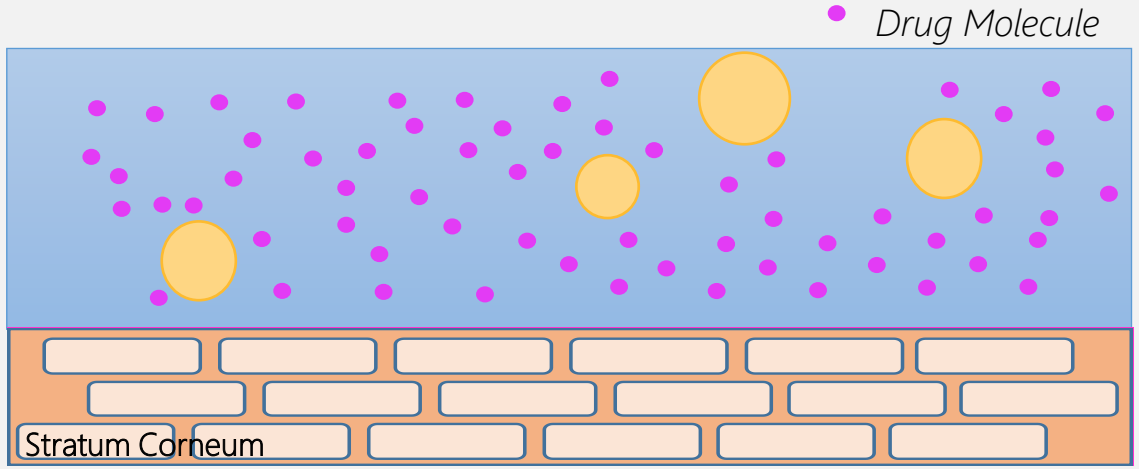
Solubility in Continuous Phase

Globule Size Distribution

Solubility in Dispersed Phase

Solid Particle Size Distribution



- Solubility in the dispersed phase affects partitioning and retention in the dispersed phase

$$K_{dispersed:continuous} = \frac{S_{dispered}}{S_{continuous}}$$

- This can be used to calculate the initial drug distribution in the formulation, and also dictates partitioning between the two phases

Critical Quality Attributes

pH

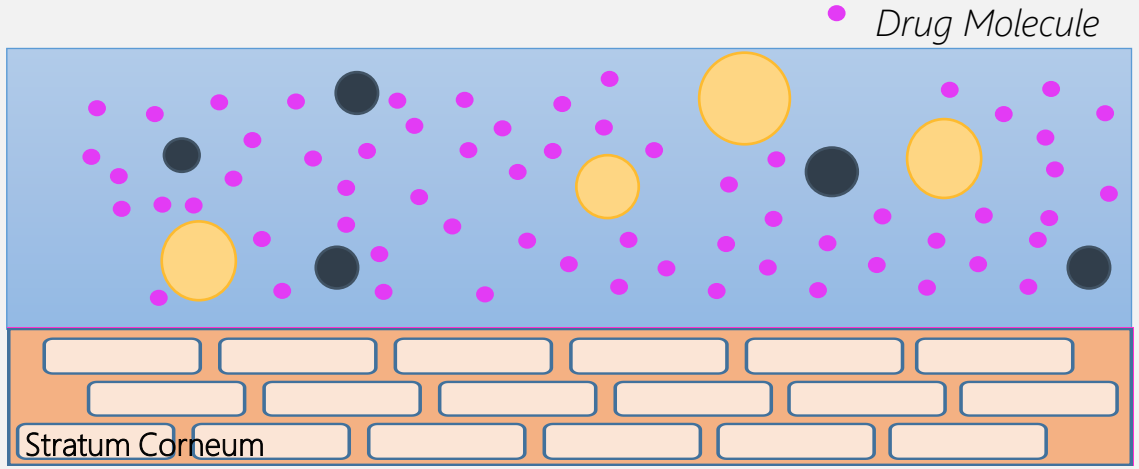
Viscosity

Solubility in Continuous Phase

Globule Size Distribution

Solubility in Dispersed Phase

Solid Particle Size Distribution



- Smaller particles dissolve faster
- If particles are too larger dissolution can become rate limiting

Drug Product Metamorphosis

Primary Formulation

Shear effects

Loss of propellants

Dispensing

Secondary Formulation

Absorption

Evaporation

Tertiary Formulation

Time

Volume

API Concentration

Solubility?

Precipitate?

pH?

Viscosity?

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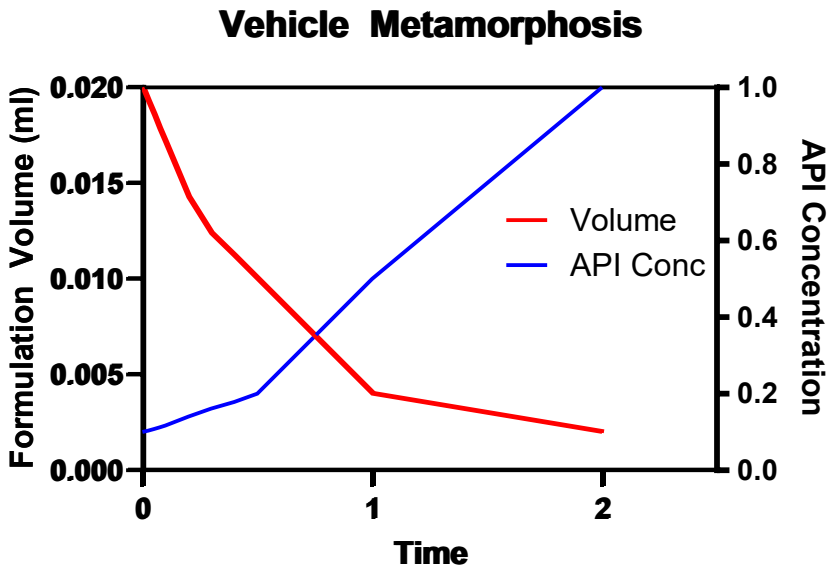
Modelling Drug Product Metamorphosis

- It is fairly easy to model a change in volume over time and feedback to modify API concentration over time

$$\frac{dM_{SC,lip1}}{dt} = \left(\frac{D_{lip,1} * A_t}{L_{eff1}}\left(\left(\frac{K_{lip:v}\, f_{ni}\ M_{form,i}}{V_{form,i}}\right) - \left(\frac{M_{SC,lip1}}{V_{lip1}}\right)\right)\right) - \left(\frac{D_{lip,2} * A_t}{L_{eff2}}\left(\left(\frac{M_{SC,lip1}}{V_{lip1}}\right) - \left(\frac{M_{SC,lip2}}{V_{lip2}}\right)\right)\right)$$



- It may be logical to assume this will increase the rate of drug absorption proportionally, but this is almost never the case

- This would only happen when:
  - *The vehicle composition remains the same, i.e., it is a single component system*
  - *There is solubilisation capacity for all the drug in the reduced volume*

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Modelling Drug Product Metamorphosis

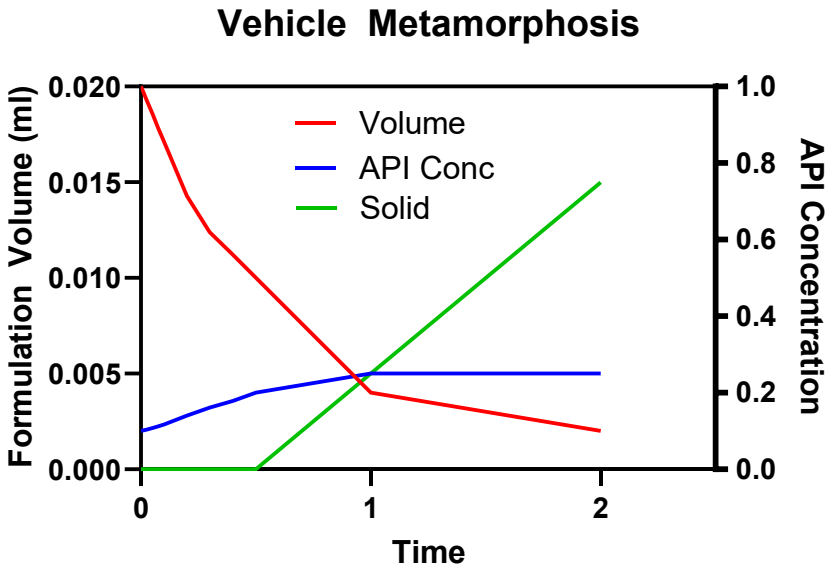
If there is NOT solubilisation capacity for all the drug in the reduced volume

- The API reaches a solubility limit and begins to precipitate, therefore the concentration plateaus around this solubility limit

- So M_{form} decreases significantly, meaning the total concentration does not increase linearly with volume depletion and therefore neither does absorption

$$\frac{dM_{SC,lip1}}{dt} = \left(\frac{D_{lip,1} * A_t}{L_{eff1}}\left(\left(\frac{K_{lip:v}\, f_u\, M_{form,i}}{V_{form,i}}\right) - \left(\frac{M_{SC,lip1}}{V_{lip1}}\right)\right)\right) - \left(\frac{D_{lip,2} * A_t}{L_{eff2}}\left(\left(\frac{M_{SC,lip1}}{V_{lip1}}\right) - \left(\frac{M_{SC,lip2}}{V_{lip2}}\right)\right)\right)$$

- This can be simulated if we know the API solubility, most simply by just capping the concentration. Or applying a supersaturation model



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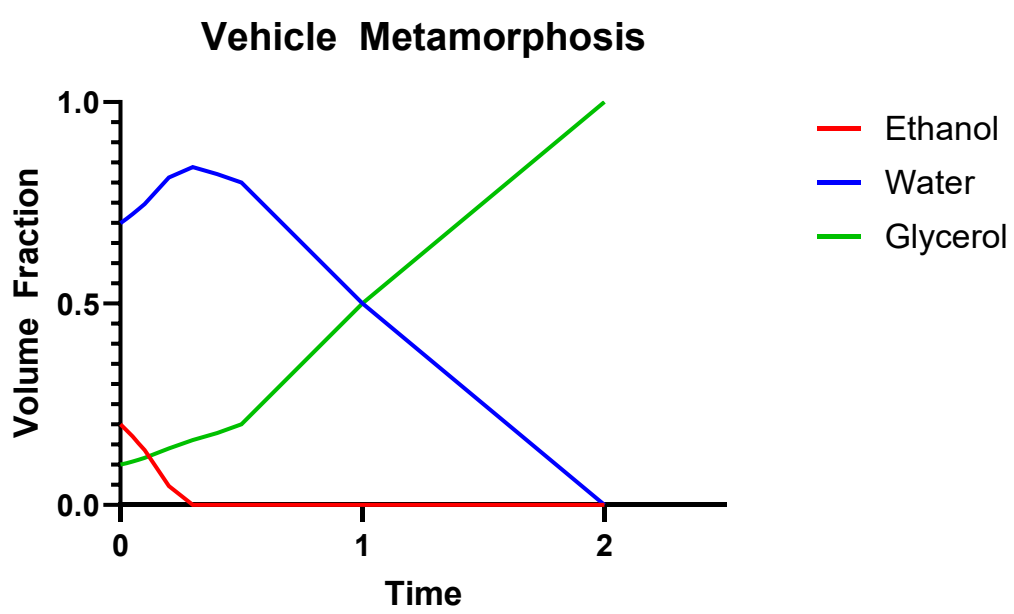
Modelling Drug Product Metamorphosis

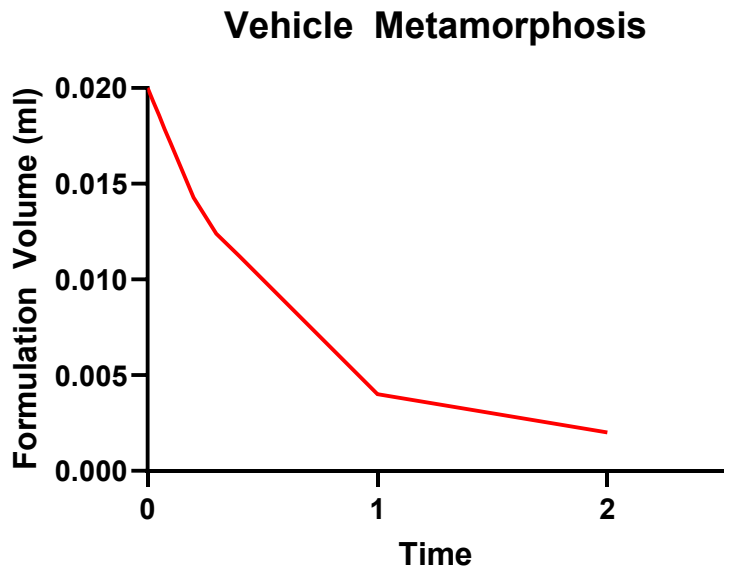
If the vehicle composition is NOT a single component system (basically, every single drug product on the market)

Composition	% v/v
Glycerol	10
Ethanol	20
Water	70

- Thing get a bit more complicated….

- If we have other components, applying a volume change is not sufficient





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Modelling Drug Product Metamorphosis

If the vehicle composition is NOT a single component system (basically, every single drug product on the market)

Composition	% v/v	Solubility
Glycerol	10	10
Ethanol	20	122
Water	70	0.095

- Thing get a bit more complicated….

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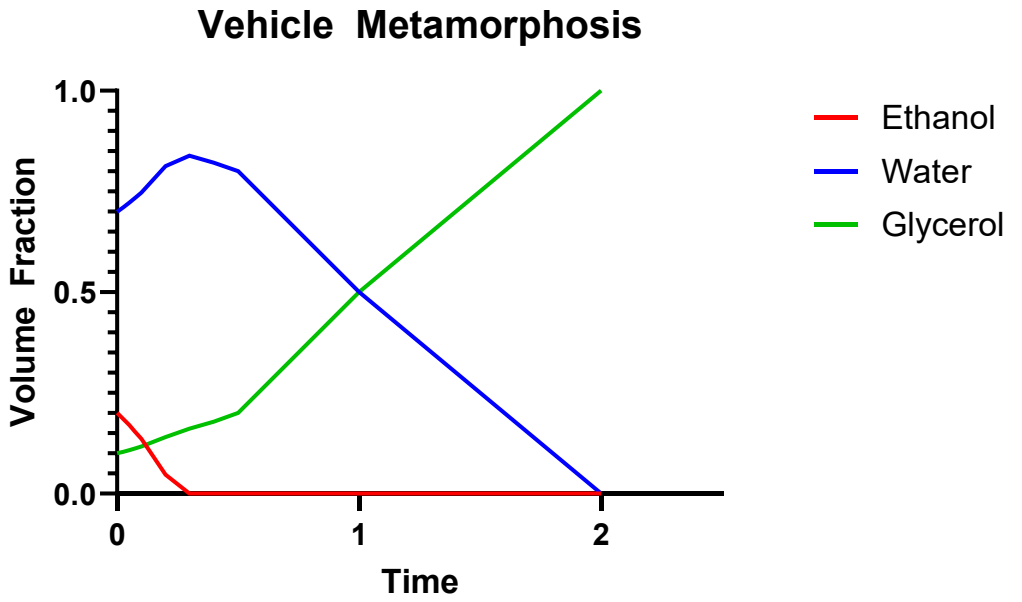

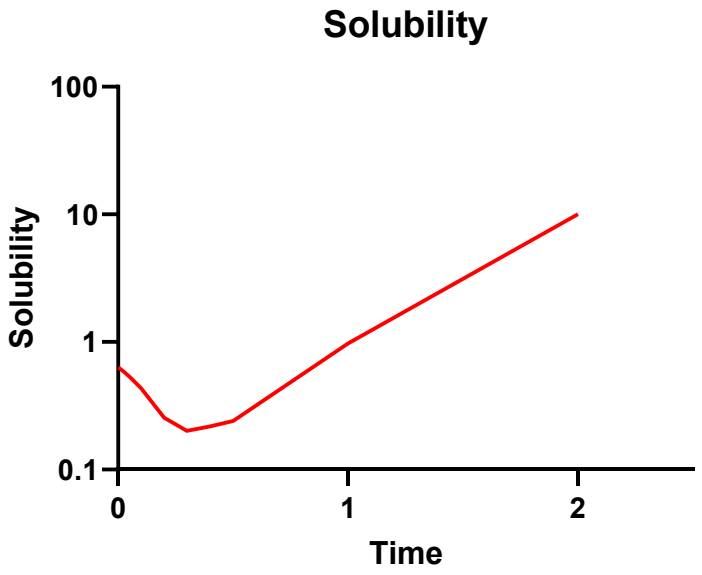

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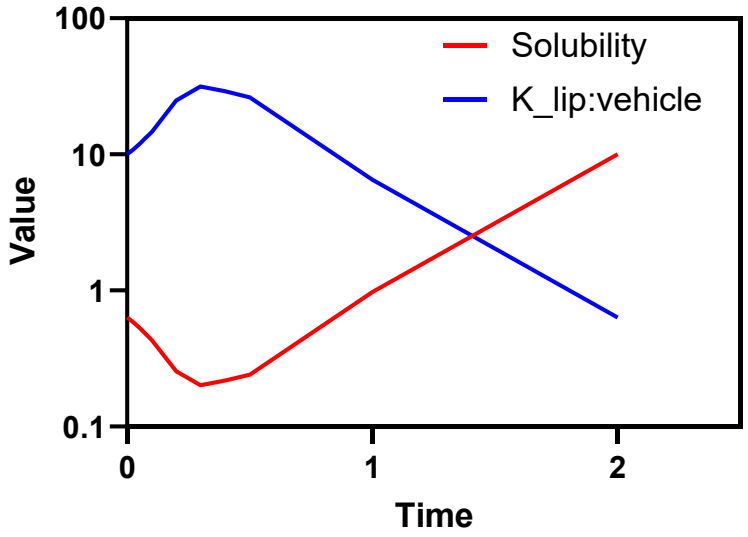

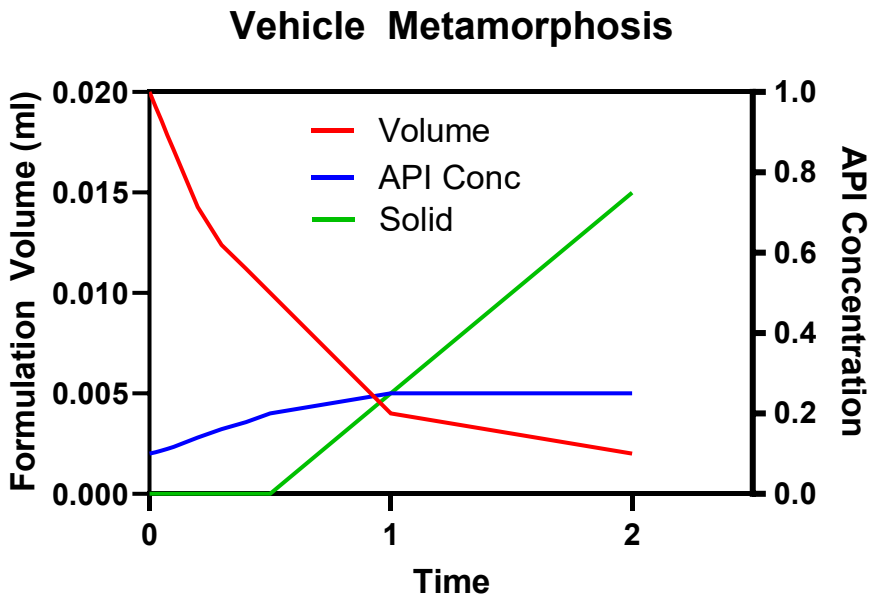

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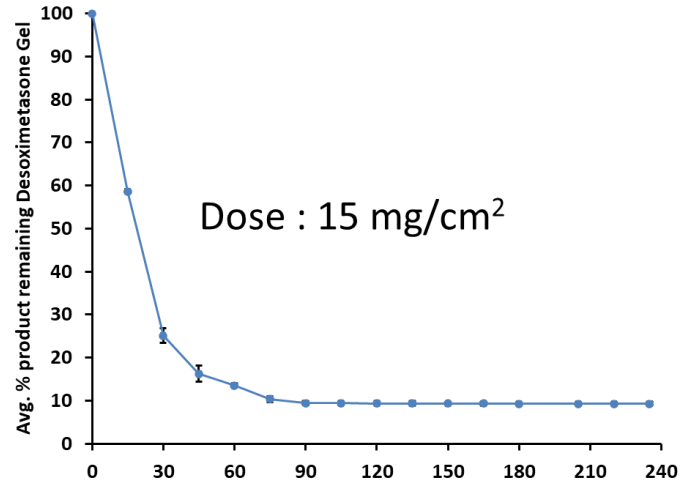
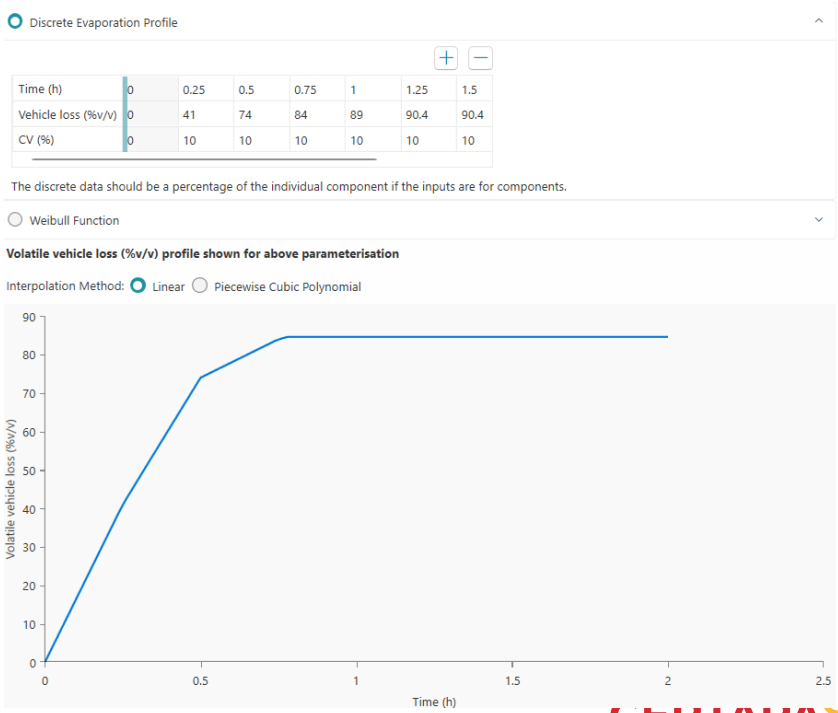
Simulating evaporation of individual components

- In order to account for this, we need to know the composition of the formulation at each time point
- However, this data is very difficult to measure, usually "loss on drying" data is measured which just gives us the volume loss.
- We have had the ability to enter this in the simulator for a long time
- A major aim of this work is to develop models to predict and simulate evaporation of individual components.



