Topical Formulations for Dermal and Transdermal Drug Delivery

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The National Academies of
SCIENCES • ENGINEERING • MEDICINE

COMMITTEE TO ASSESS THE AVAILABLE SCIENTIFIC DATA REGARDING THE SAFETY AND EFFECTIVENESS OF INGREDIENTS USED IN COMPOUNDED TOPICAL PAIN CREAMS

Topical Formulations

Solution

Skin

PEG base

Buccal

Gel

Ocular

Jelly

Vaginal

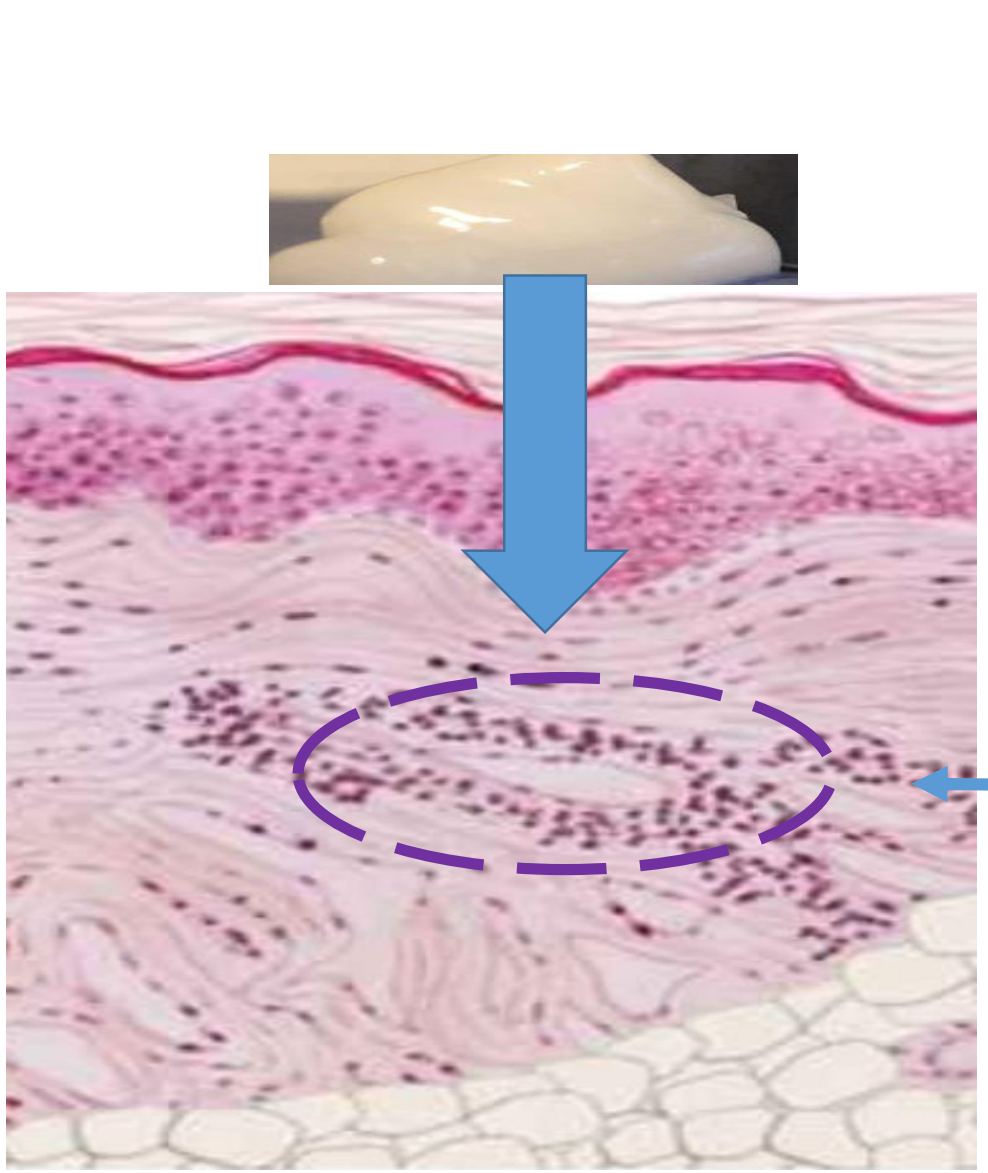
Ointment

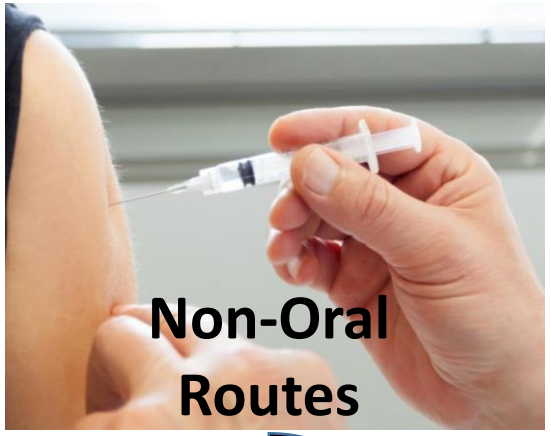
Rectal

Foam

Skin

Topical Route Versus Systemic Routes

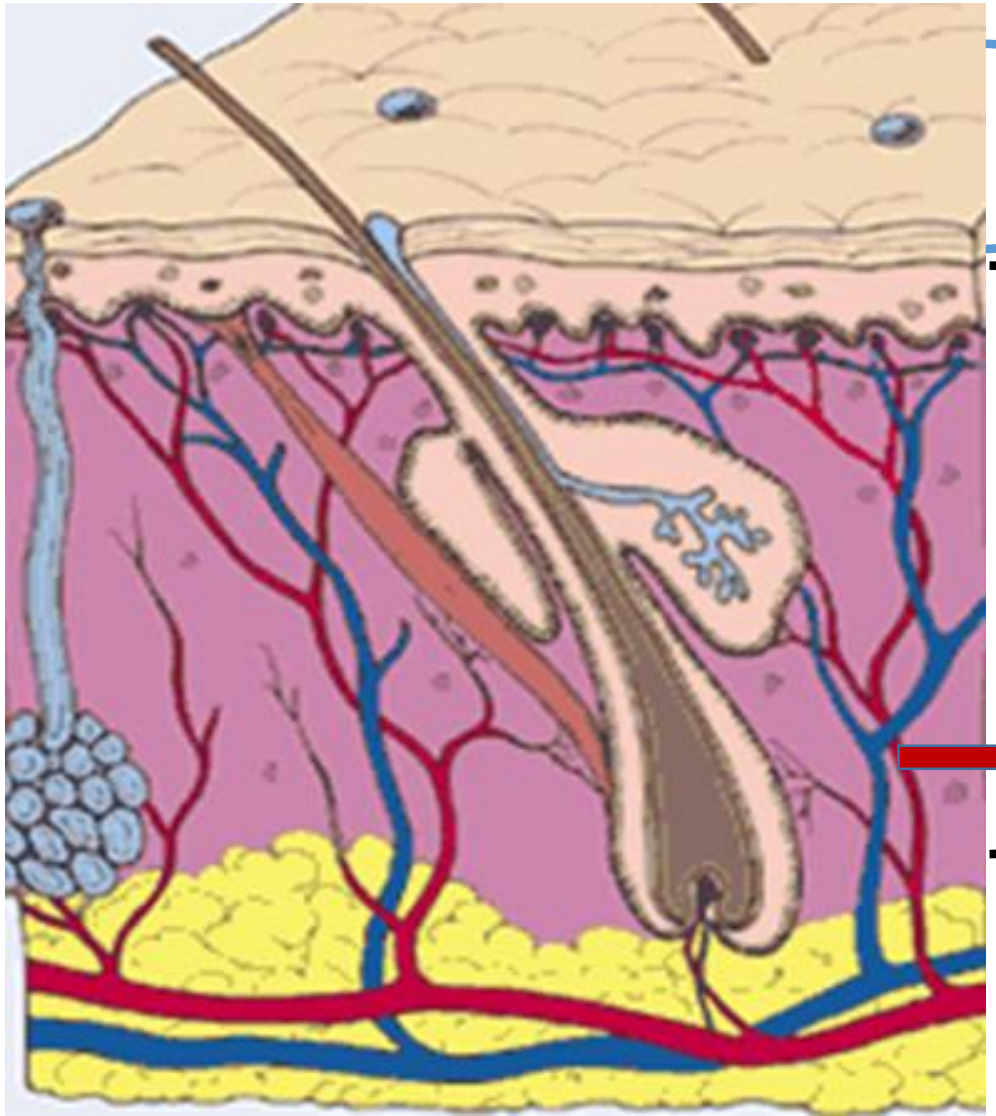




Huge doses in Systemic circulation

Undesired effects, Allergies, Toxicity