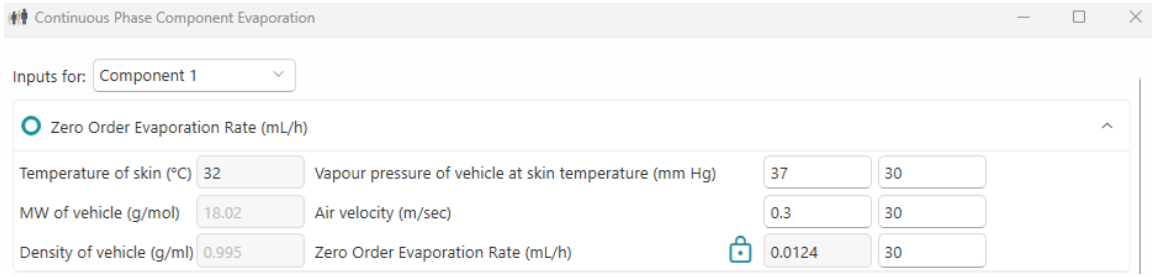


Simulating evaporation of individual components

- We can identify which solvents are evaporating by simple intuition, or by looking at the vapor pressure

Composition	% v/v	Solubility
Glycerol	10	10
Ethanol	20	122
Water	70	0.095

- There are only a handful of solvents commonly used in topical products which evaporate, namely IPA, Ethanol, Water - to some extent Propylene Glycol.
- In this case, Ethanol and Water will be evaporating, Glycerol is non-volatile
- We can predict the evaporation of individual components using their vapour pressure (using EPA method)
- However, evaporation rates may be different from mixtures



- We are currently undertaking a large number of evaporation studies in collaboration with Topical Proucts Testing (Dr Murthy) to allow us to build better predictive models for evaporation from mixtures.

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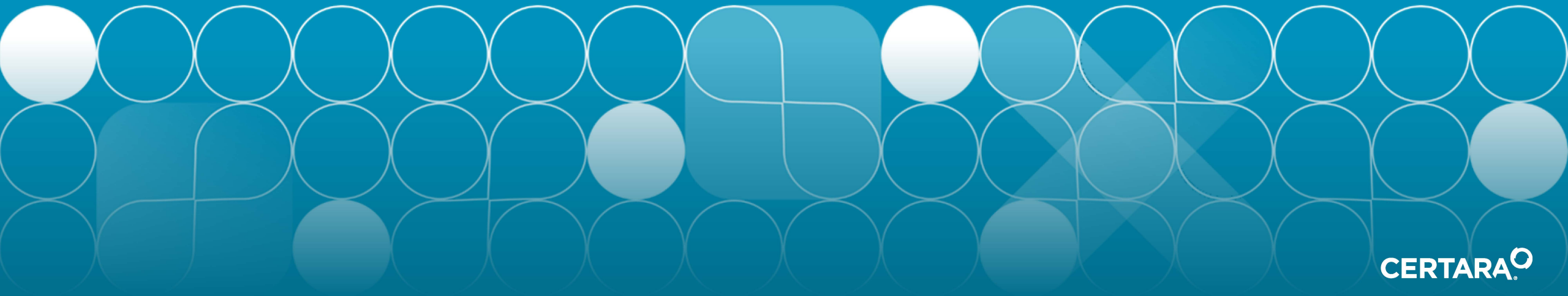
Case Study:
Desoximetasone – Topicort Gel 0.05%



Topicort Spray

Published in 2022

- One approach is to assume the tertiary composition when parameterising the model
- This makes sense for something like a spray, IPA evaporation is rapid and may be complete in less than 15 mins.

A mechanistic physiologically based model to assess the effect of study design and modified physiology on formulation safe space for virtual bioequivalence of dermatological drug products

J. F. Clarke[1,2]*, K. Thakur[1] and S. Polak[1,2]

[1]Simcyp Division, Certara UK, Sheffield, United Kingdom, [2]Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

TABLE 2 Quantitative composition (Q2) of Topicort® Spray.

Component	Primary/secondary (% w/w)	Tertiary (% w/w)	Density (g/ml)	Primary/secondary (% v/v)	Tertiary (% v/v)
Desoximetasone	0.25	0.33	1.3	0.16	0.21
Glyceryl oleate	0.9	1.17	1	0.75	1.00
Isopropyl alcohol	23.4	0.00	0.774	25.17	0.00
Isopropyl myristate	31.38	40.96	0.85	30.74	41.08
L-Menthol	0.05	0.07	0.89	0.05	0.06
Mineral oil	44.03	57.47	0.85	43.13	57.64

- However, this may not be appropriate for slower evaporating components, such as water!

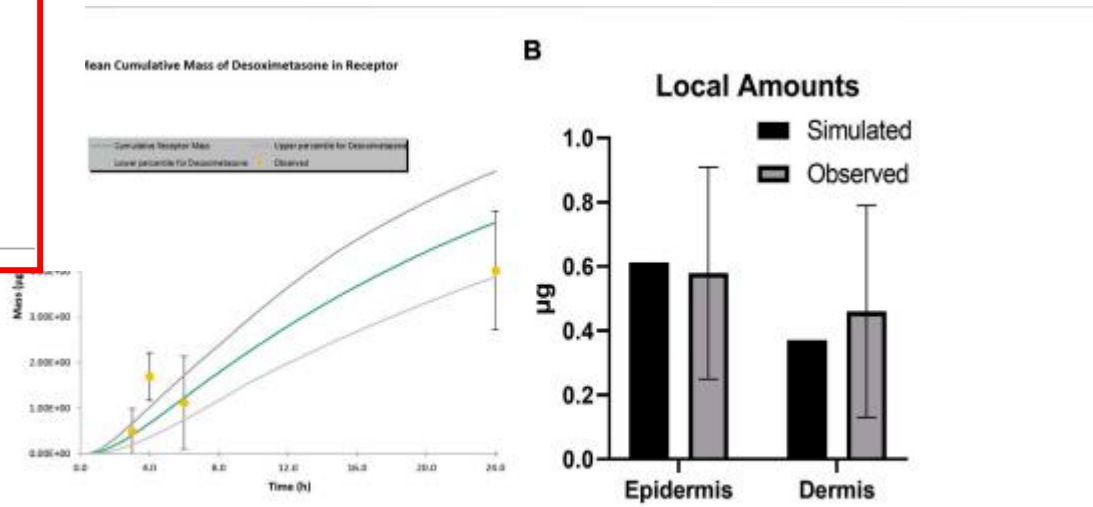


FIGURE 1
Simulated and observed IVPT results for Topicort® Spray 0.25% (A) Receptor Profile (B) Local amounts.

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Desoximetasone

Physicochemical Properties

Molecular weight (g/mol)	376.46
Log $P_{o:w}$	2.35
	Neutral
pKa 1	6.5
pKa 2	0
Polar surface area (Å^2)	50
Hydrogen bond donors	0
Hydrogen bond acceptors	4
Fraction unbound in plasma	0.145

All permeability parameters were predicted from Phys chem or default values

Drug Partition Coefficients

Stratum Corneum Lipid : Water K_p	49.553	Dermis : Viable Epidermis K_p	1
Stratum Corneum Lipid : Vehicle K_p	49.553	Receptor : Membrane K_p	3.6448
Stratum Corneum Lipid : Viable Epidermis K_p	17.158	Dermis : Sebum K_p	0.040393
Sebum : Water K_p	71.498		
Sebum : Vehicle K_p	71.498		

Drug Diffusion Coefficients (cm² /h)

SC Lipid (D_{scLip})	0.00038818	Dermis (D_D)	0.00050067
Viable Epidermis (D_{VE})	0.0011645	Sebum (D_{SB})	0.0011698
Buffer (D_{Buffer})	0.026552		

Keratin Binding Kinetics

Steady State

fu_{SC} Fraction Unbound in SC 0.12518 $K_{D,keratin}$ 598.01

Corneocyte Parameters

Stratum Corneum Lipid : Corneocyte Kp	1.43
Corneocyte membrane permeability (cm/h)	0.01
Fraction of drug non-ionised in corneocyte ($f_{ni,corn}$)	1

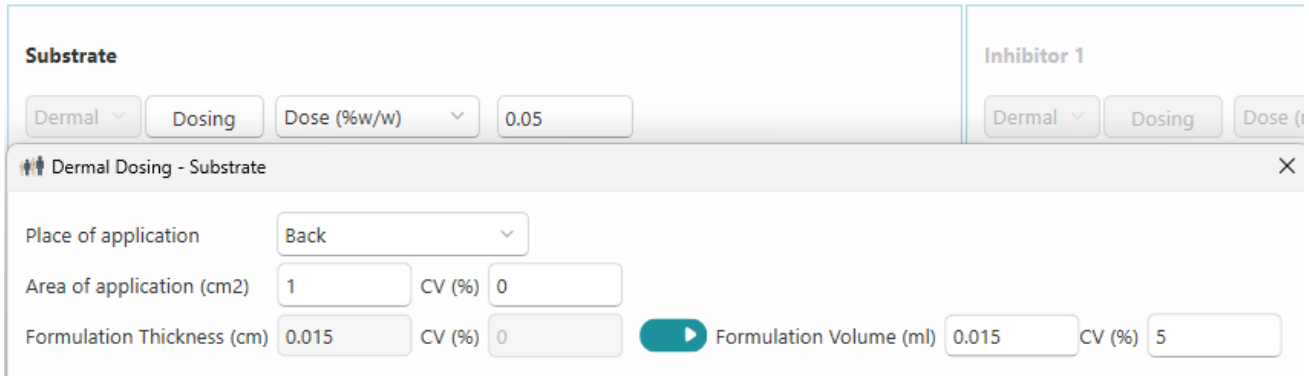
CERTARA

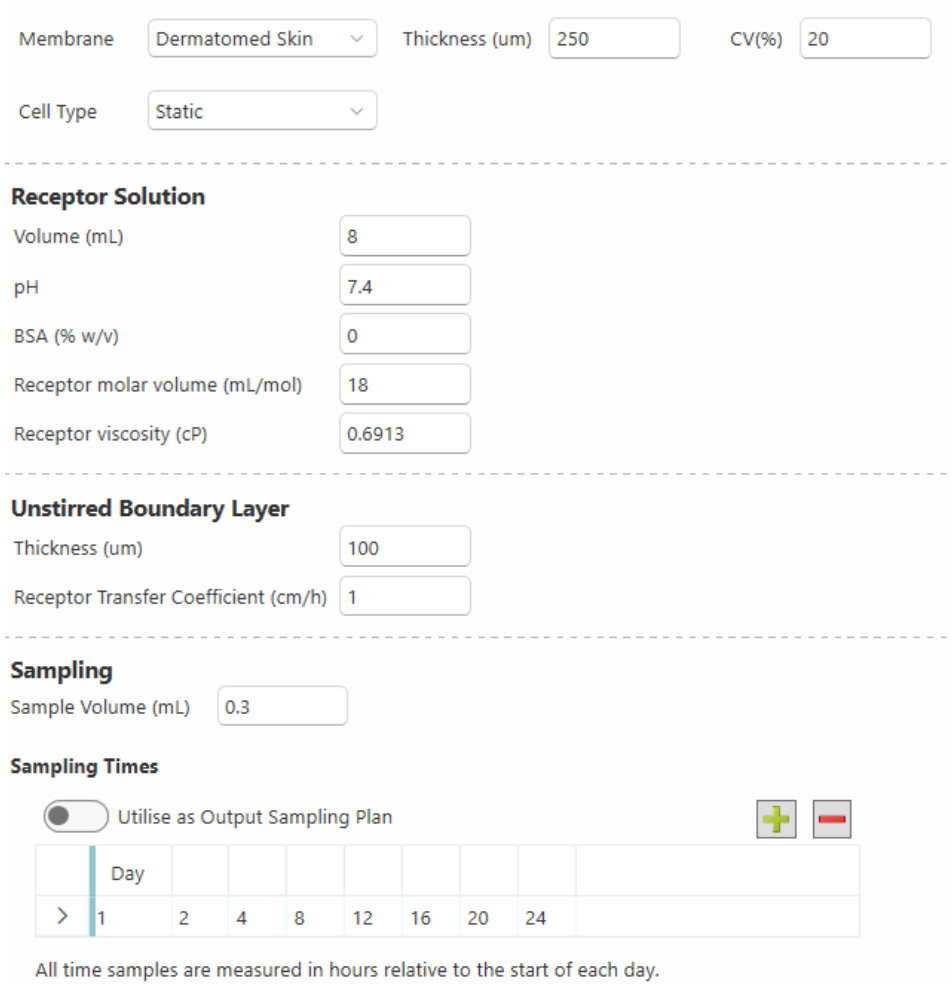
Topicort Gel

Topicort Gel will be used as an example

- We will build up the formulation model one parameter at a time and investigate the effects of each
- We will compare against IVPT data generated for Topicort Gel by Topical Products Testing LLC (Dr Murthy)

- IVPT setup:
- Dosing: 15mg/cm^2





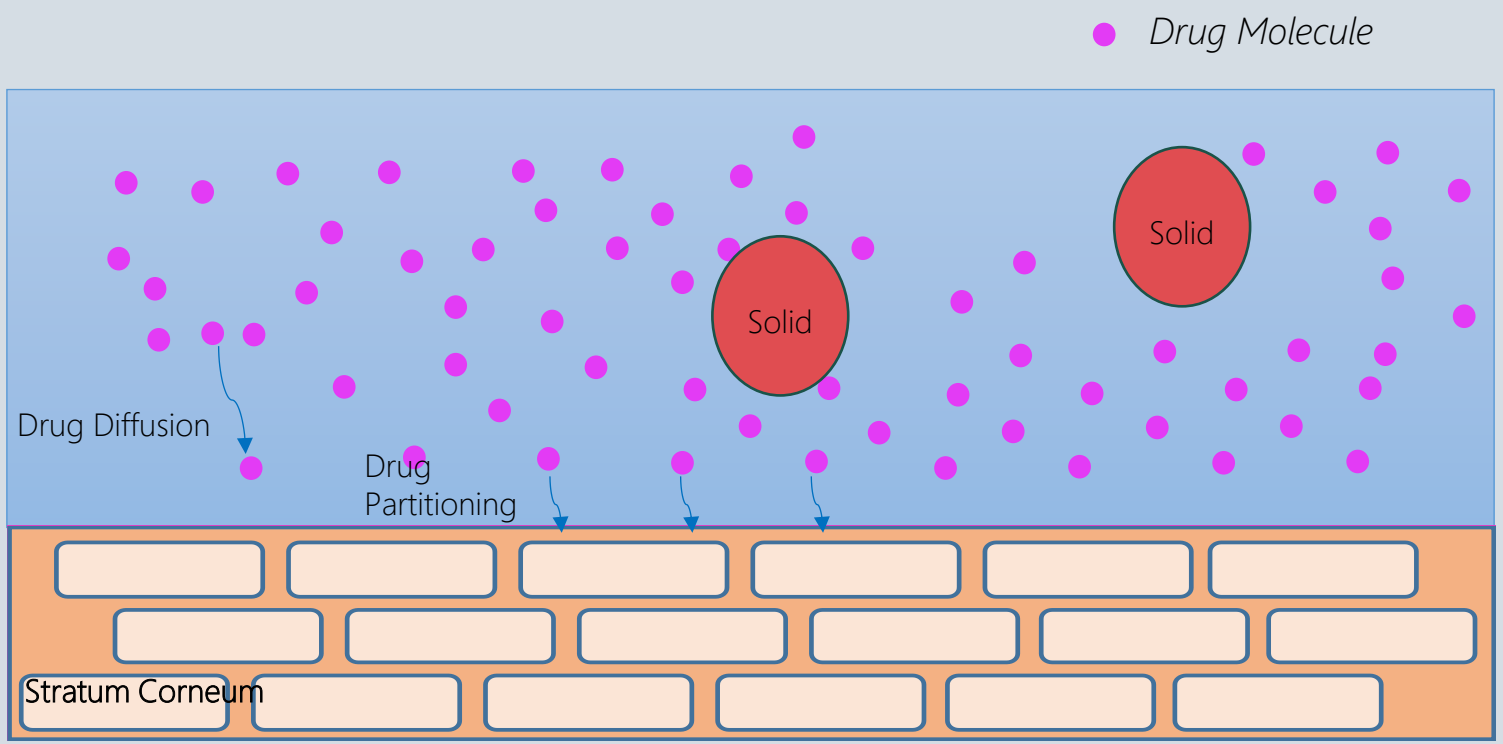
CERTARA

Formulation Parameterisation

Aqueous Solution

Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0, if 0.05% w/w.



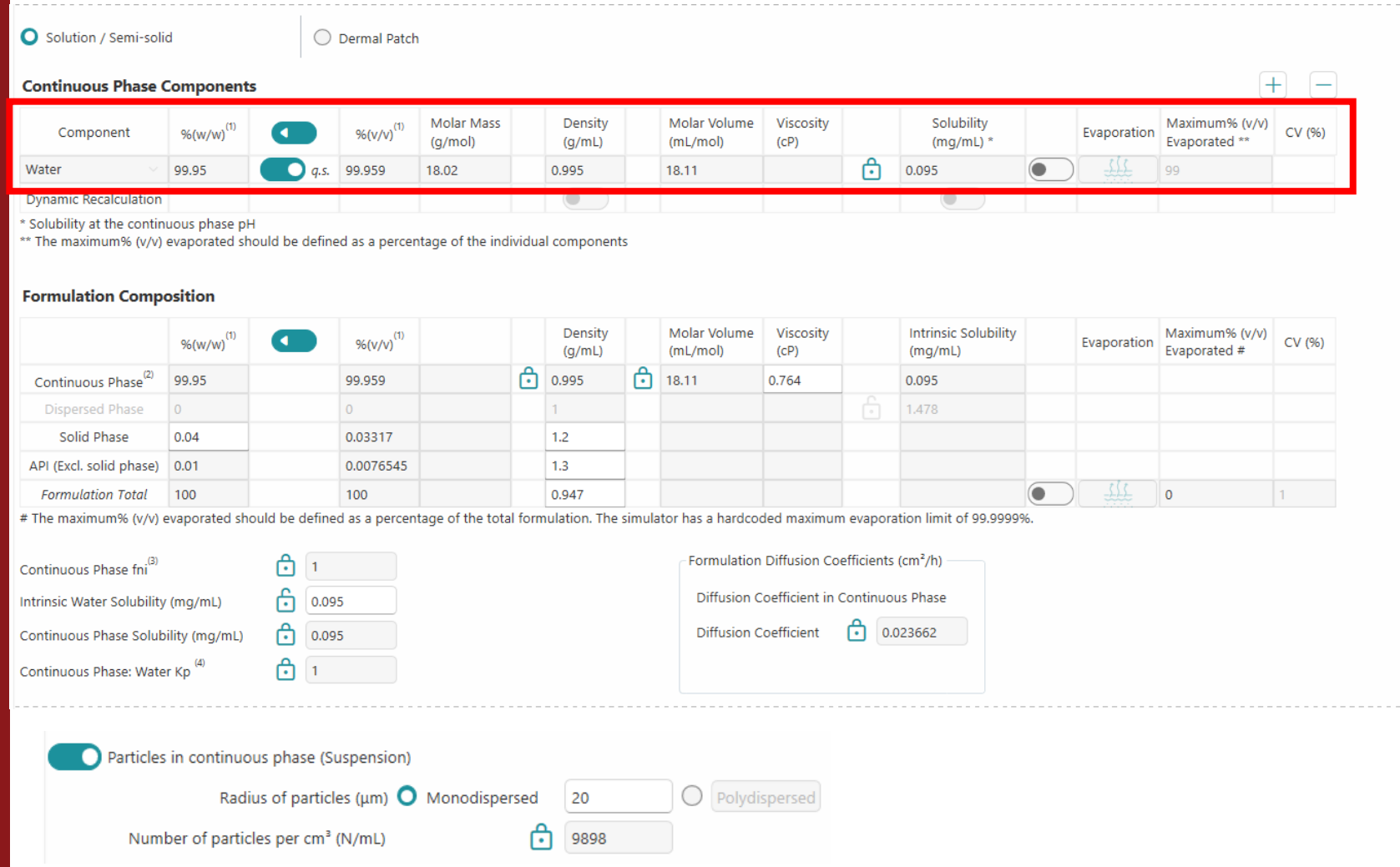
Formulation Parameterisation

Aqueous Solution

Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0, if 0.05% w/w.

Water is the only component defined



Formulation Parameterisation

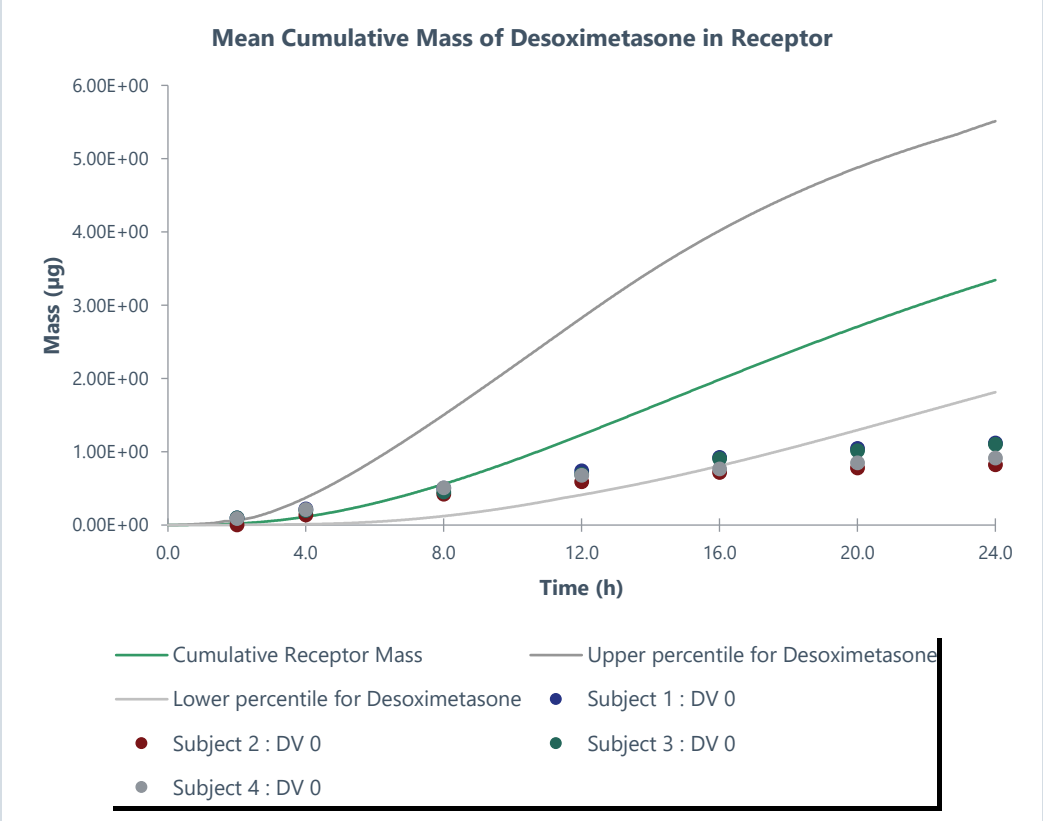
Aqueous Solution

Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0, if 0.05% w/w.

Water is the only component defined

Absorption is predicted to be significantly higher than from Topicort Gel



Formulation Parameterisation

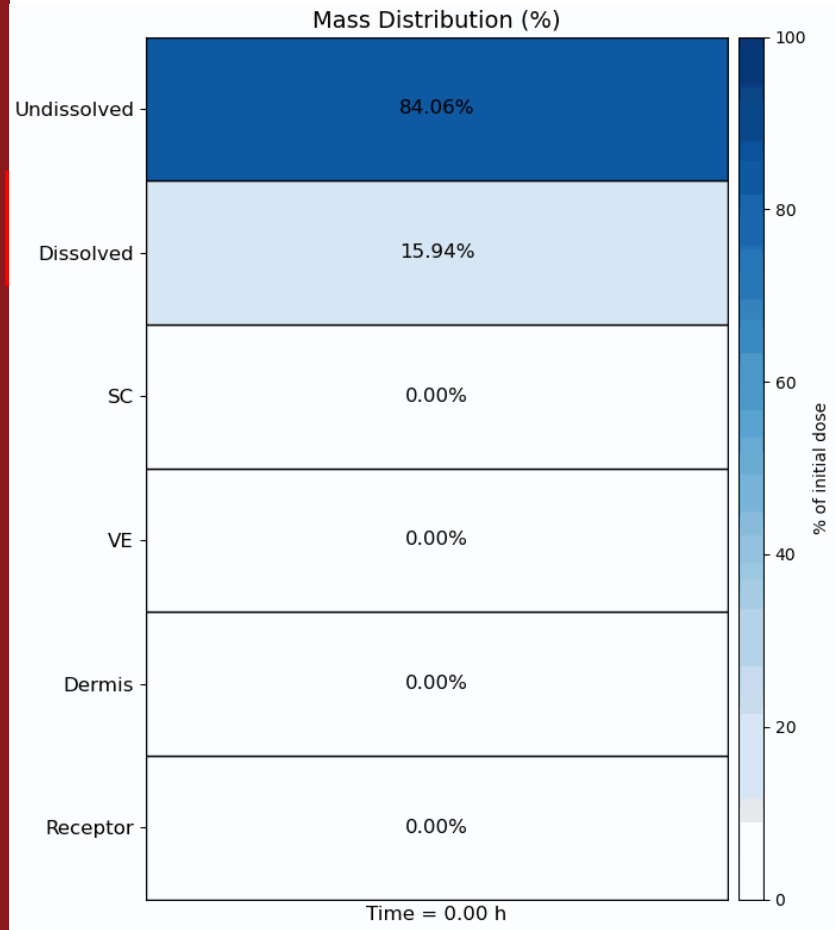
Solution 0.05% DSM

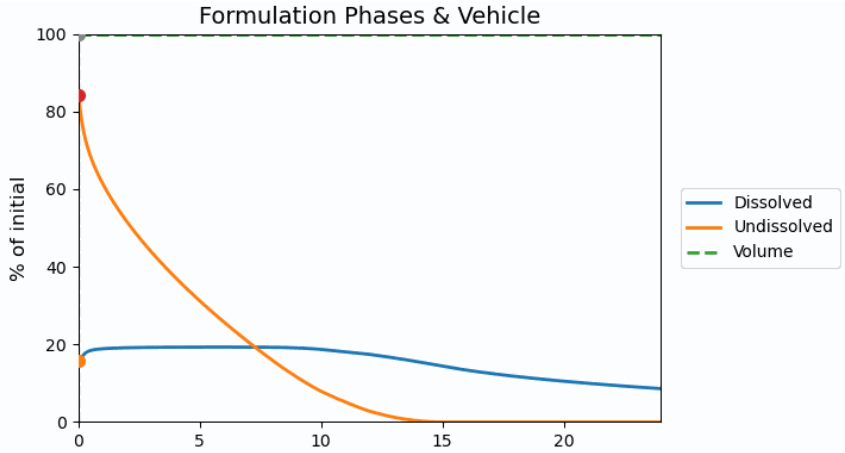
Aqueous Solution

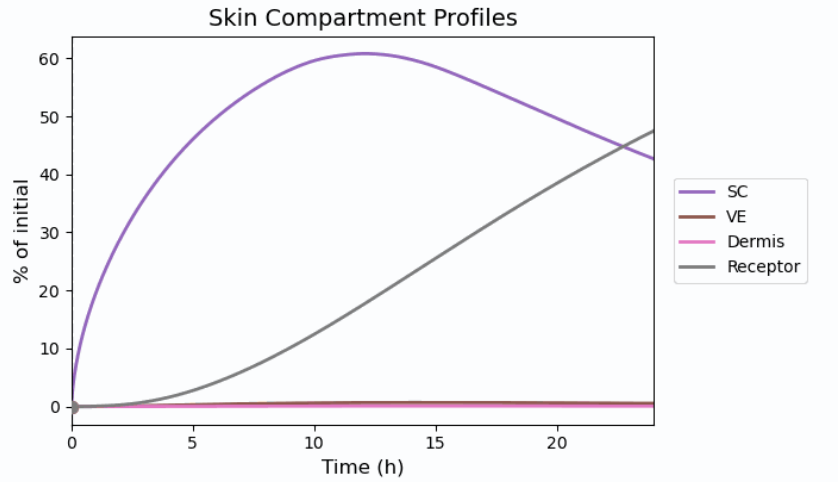
Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0

Water is the only component defined







Formulation Parameterisation

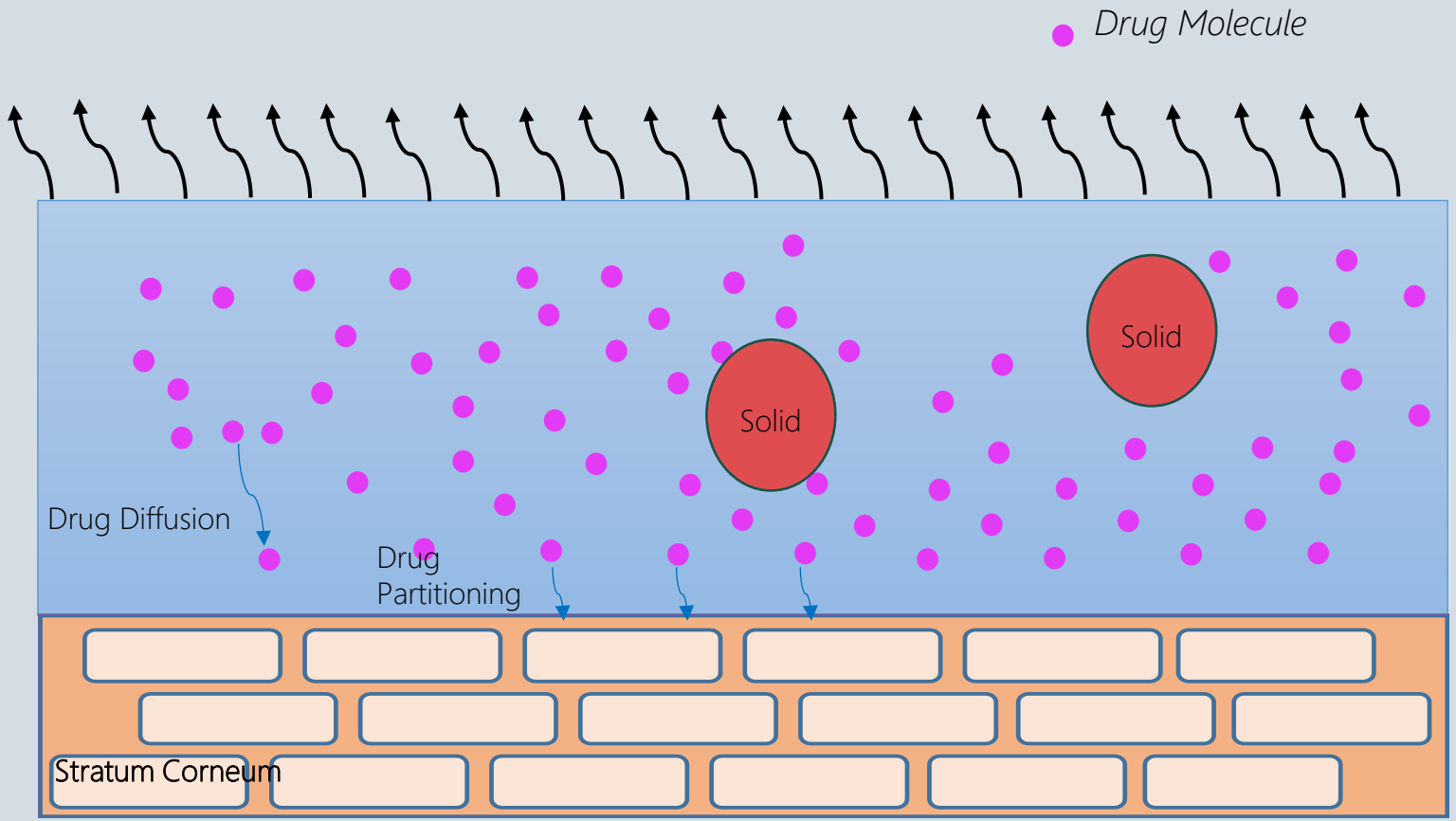
Solution

Aqueous Solution

Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0

In reality, the water would evaporate



Formulation Parameterisation

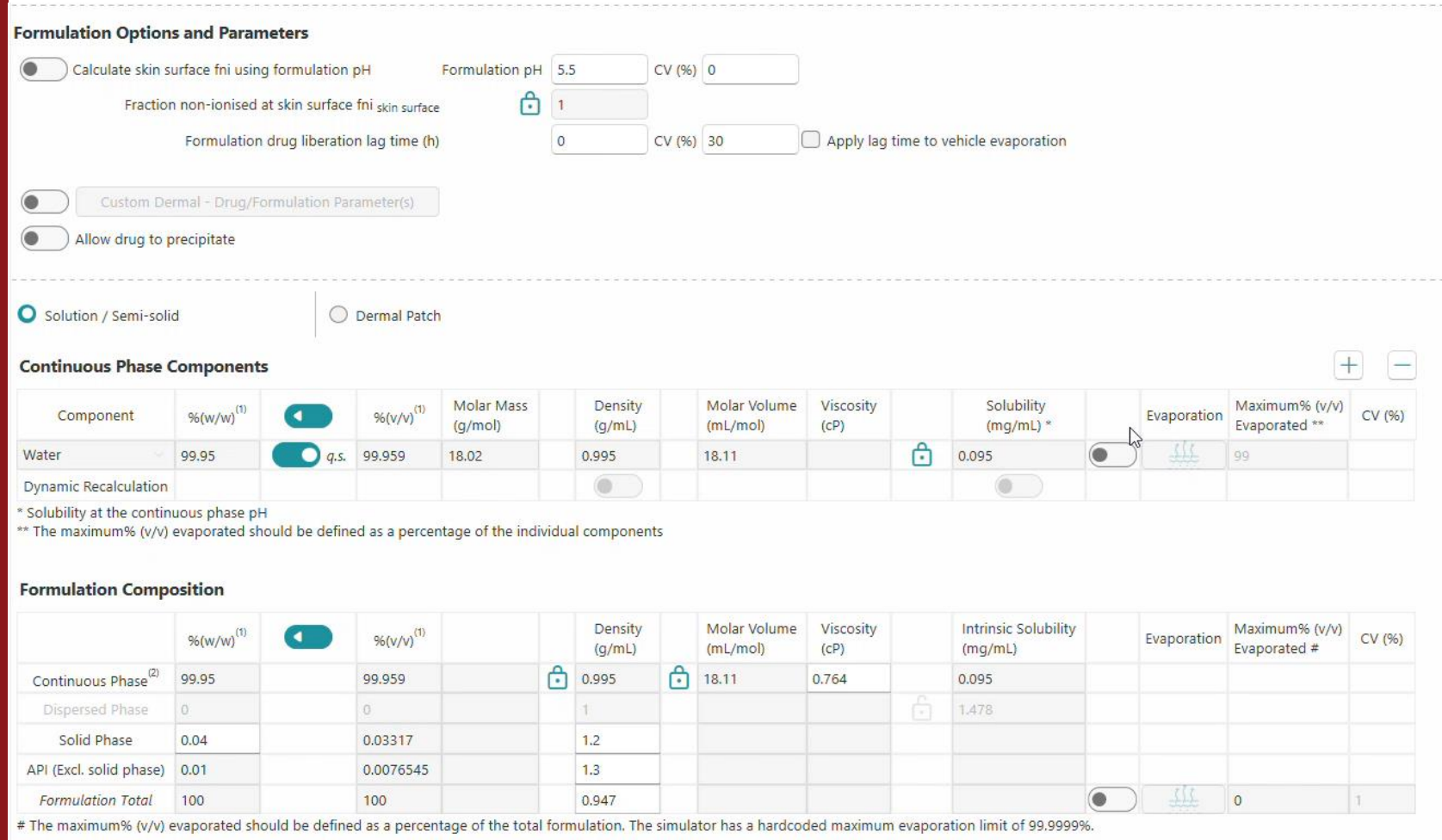
Solution

Aqueous Solution

Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0

In reality, the water would evaporate



Formulation Options and Parameters

Calculate skin surface fni using formulation pH | Formulation pH 5.5 | CV (%) 0

Fraction non-ionised at skin surface fni skin surface 1

Formulation drug liberation lag time (h) 0 | CV (%) 30 | Apply lag time to vehicle evaporation

Custom Dermal - Drug/Formulation Parameter(s)

Allow drug to precipitate

Solution / Semi-solid | Dermal Patch

Continuous Phase Components

Component	%(w/w)(1)		%(v/v)(1)	Molar Mass (g/mol)	Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Solubility (mg/mL) *	Evaporation	Maximum% (v/v) Evaporated **	CV (%)
Water	99.95	q.s.	99.959	18.02	0.995	18.11		0.095		99	
Dynamic Recalculation											

* Solubility at the continuous phase pH

** The maximum% (v/v) evaporated should be defined as a percentage of the individual components

Formulation Composition

	%(w/w)(1)		%(v/v)(1)		Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Intrinsic Solubility (mg/mL)	Evaporation	Maximum% (v/v) Evaporated #	CV (%)
Continuous Phase(2)	99.95		99.959		0.995	18.11	0.764	0.095			
Dispersed Phase	0		0		1			1.478			
Solid Phase	0.04		0.03317		1.2						
API (Excl. solid phase)	0.01		0.0076545		1.3						
Formulation Total	100		100		0.947					0	1

The maximum% (v/v) evaporated should be defined as a percentage of the total formulation. The simulator has a hardcoded maximum evaporation limit of 99.9999%.

Q3

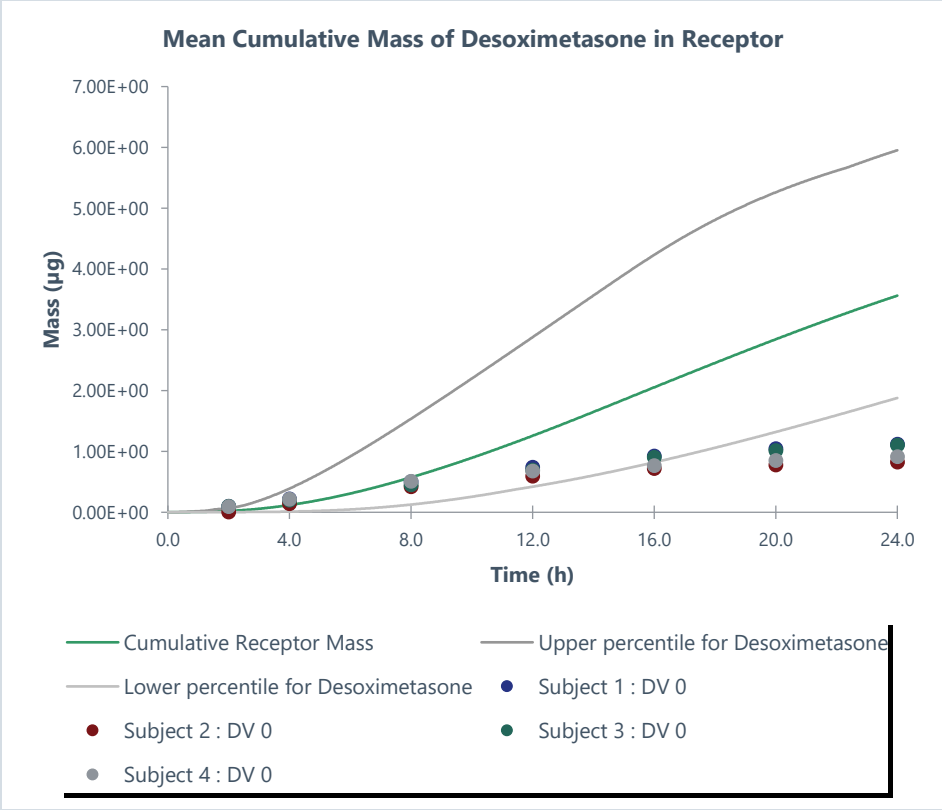
Formulation Parameterisation

Aqueous Solution

Solubility in water is only 0.095 mg/ml

Therefore, most of the drug is in the solid phase at t=0

In reality, the water would evaporate



Q3

Formulation Parameterisation

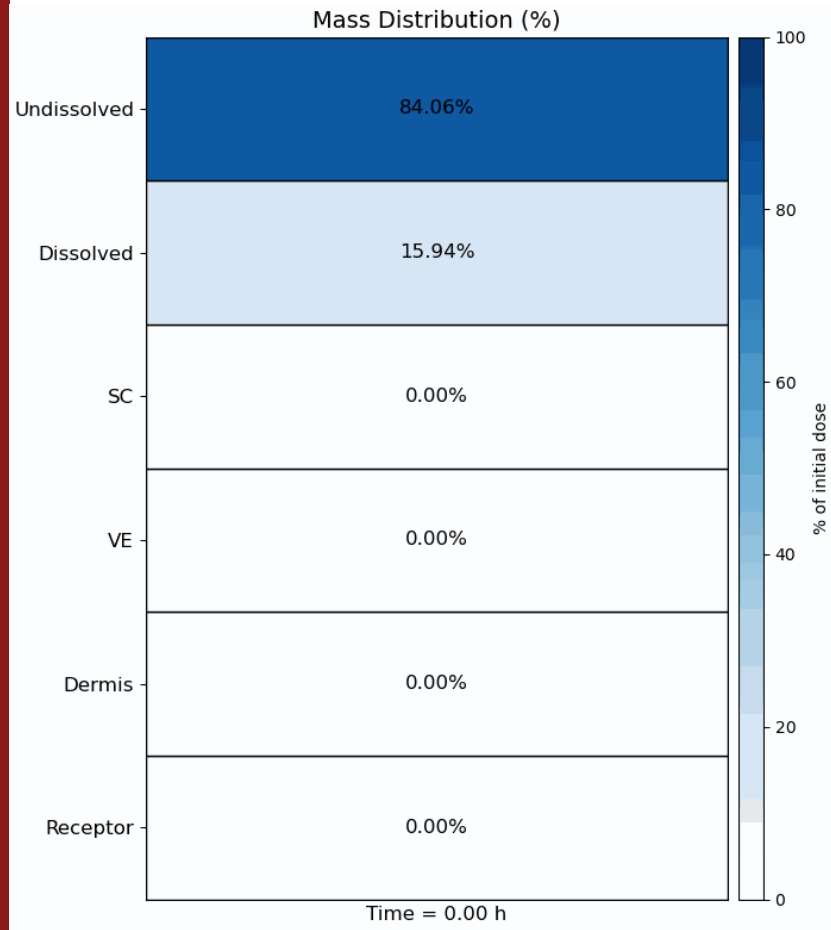
Aqueous Solution

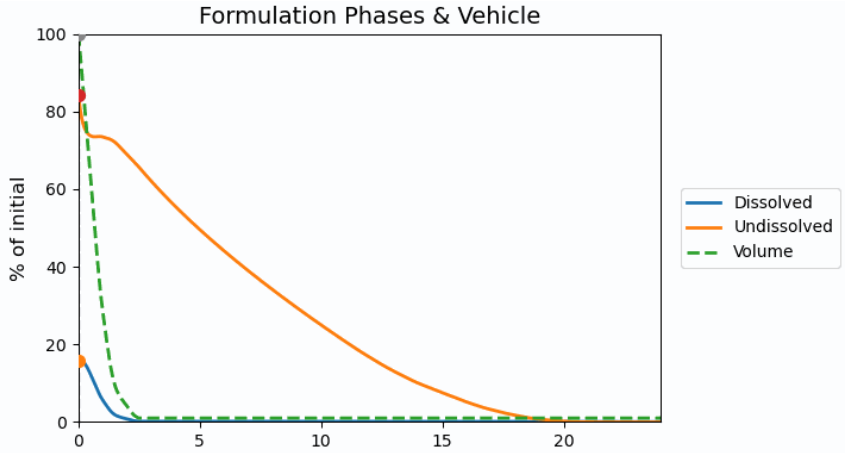
Solubility in water is only 0.095 mg/ml

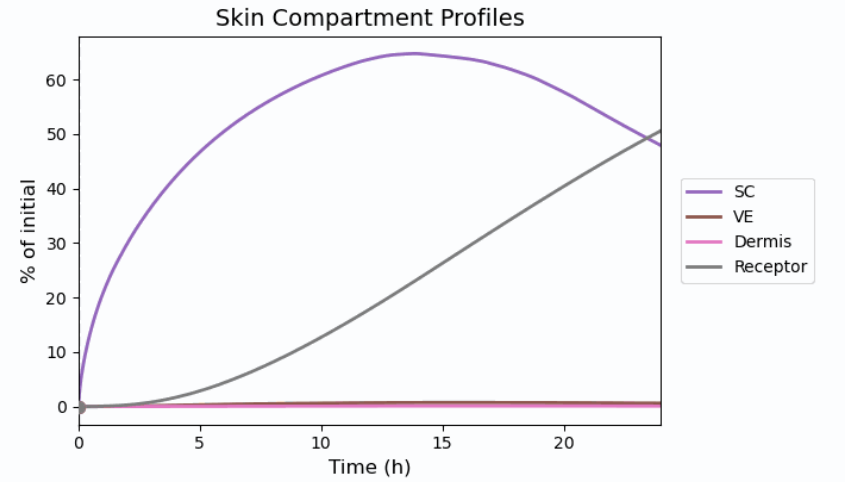
Therefore, most of the drug is in the solid phase at t=0

In reality, the water would evaporate

Concentration in the continuous phase is maintained because solid drug dissolves quickly.







Formulation Parameterisation

Aqueous Solution

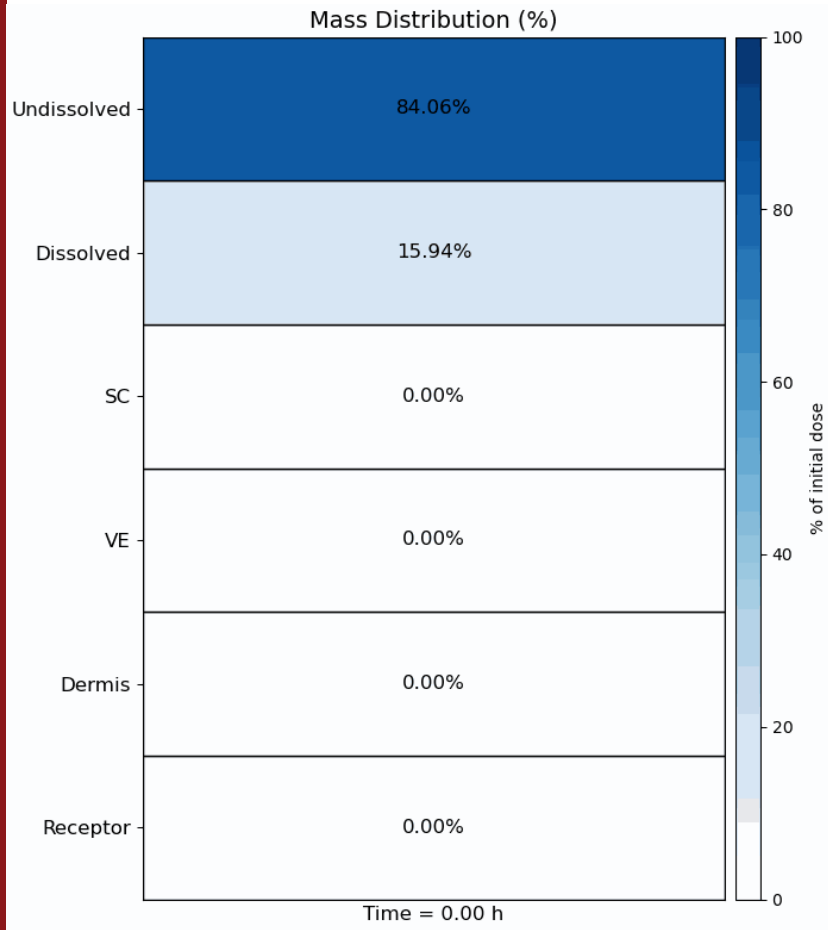
Solubility in water is only 0.095 mg/ml

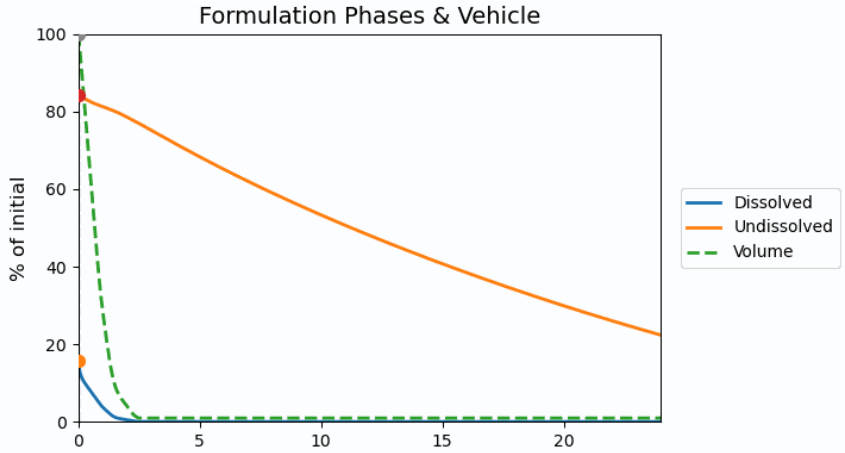
Therefore, most of the drug is in the solid phase at t=0

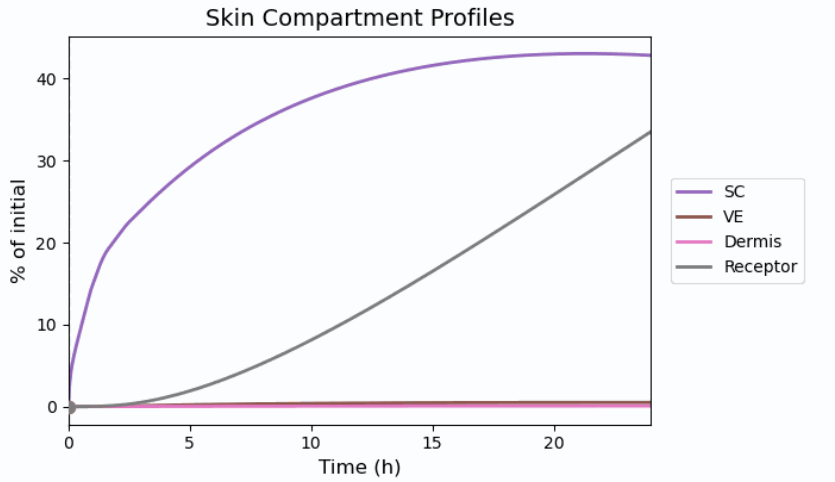
In reality, the water would evaporate

Concentration in the continuous phase is maintained because solid drug dissolves quickly.

What happens with a larger particle size?







Topicort Gel

Composition	% w/w
Carbopol 940	1 (?)
Docusate Sodium	negligible
Edetate disodium	negligible
Isopropyl myristate	4
SDAG -3 95% Alcohol	20
Trolamine	negligible
Water	q.s.

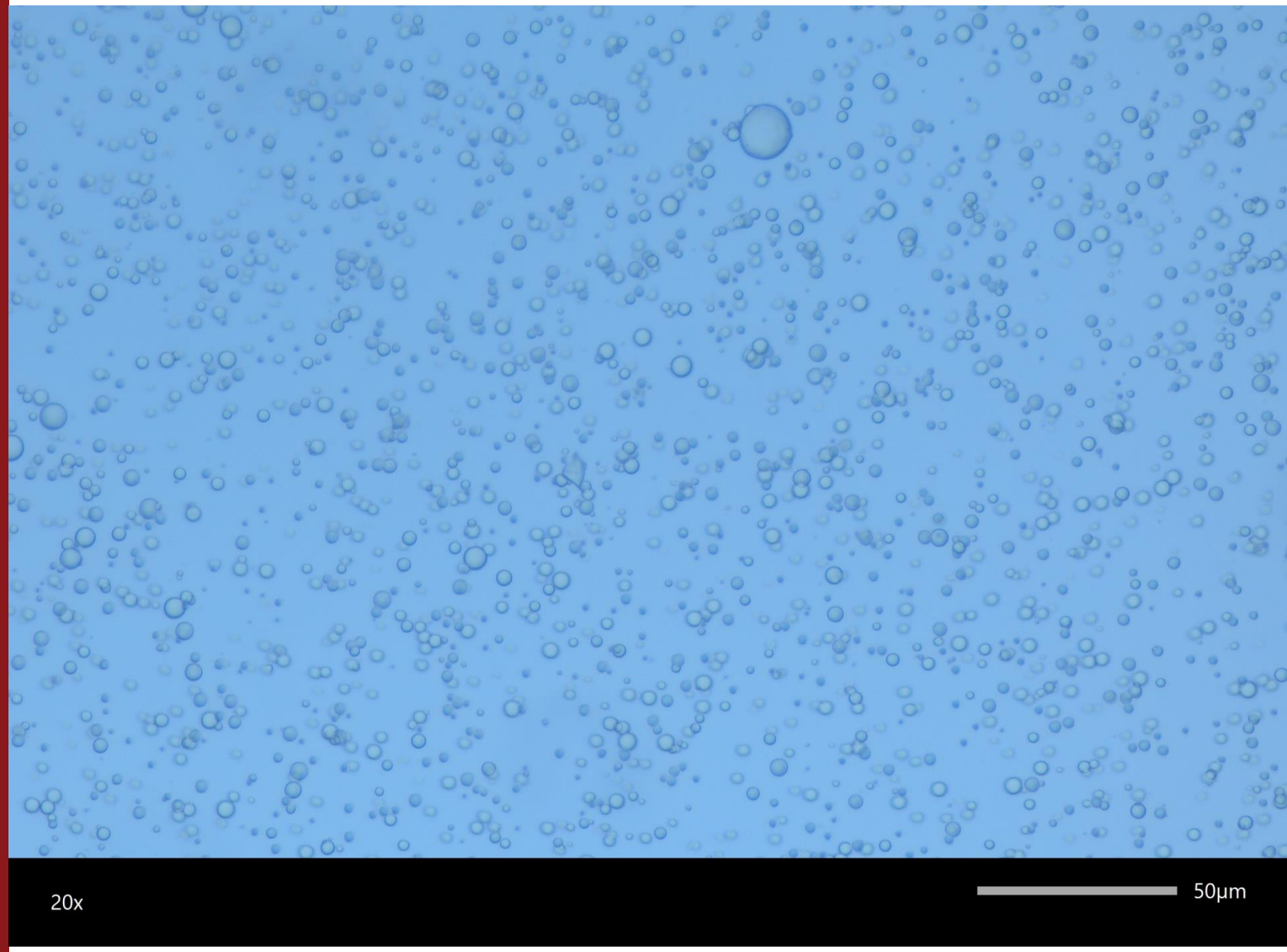
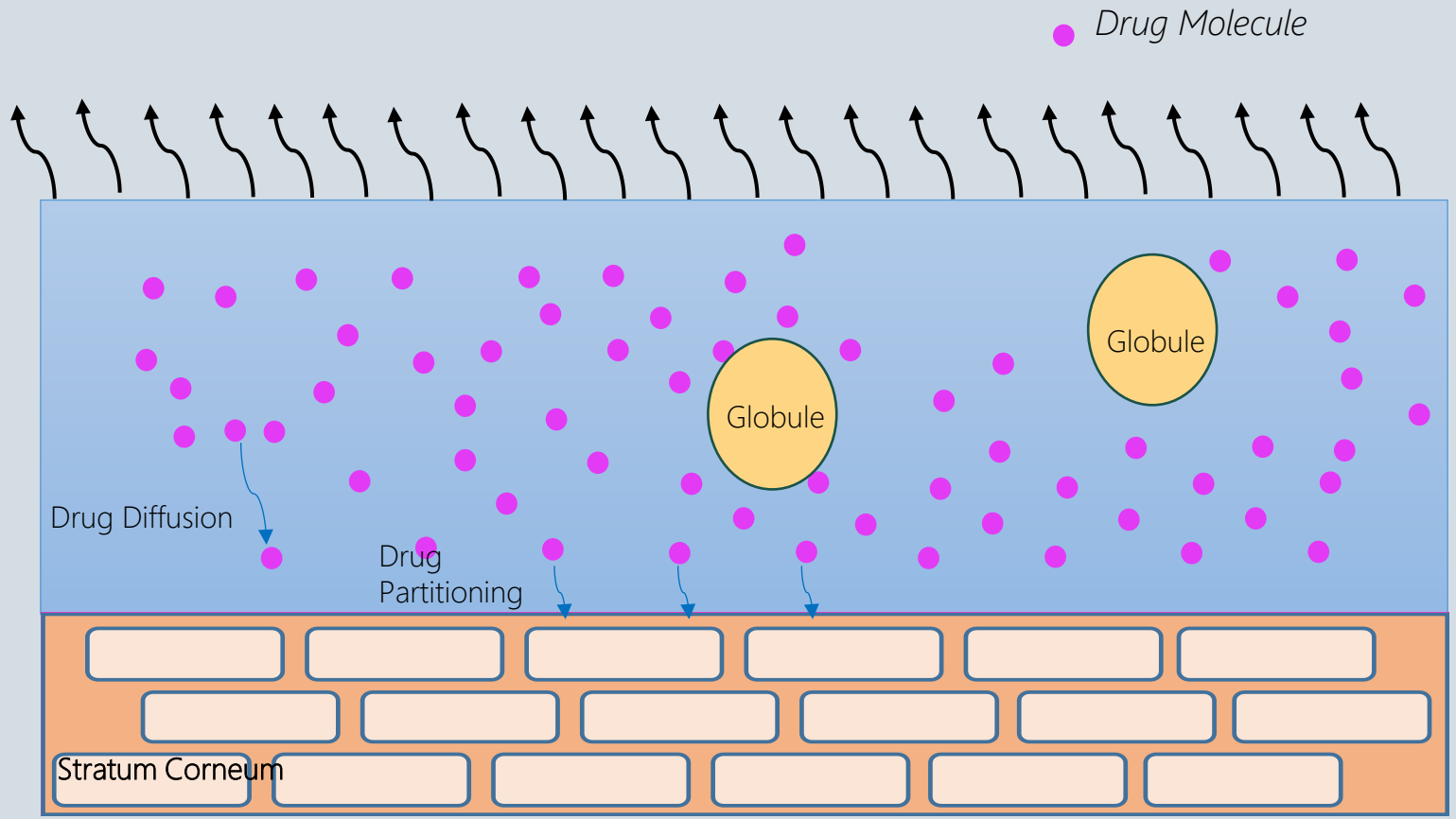


Image by Topical Product Testing LLC (Dr Murthy)

Topicort Gel

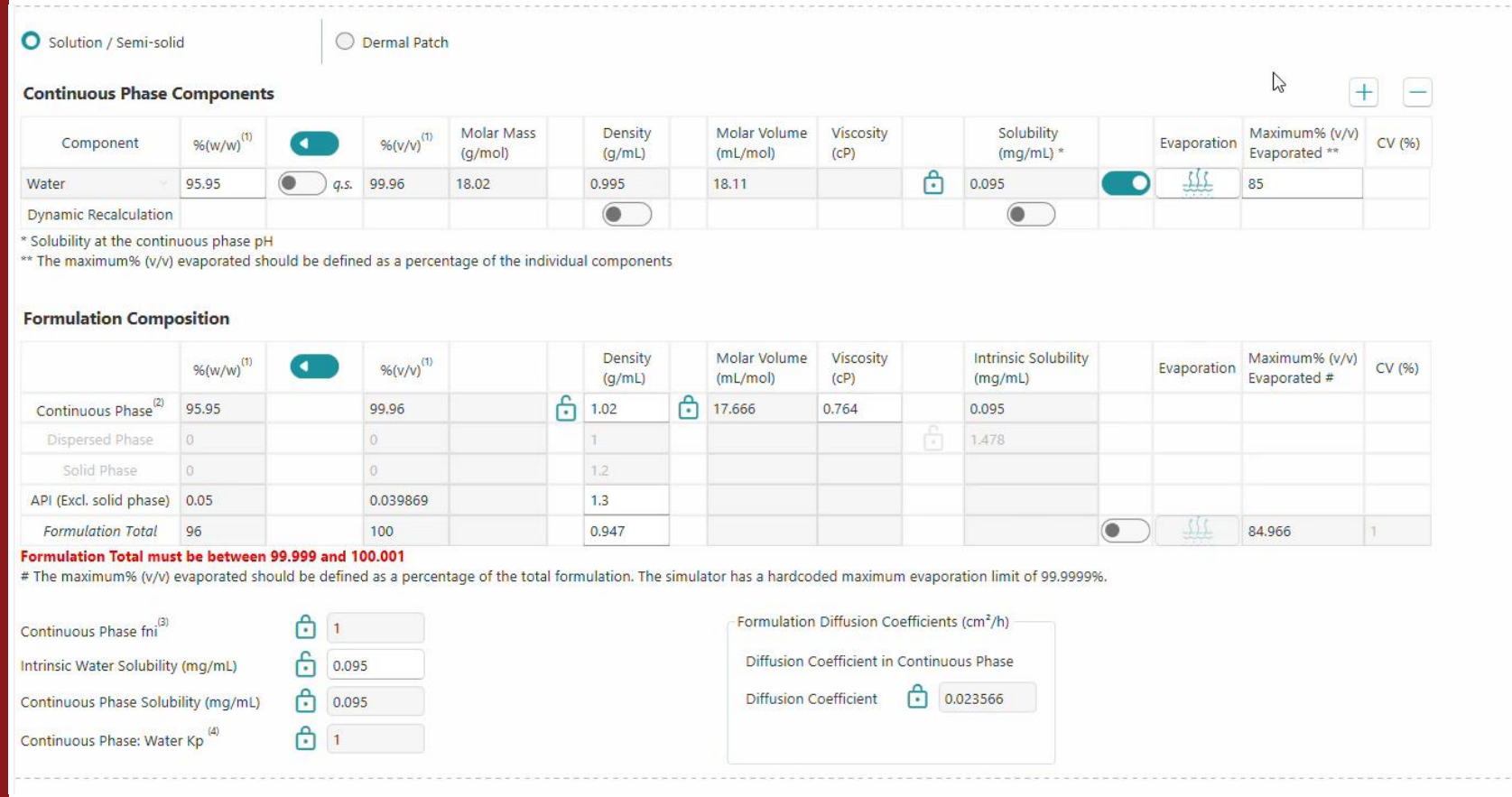
Emulsion

Isopropyl Myristate is the dispersed phase



Topicort Gel

Composition	% w/w
SDAG -3 95% Alcohol	20
Water	q.s.

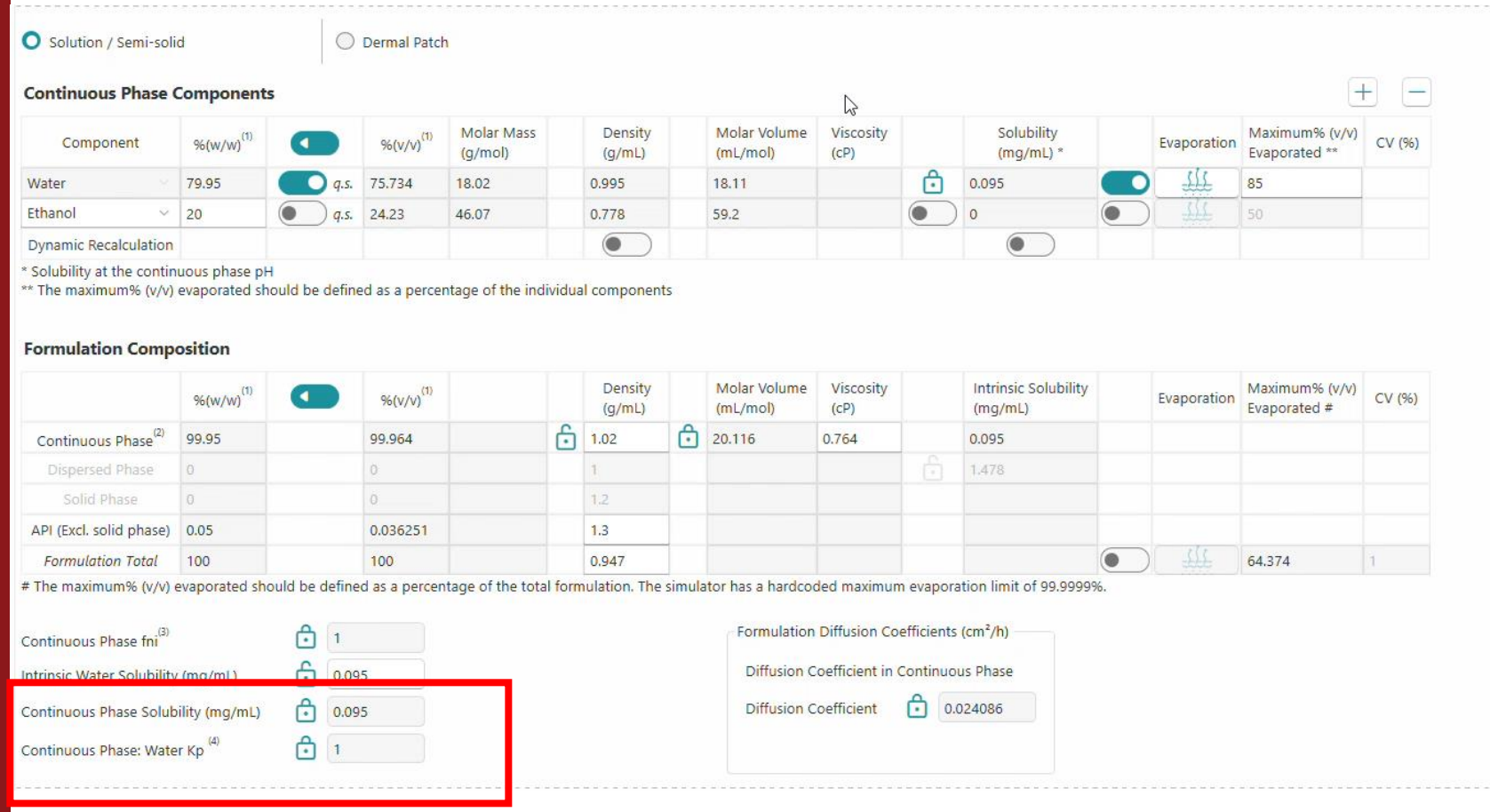


Topicort Gel

Composition	% w/w
SDAG -3 95% Alcohol	20
Water	q.s.

	Desoximetasone
Solubility in IPM	1.478 mg/ml
Solubility in Ethanol	122 mg/ml

Solubility data measured by Topical Product Testing LLC (Dr Murthy)



Solution / Semi-solid | Dermal Patch

Continuous Phase Components

Component	%(w/w)[1]		%(v/v)[1]	Molar Mass (g/mol)	Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Solubility (mg/mL) *	Evaporation	Maximum% (v/v) Evaporated **	CV (%)
Water	79.95	q.s.	75.734	18.02	0.995	18.11		0.095		85	
Ethanol	20	q.s.	24.23	46.07	0.778	59.2		0		50	
Dynamic Recalculation											

* Solubility at the continuous phase pH
** The maximum% (v/v) evaporated should be defined as a percentage of the individual components

Formulation Composition

	%(w/w)[1]		%(v/v)[1]	Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Intrinsic Solubility (mg/mL)	Evaporation	Maximum% (v/v) Evaporated #	CV (%)
Continuous Phase[2]	99.95		99.964	1.02	20.116	0.764	0.095			
Dispersed Phase	0		0	1			1.478			
Solid Phase	0		0	1.2						
API (Excl. solid phase)	0.05		0.036251	1.3						
Formulation Total	100		100	0.947					64.374	1

The maximum% (v/v) evaporated should be defined as a percentage of the total formulation. The simulator has a hardcoded maximum evaporation limit of 99.9999%.

Continuous Phase fni[3]	1
Intrinsic Water Solubility (mg/mL)	0.095
Continuous Phase Solubility (mg/mL)	0.095
Continuous Phase: Water Kp[4]	1

Formulation Diffusion Coefficients (cm²/h)

Diffusion Coefficient in Continuous Phase	
Diffusion Coefficient	0.024086

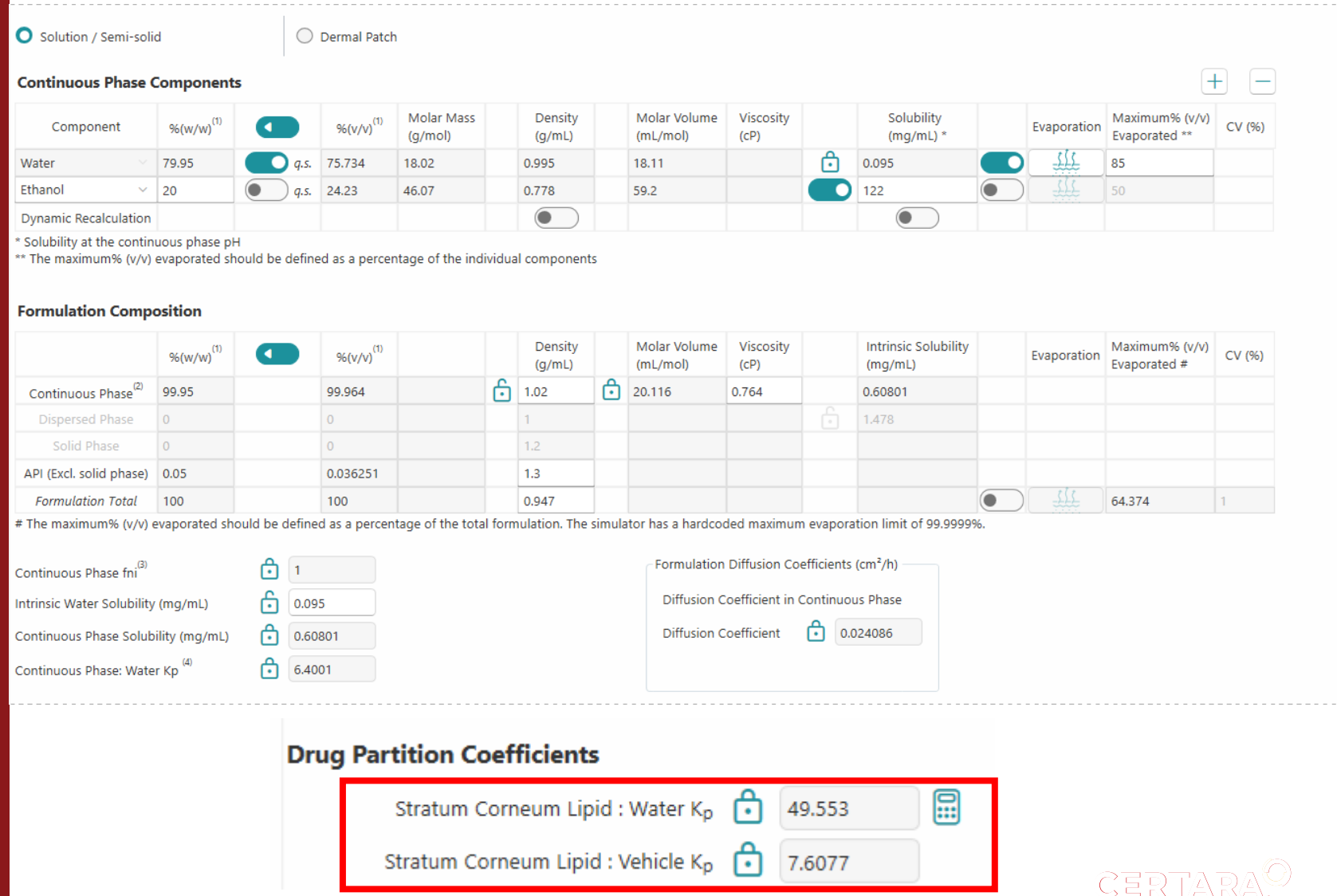
Topicort Gel

Composition	% w/w
SDAG -3 95% Alcohol	20
Water	q.s.

This solubility is now sufficient to dissolve the entire 0.05% DSM

	Desoximetasone
Solubility in IPM	1.478 mg/ml
Solubility in Ethanol	122 mg/ml

Solubility data measured by Topical Product Testing LLC (Dr Murthy)



Solution / Semi-solid | Dermal Patch

Continuous Phase Components

Component	%(w/w)[1]		%(v/v)[1]	Molar Mass (g/mol)	Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Solubility (mg/mL) *	Evaporation	Maximum% (v/v) Evaporated **	CV (%)
Water	79.95	q.s.	75.734	18.02	0.995	18.11		0.095		85	
Ethanol	20	q.s.	24.23	46.07	0.778	59.2		122		50	
Dynamic Recalculation											

* Solubility at the continuous phase pH
** The maximum% (v/v) evaporated should be defined as a percentage of the individual components

Formulation Composition

	%(w/w)[1]		%(v/v)[1]		Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Intrinsic Solubility (mg/mL)	Evaporation	Maximum% (v/v) Evaporated #	CV (%)
Continuous Phase[2]	99.95		99.964		1.02	20.116	0.764	0.60801			
Dispersed Phase	0		0		1			1.478			
Solid Phase	0		0		1.2						
API (Excl. solid phase)	0.05		0.036251		1.3						
Formulation Total	100		100		0.947					64.374	1

\# The maximum% (v/v) evaporated should be defined as a percentage of the total formulation. The simulator has a hardcoded maximum evaporation limit of 99.9999%.

Continuous Phase fni[3] 1
Intrinsic Water Solubility (mg/mL) 0.095
Continuous Phase Solubility (mg/mL) 0.60801
Continuous Phase: Water Kp[4] 6.4001

Formulation Diffusion Coefficients (cm²/h)
Diffusion Coefficient in Continuous Phase
Diffusion Coefficient 0.024086

Drug Partition Coefficients

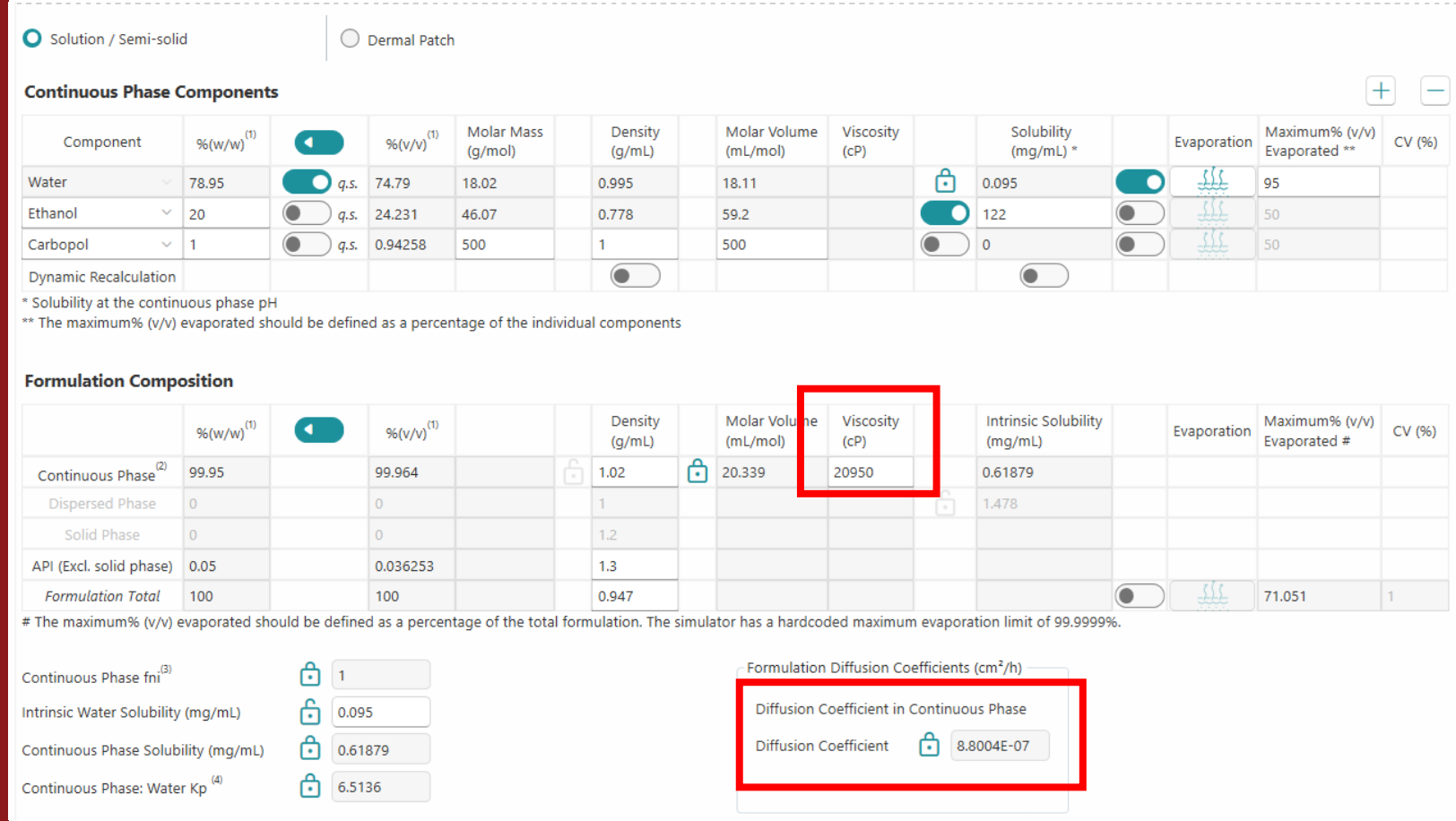
Stratum Corneum Lipid : Water K_p 49.553
Stratum Corneum Lipid : Vehicle K_p 7.6077

Topicort Gel

Composition	% w/w
Carbopol	1
SDAG -3 95% Alcohol	20
Water	q.s.

	Desoximetasone
Viscosity (low shear rate)	20 950 cP

Viscosity data measured by Topical Product Testing LLC (Dr Murthy)



Solution / Semi-solid | Dermal Patch

Continuous Phase Components

Component	%(w/w)[1]		%(v/v)[1]	Molar Mass (g/mol)	Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)		Solubility (mg/mL) *		Evaporation	Maximum% (v/v) Evaporated **	CV (%)
Water	78.95	q.s.	74.79	18.02	0.995	18.11			0.095			95	
Ethanol	20	q.s.	24.231	46.07	0.778	59.2			122			50	
Carbopol	1	q.s.	0.94258	500	1	500			0			50	
Dynamic Recalculation													

* Solubility at the continuous phase pH

** The maximum% (v/v) evaporated should be defined as a percentage of the individual components

Formulation Composition

	%(w/w)[1]		%(v/v)[1]		Density (g/mL)		Molar Volume (mL/mol)	Viscosity (cP)		Intrinsic Solubility (mg/mL)		Evaporation	Maximum% (v/v) Evaporated #	CV (%)
Continuous Phase[2]	99.95		99.964		1.02		20.339	20950		0.61879				
Dispersed Phase	0		0		1					1.478				
Solid Phase	0		0		1.2									
API (Excl. solid phase)	0.05		0.036253		1.3									
Formulation Total	100		100		0.947								71.051	1

\# The maximum% (v/v) evaporated should be defined as a percentage of the total formulation. The simulator has a hardcoded maximum evaporation limit of 99.9999%.

Continuous Phase fni[3]	1
Intrinsic Water Solubility (mg/mL)	0.095
Continuous Phase Solubility (mg/mL)	0.61879
Continuous Phase: Water Kp[4]	6.5136

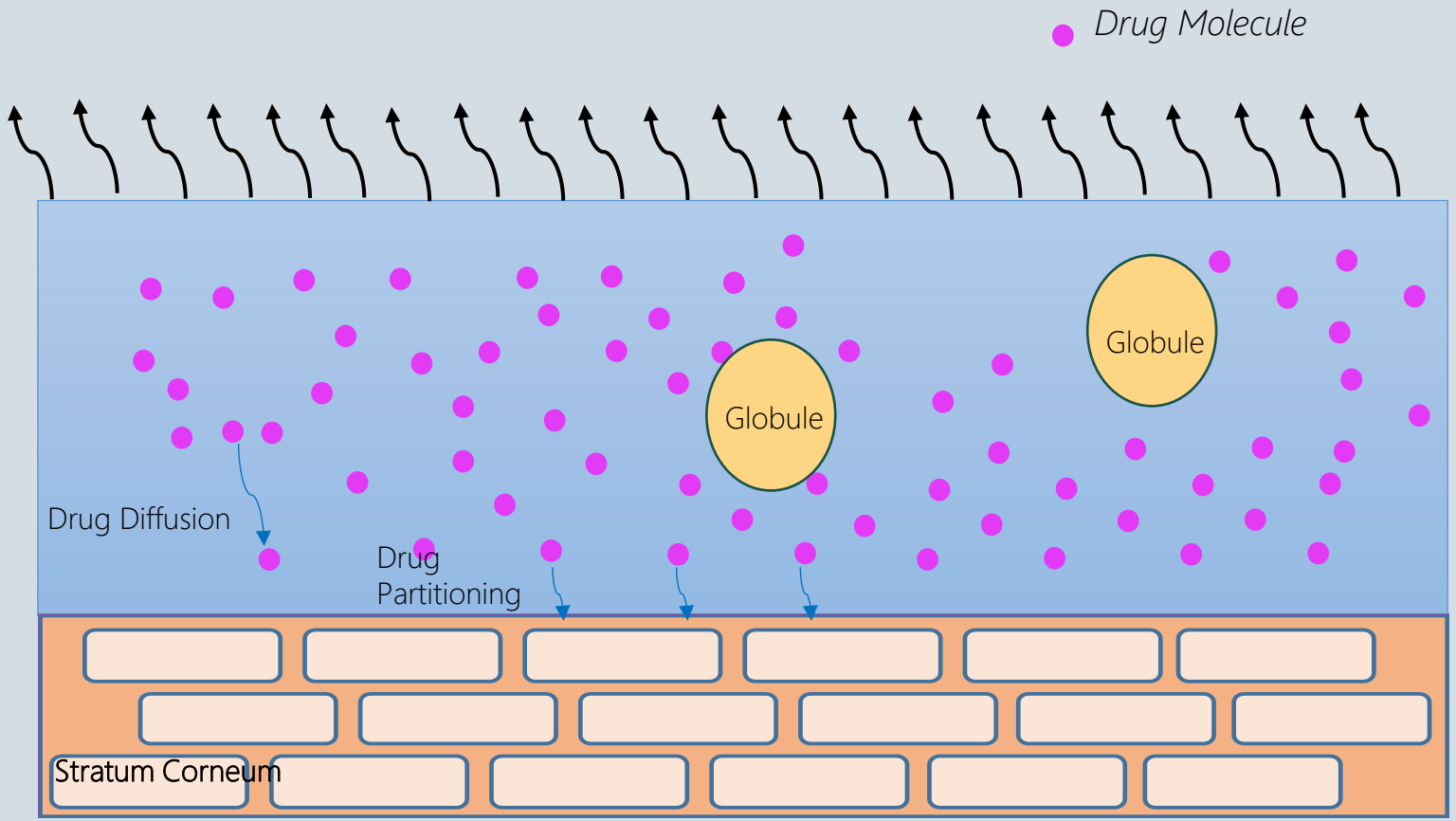
Formulation Diffusion Coefficients (cm²/h)

Diffusion Coefficient in Continuous Phase

Diffusion Coefficient 8.8004E-07

Topicort Gel

Composition	% w/w
IPM	4
Carbopol	1
SDAG -3 95% Alcohol	20
Water	q.s.

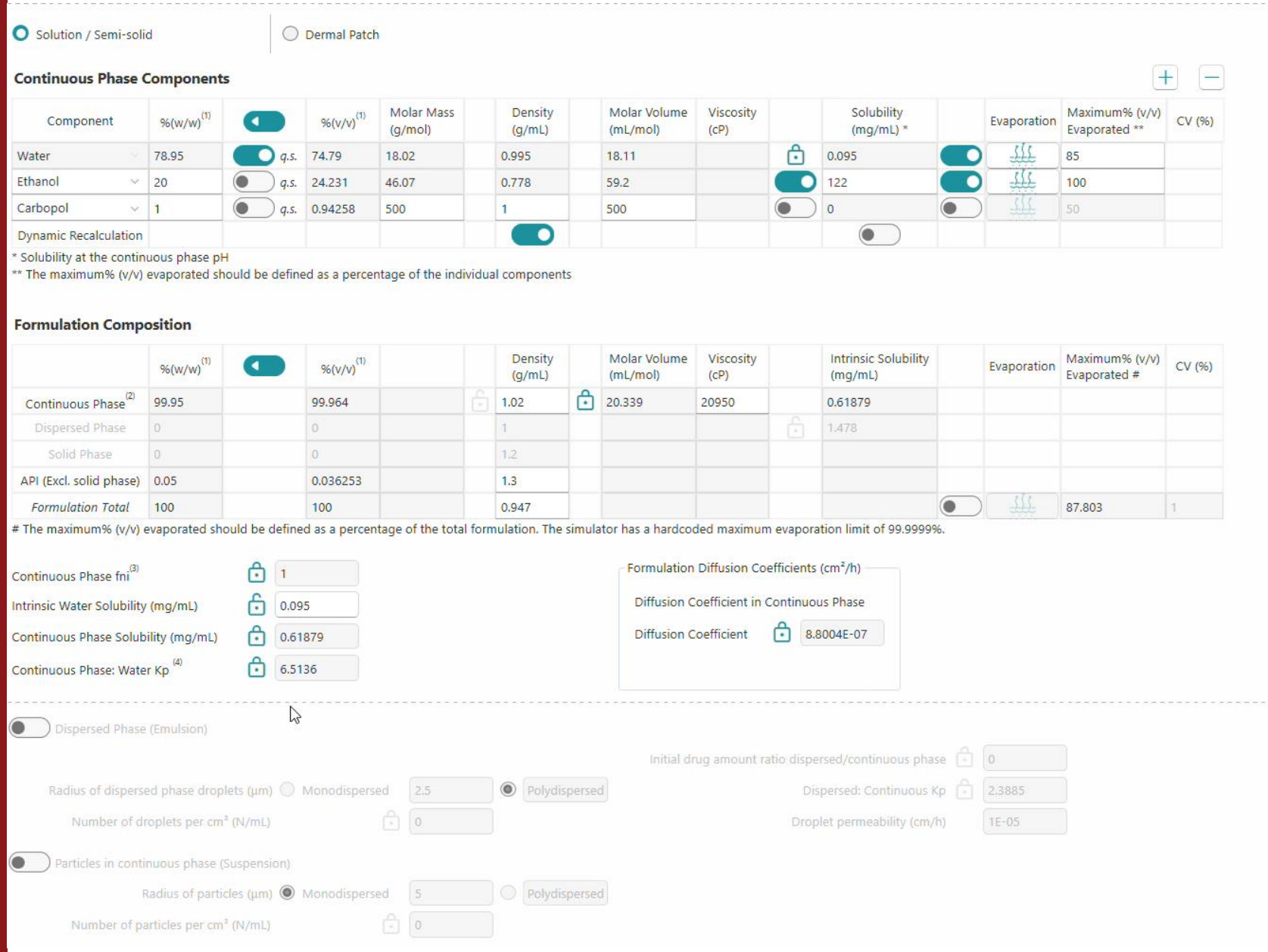


Topicort Gel

Composition	% w/w
Isopropyl myristate	**4**
Carbopol	1
SDAG -3 95% Alcohol	20
Water	q.s.

Adding in the Dispersed Phase

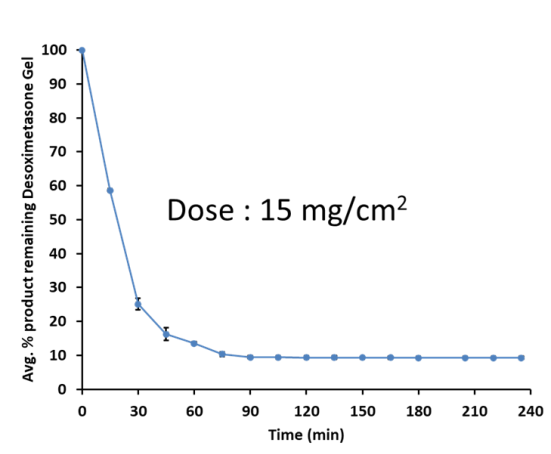
Desoximetasone gel(0.05%)	Diameter (um)		
	D10	D50	D 90
	1.8	2.5	3.4



Topicort Gel

Composition	% w/w
IPM	4
Carbopol	1
SDAG -3 95% Alcohol	20
Water	q.s.

Loss on drying data added to "Formulation Total"



Evaporation data measured by Topical Product Testing LLC (Dr Murthy)

Solution / Semi-solid | Dermal Patch

Continuous Phase Components

Component	%(w/w)[1]		%(v/v)[1]	Molar Mass (g/mol)	Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Solubility (mg/mL) *	Evaporation	Maximum% (v/v) Evaporated **	CV (%)
Water	74.95	q.s.	71.015	18.02	0.995	18.11		0.095		85	
Ethanol	20	q.s.	24.235	46.07	0.778	59.2		122		100	
Carbopol	1	q.s.	0.94276	500	1	500		0		50	
Dynamic Recalculation											

* Solubility at the continuous phase pH
** The maximum% (v/v) evaporated should be defined as a percentage of the individual components

Formulation Composition

	%(w/w)[1]		%(v/v)[1]		Density (g/mL)	Molar Volume (mL/mol)	Viscosity (cP)	Intrinsic Solubility (mg/mL)	Evaporation	Maximum% (v/v) Evaporated #	CV (%)
Continuous Phase[2]	95.95		96.193		1.02	20.468	20950	0.66617			
Dispersed Phase	4		3.771		1			1.478			
Solid Phase	0		0		1.2						
API (Excl. solid phase)	0.05		0.03626		1.3						
Formulation Total	100		100		0.947					0	1

The maximum% (v/v) evaporated should be defined as a percentage of the total formulation. The simulator has a hardcoded maximum evaporation limit of 99.9999%.

Continuous Phase fni[3]: 1
Intrinsic Water Solubility (mg/mL): 0.095
Continuous Phase Solubility (mg/mL): 0.66617
Continuous Phase: Water Kp[4]: 7.0123

Formulation Diffusion Coefficients (cm²/h)
Diffusion Coefficient in Continuous Phase
Diffusion Coefficient: 8.8101E-07

Dispersed Phase (Emulsion)

Initial drug amount ratio dispersed/continuous phase: 0.086945
Radius of dispersed phase droplets (µm): Monodispersed 2.5 Polydispersed
Dispersed: Continuous Kp: 2.2187
Number of droplets per cm³ (N/mL): 4.1658E+09
Droplet permeability (cm/h): 1E-05

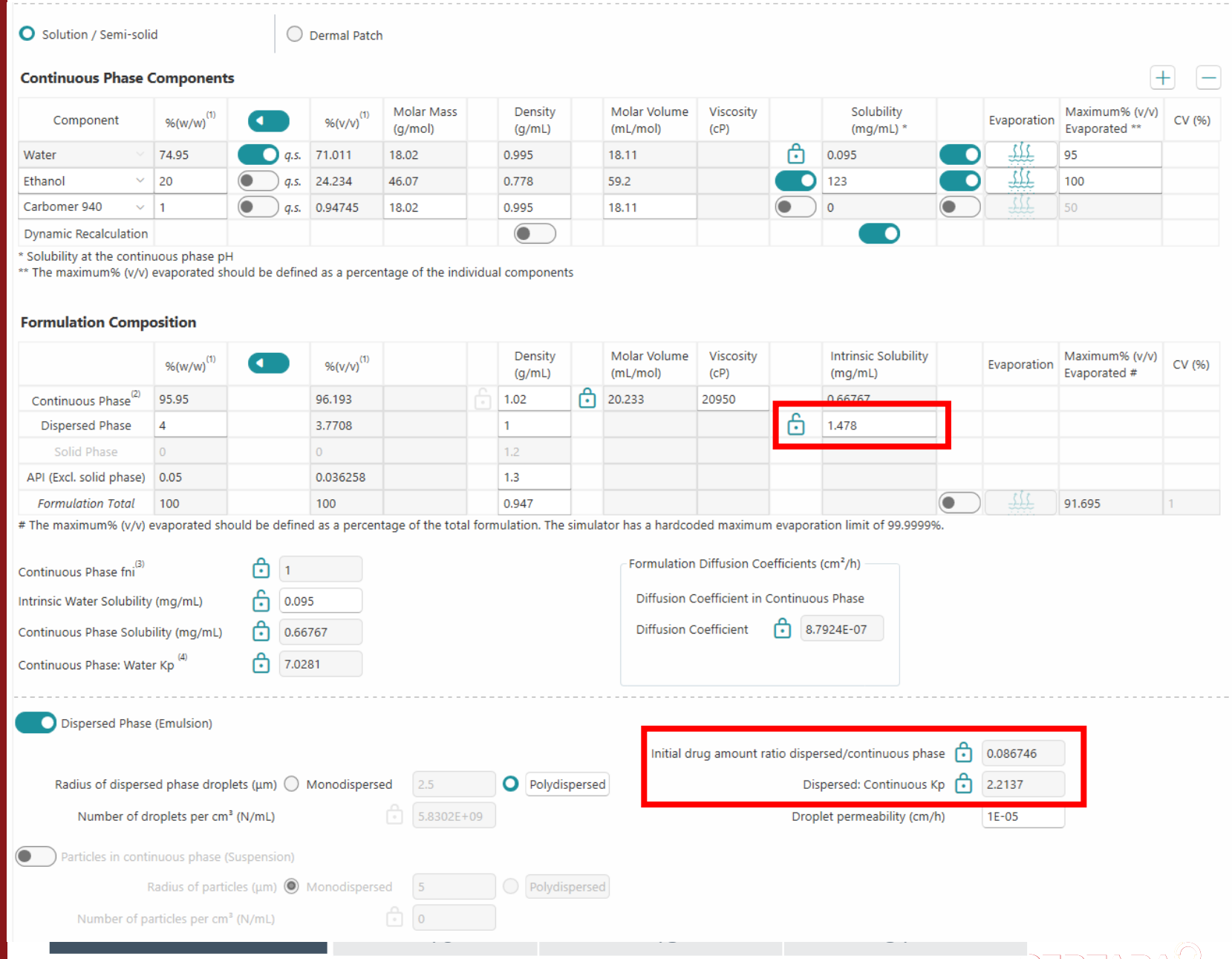
Topicort Gel

Emulsion

Isopropyl Myristate is the dispersed phase

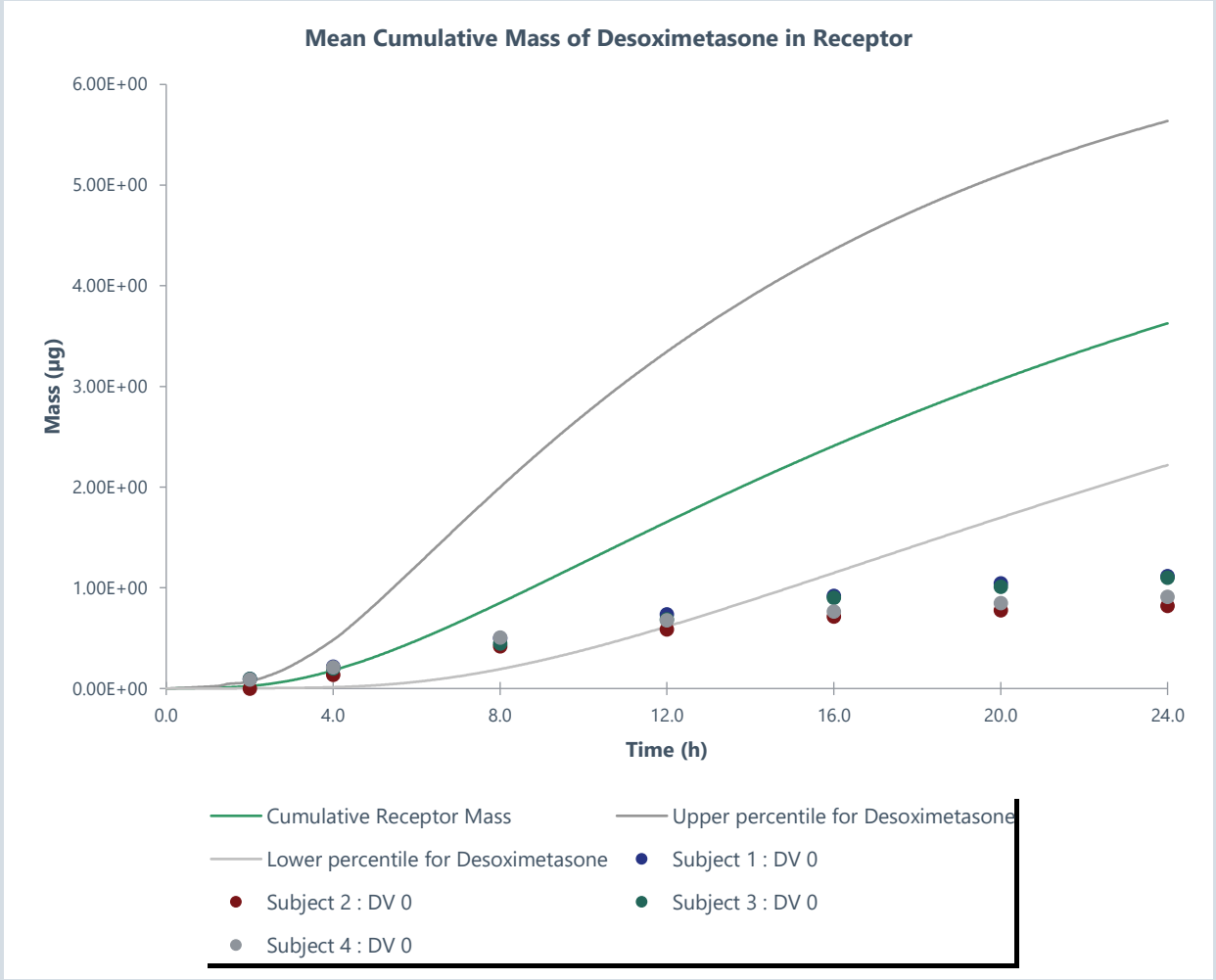
	Desoximetasone Gel (0.05%)
Density	1.02±0.002
pH	5.82±0.0015
Solubility in IPM	1.478 mg/ml
Solubility in Ethanol	122 mg/ml

Q3 Parameters measured by Topical Product Testing LLC (Dr Murthy)



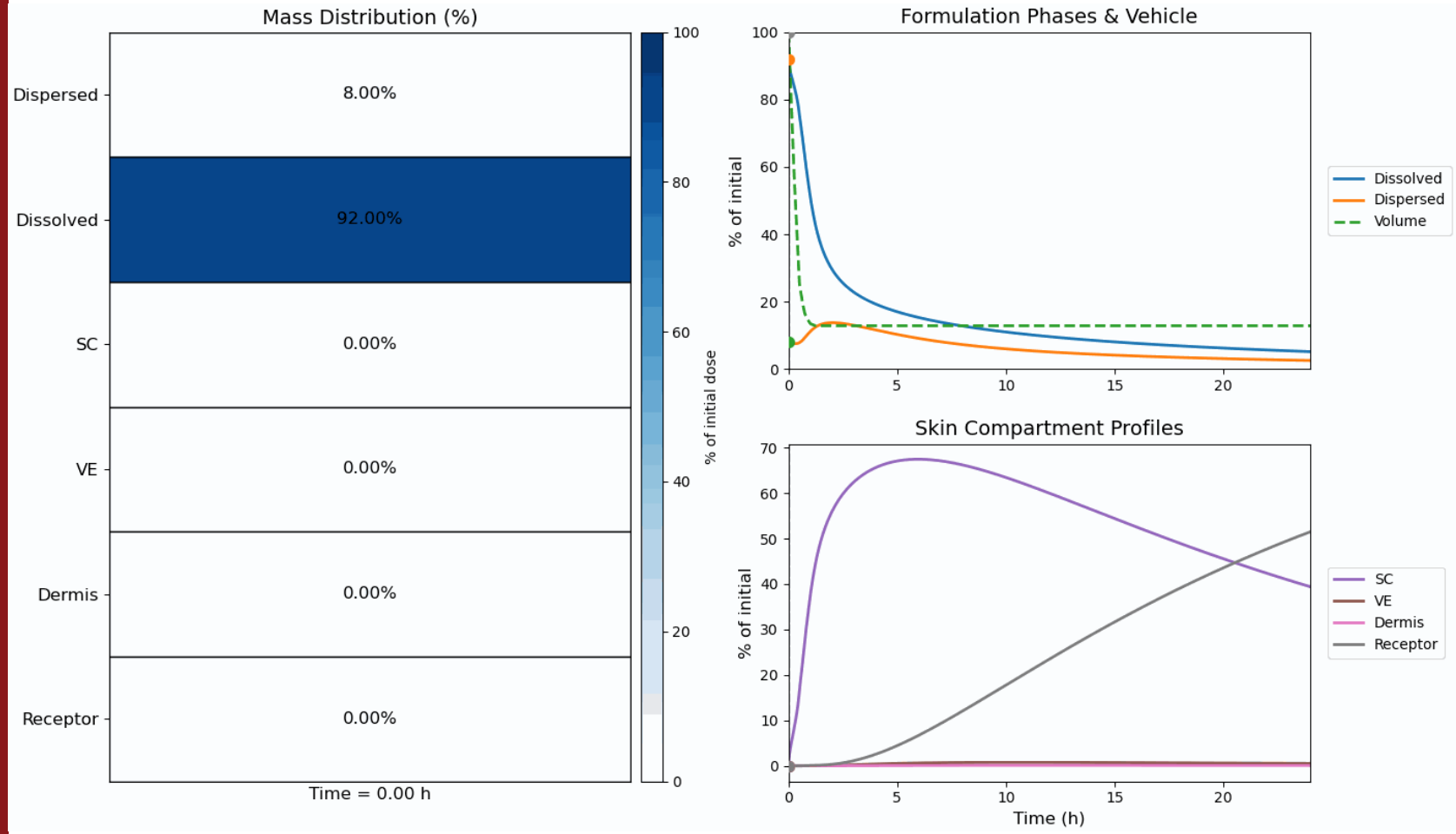
Topicort Gel

Receptor profiles are still over predicted



Topicort Gel

Receptor profiles are still over predicted

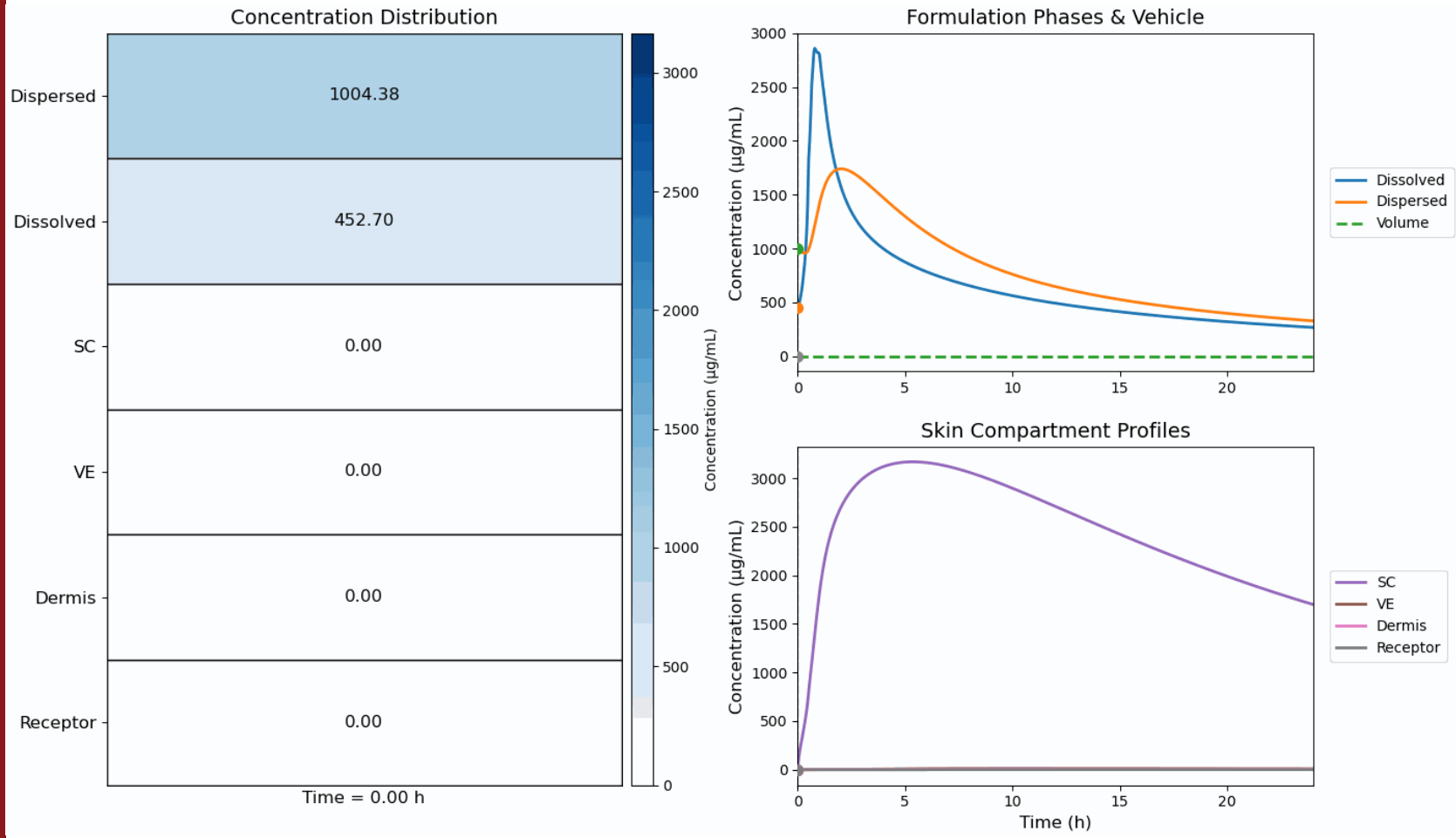


Topicort Gel

Concentration plotted instead of Mass

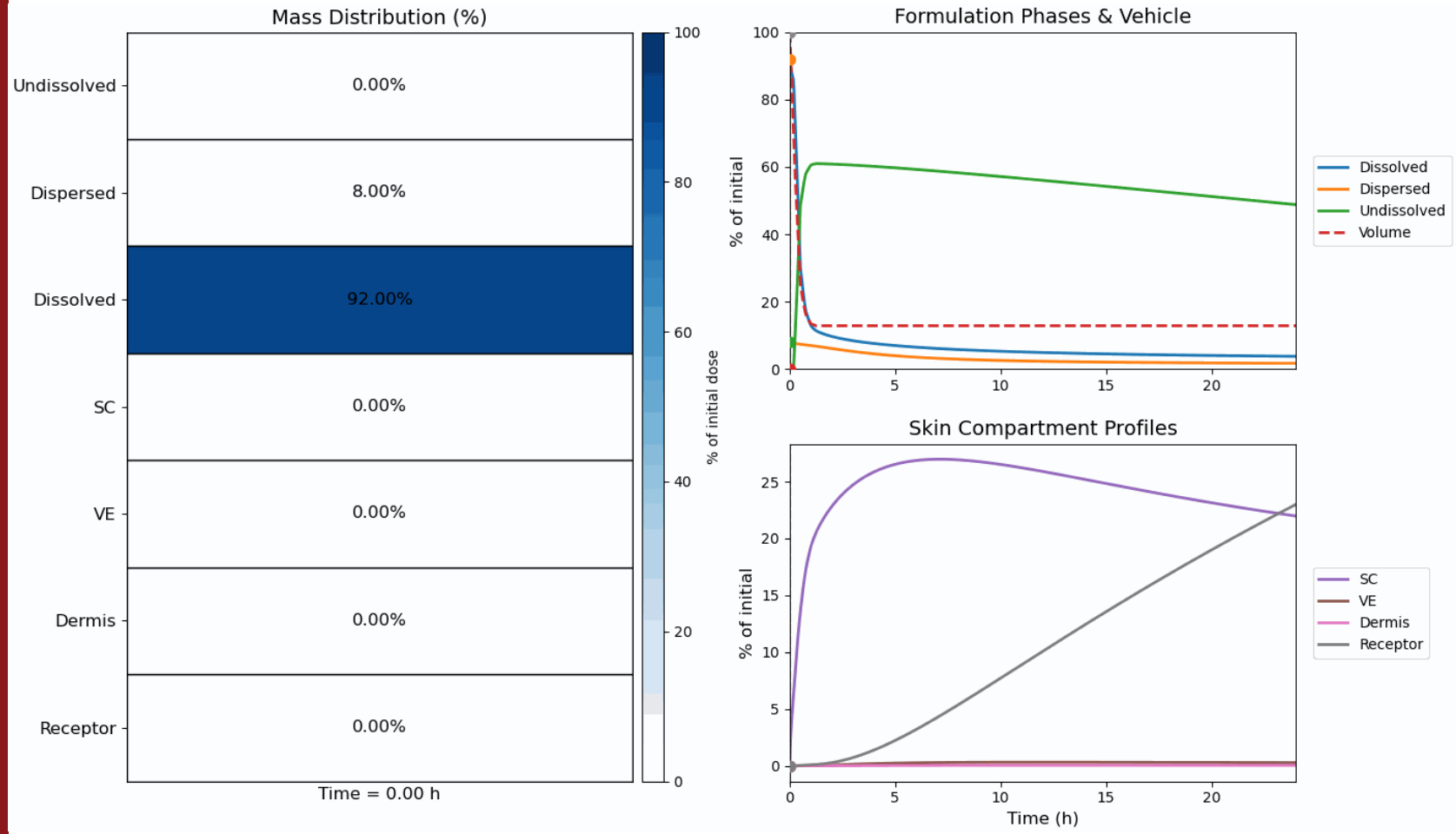
Solubility in 20/80 ethanol water is 0.66 mg/ml

We need to account for precipitation



Topicort Gel

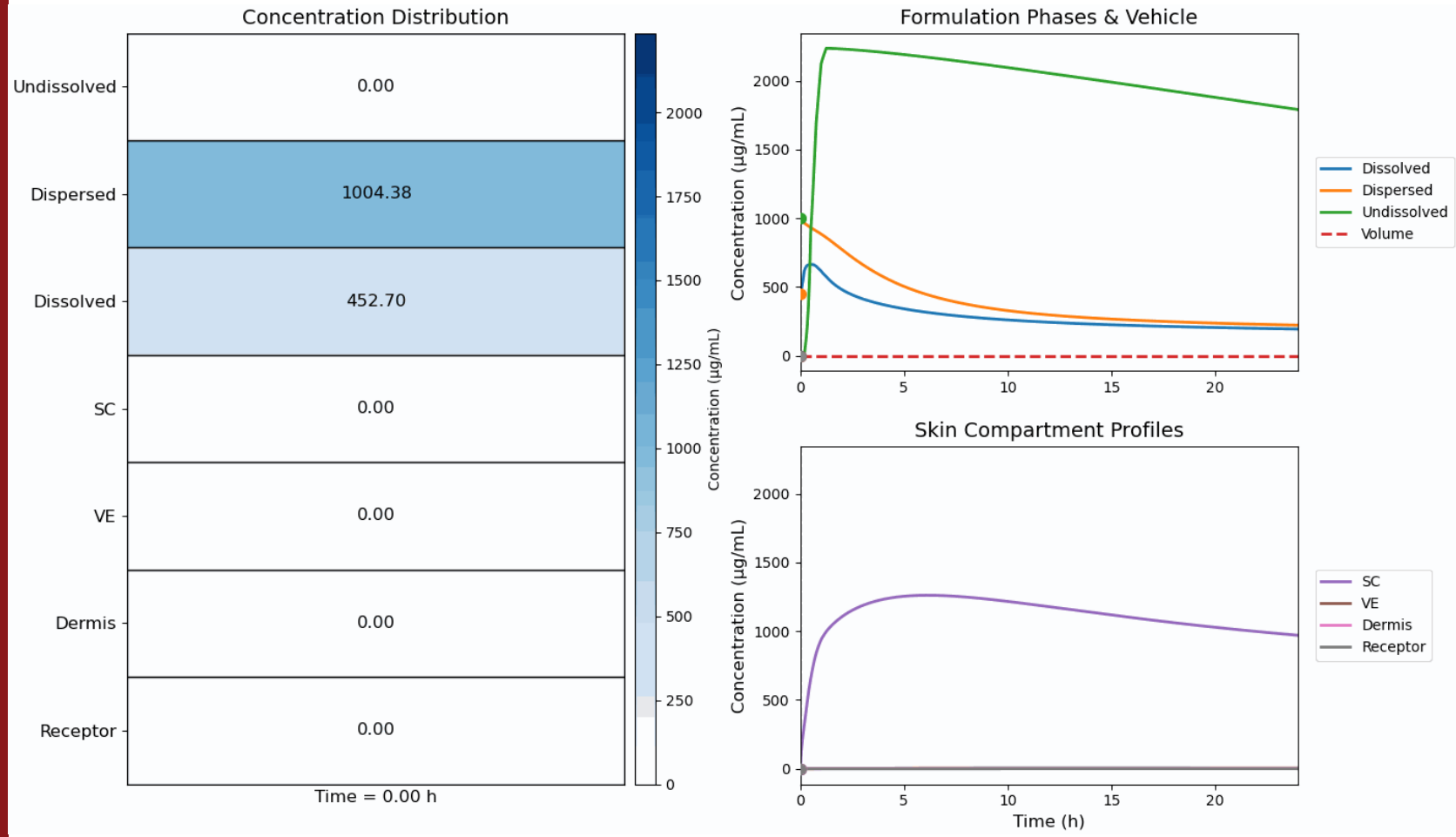
With Precipitation active



Topicort Gel

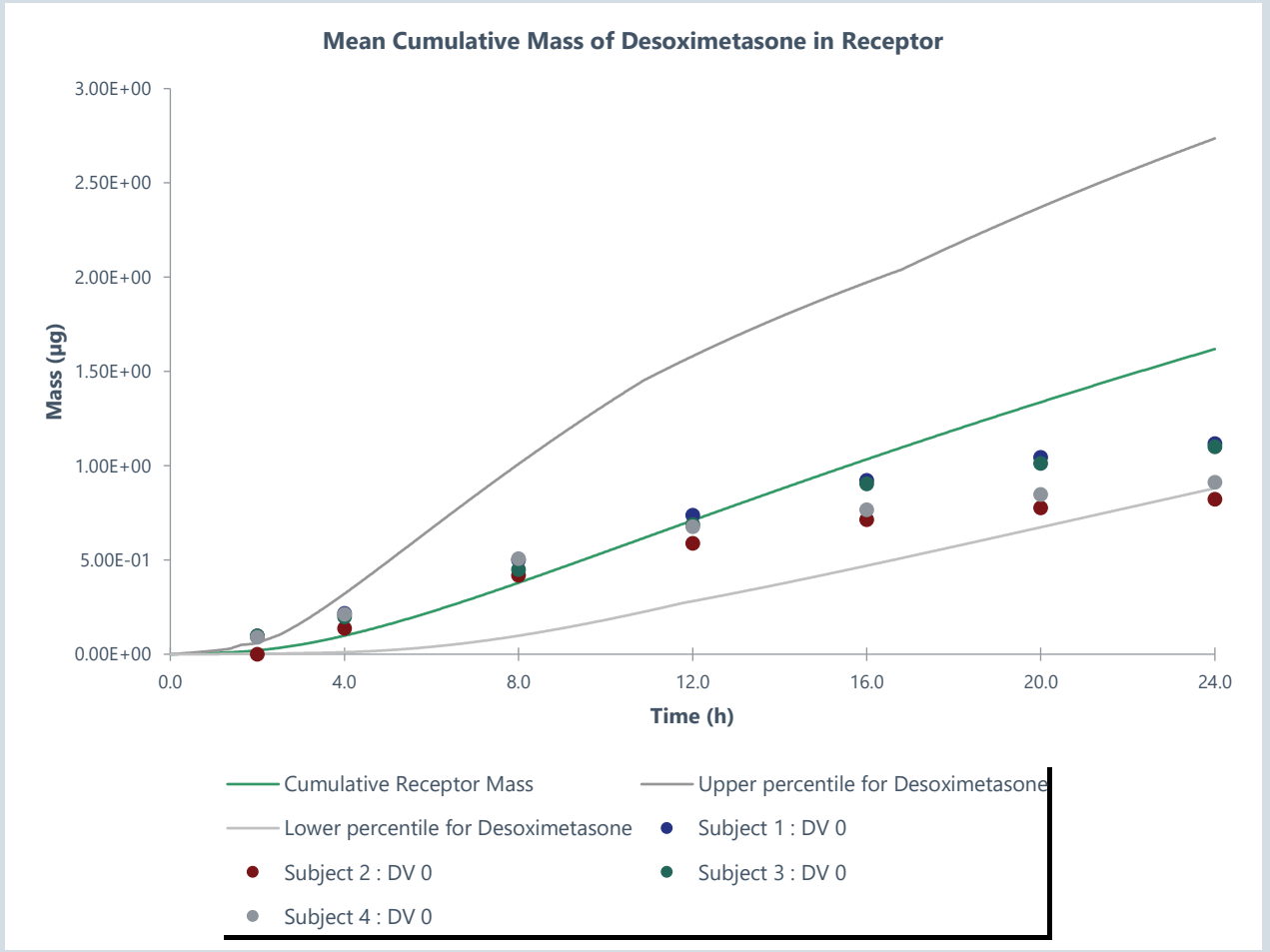
With Precipitation active

Concentrations



Topicort Gel

The results are greatly improved but we are still missing the plateau observed in the IVPT study



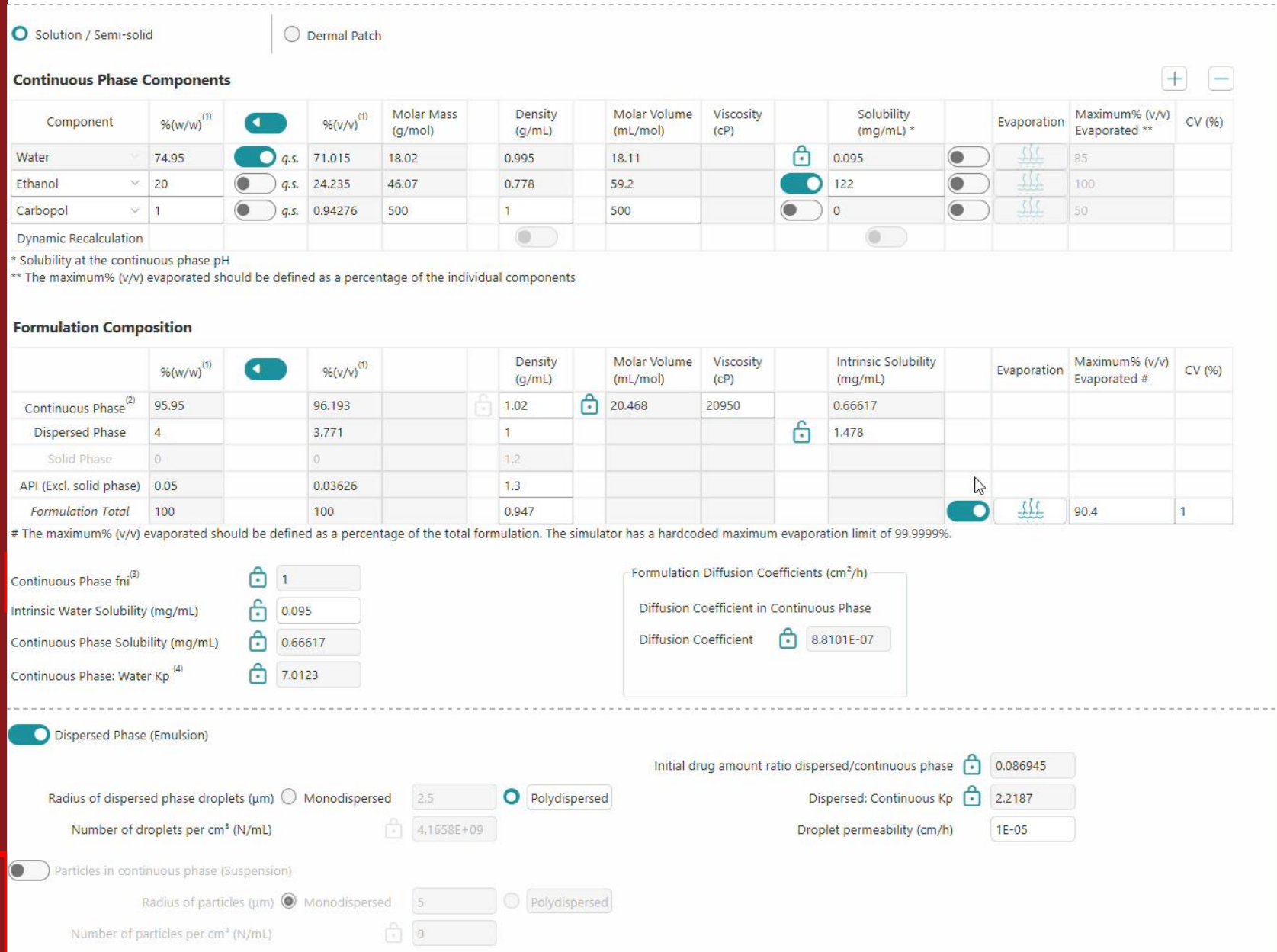
Topicort Gel

Continuous phase Solubility is 0.66 mg/ml

This is for the primary formulation; however, we have a changing composition over time.

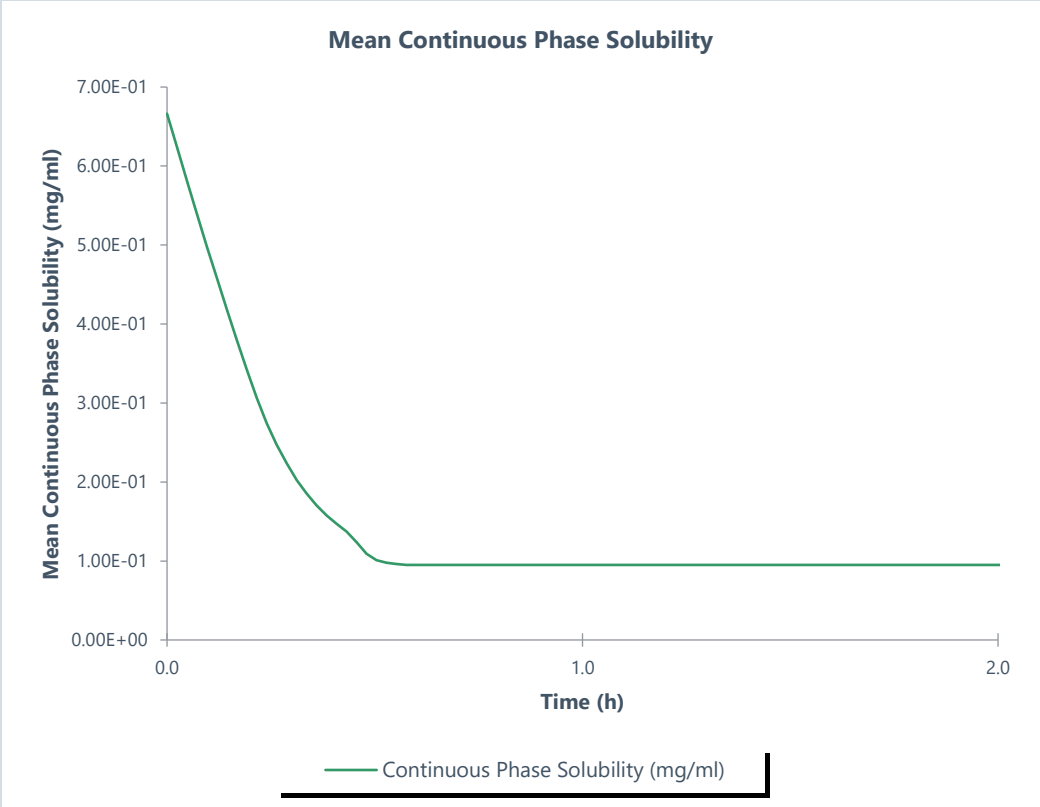
In order to simulate this, we need to define evaporation of individual components

Composition	% w/w
IPM	4
Carbopol	1
SDAG -3 95% Alcohol	20
Water	q.s.



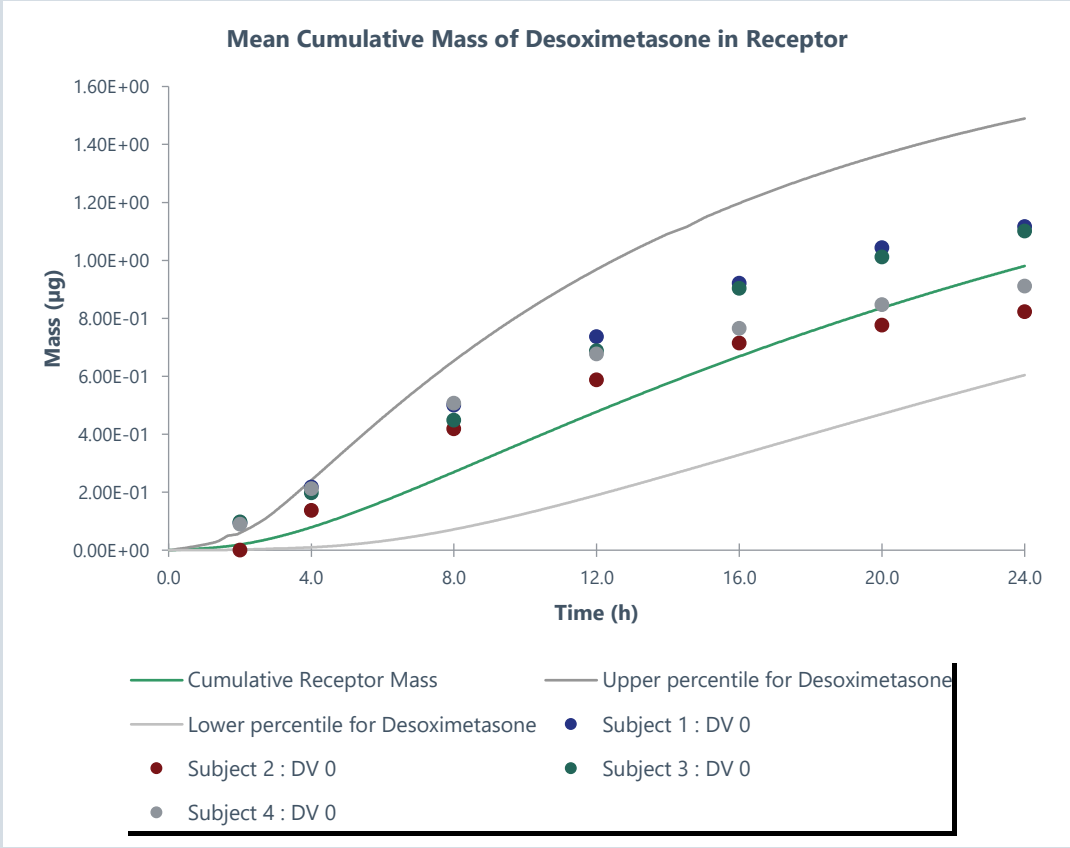
Topicort Gel

With Dynamic Recalculation turned on, the continuous phase solubility changes over time, as ethanol evaporates



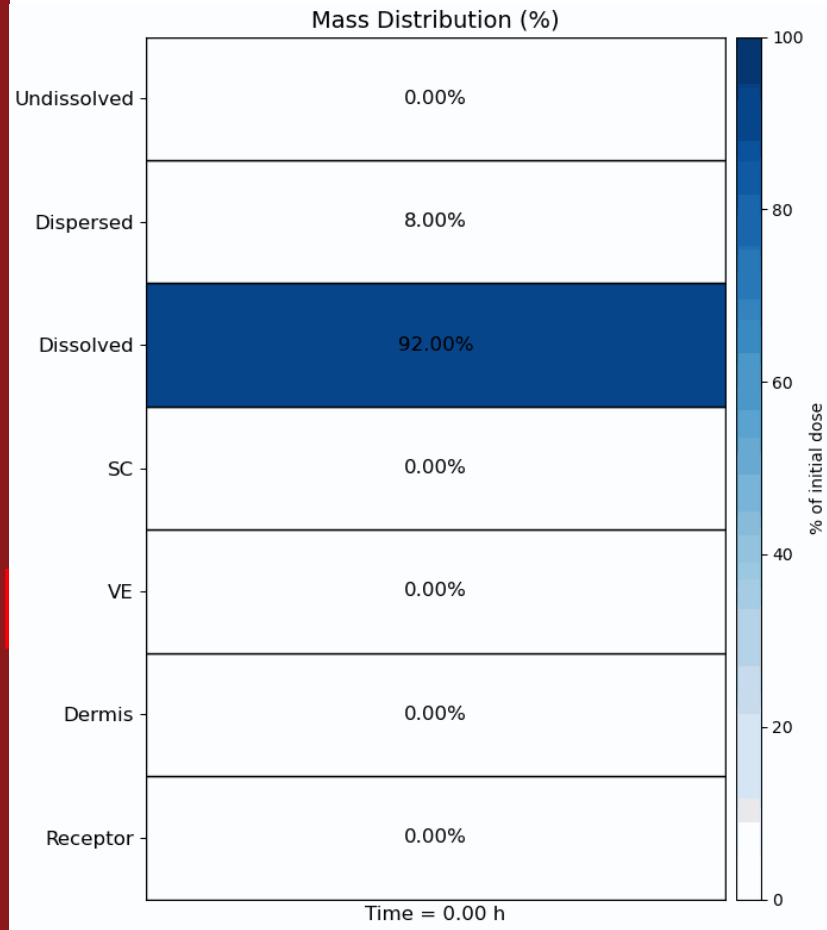
Topicort Gel

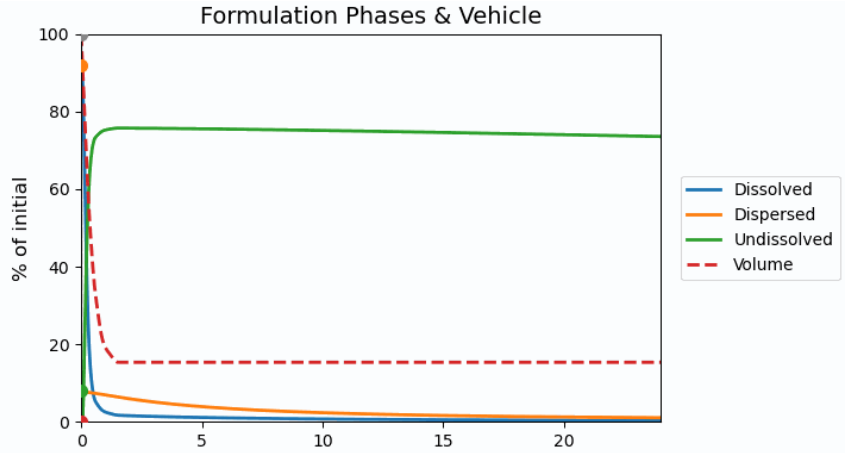
With Dynamic Recalculation turned on, the continuous phase solubility changes over time, as ethanol evaporates

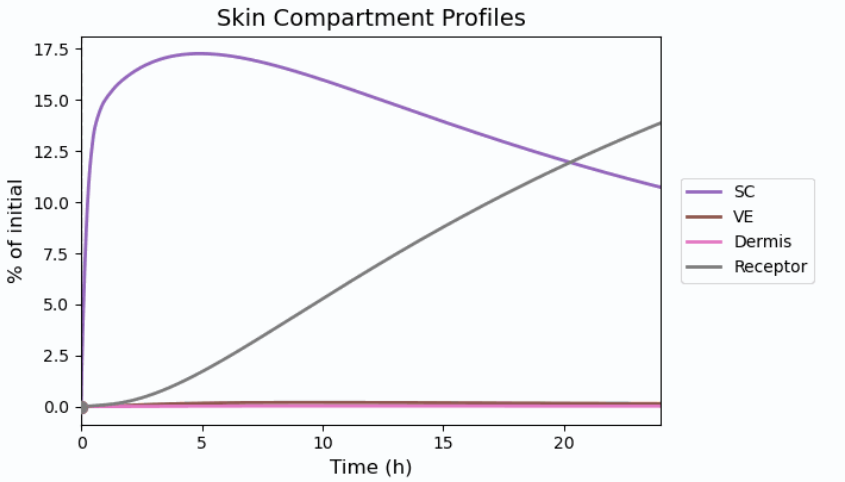


Topicort Gel

Notice the Local amount in the SC is significantly lower







Topicort Gel

Local DSM amount

Compared against skin extracted at the end of the IVPT study

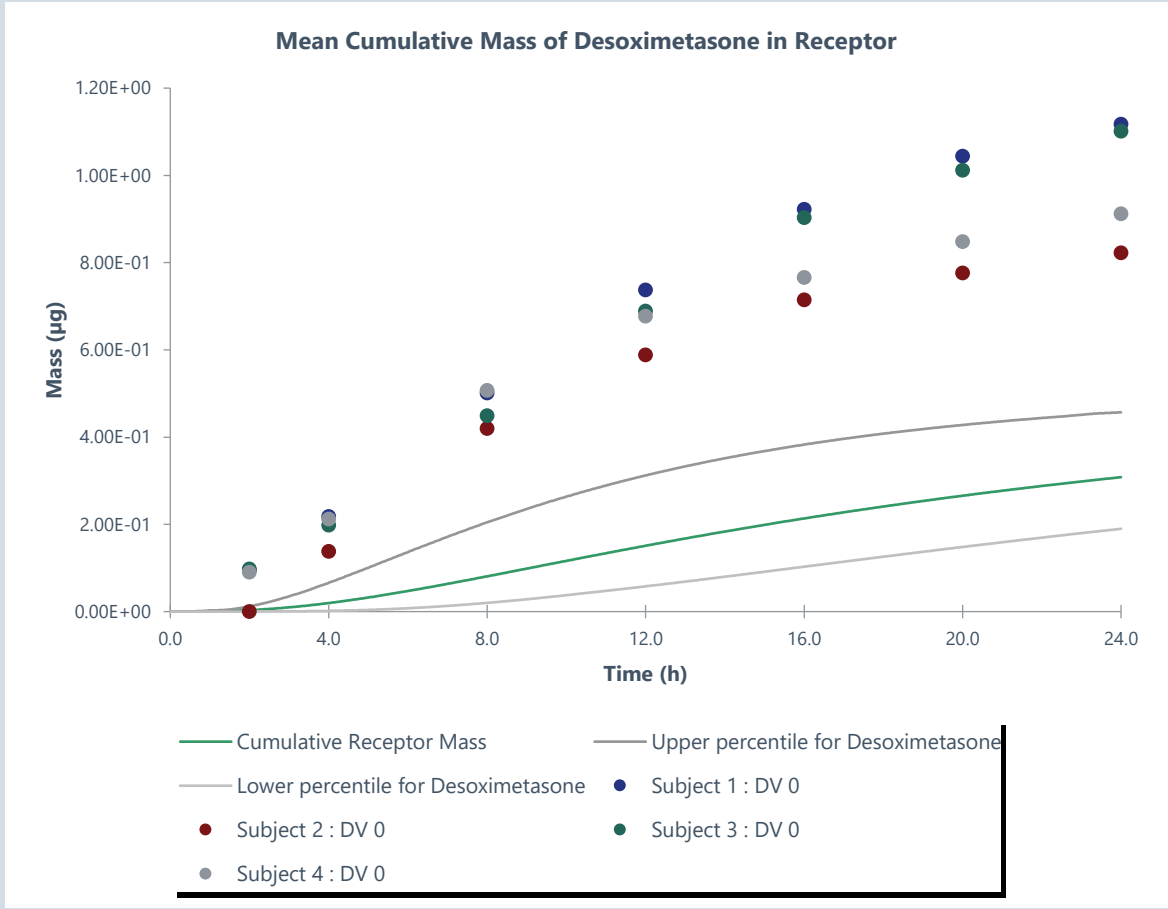
Calculated as amounts in SC + VE + Dermis

Topicort Gel

So was all this necessary?

What would have happened if we just used the tertiary formulation parameters from the start, like for Topicort Spray?

Composition	% w/w
Isopropyl myristate	**4**
Carbopol	50
SDAG -3 95% Alcohol	0
Water	50



Model Utility

What can we use the model for?

- Extrapolate to *in vivo* and predict plasma concentrations

> Mol Pharm. 2022 Sep 5;19(9):3139-3152. doi: 10.1021/acs.molpharmaceut.2c00229. Epub 2022 Aug 15.

Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model

Sumit Arora [1], James Clarke [1], Eleftheria Tsakalozou [2], Priyanka Ghosh [2], Khondoker Alam [2], Jeffery E Grice [3], Michael S Roberts [3 4], Masoud Jamei [1], Sebastian Polak [1 5]

Affiliations + expand

PMID: 35969125 DOI: 10.1021/acs.molpharmaceut.2c00229

- Perform Virtual Maximum Usage Trials

> Int J Pharm. 2025 Jul 16:682:125977. doi: 10.1016/j.ijpharm.2025.125977. Online ahead of print.

Physiologically based pharmacokinetic modelling of in vitro skin permeation of sunscreen actives under various experimental conditions

Yuri Dancik [1], Yanling Zhang [2], Krishna C Telaprolu [2], Sebastian Polak [3]

Affiliations + expand

PMID: 40681065 DOI: 10.1016/j.ijpharm.2025.125977

- Conduct a safe space analysis on various parameters for virtual bioequivalence assessment

- Predict the effect of specific formulation changes, or design new formulations

> Front Pharmacol. 2022 Dec 1:13:1007496. doi: 10.3389/fphar.2022.1007496. eCollection 2022.

A mechanistic physiologically based model to assess the effect of study design and modified physiology on formulation safe space for virtual bioequivalence of dermatological drug products

J F Clarke [1 2], K Thakur [1], S Polak [1 2]

Affiliations + expand

PMID: 36532731 PMCID: PMC9756572 DOI: 10.3389/fphar.2022.1007496

- Extrapolate to different trial designs such as:
  - *Different dose level*
  - *Different body site application*
  - *Diseased population*

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Conclusions

- Demonstrate the state of the art in mechanistic formulation modelling
- Best practices for integrating *in vitro* characterisation data into models
- Show the importance of accounting for formulation dynamics when simulating topical drug products
- In the case of Topicort Gel, accounting for the metamorphosis in the first 2 hours was crucial to capture the rate and extent of absorption
- Demonstrate the utility of mechanistic formulation models for:
  - *Formulation design*
  - *Virtual Bioequivalence*

Acknowledgments

Skin Grants Team

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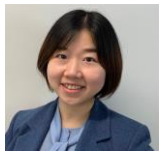

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