Dermal versus Transdermal Delivery



Skin Protectants
Antifungals
Antiseptics
Emollients

Local Delivery

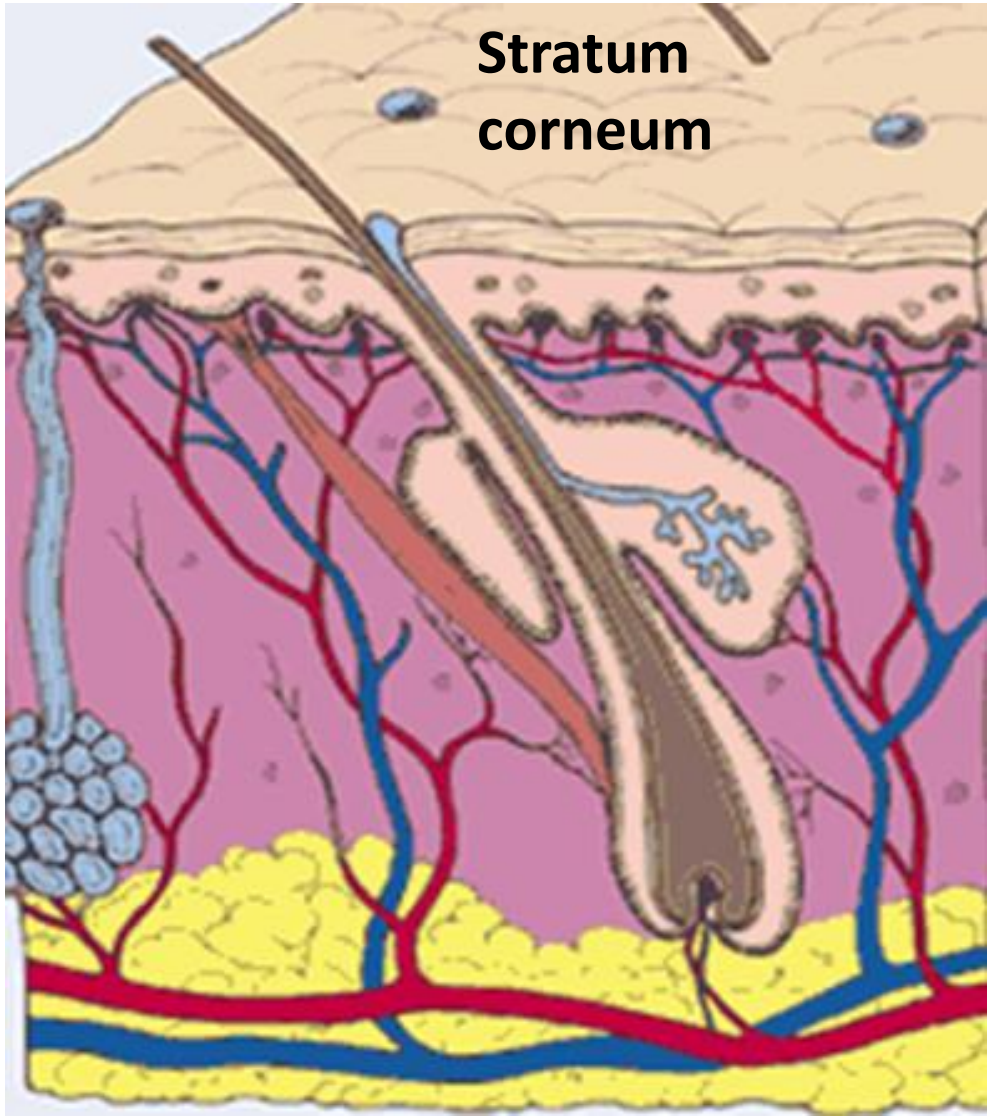
Anti-inflammatory
Local Anesthetic
Antiviral
Corticosteroids

Intradermal Delivery

Fentanyl
Hormones
Nitroglycerin
Nicotine

Transdermal Delivery
(Semisolids or patches)

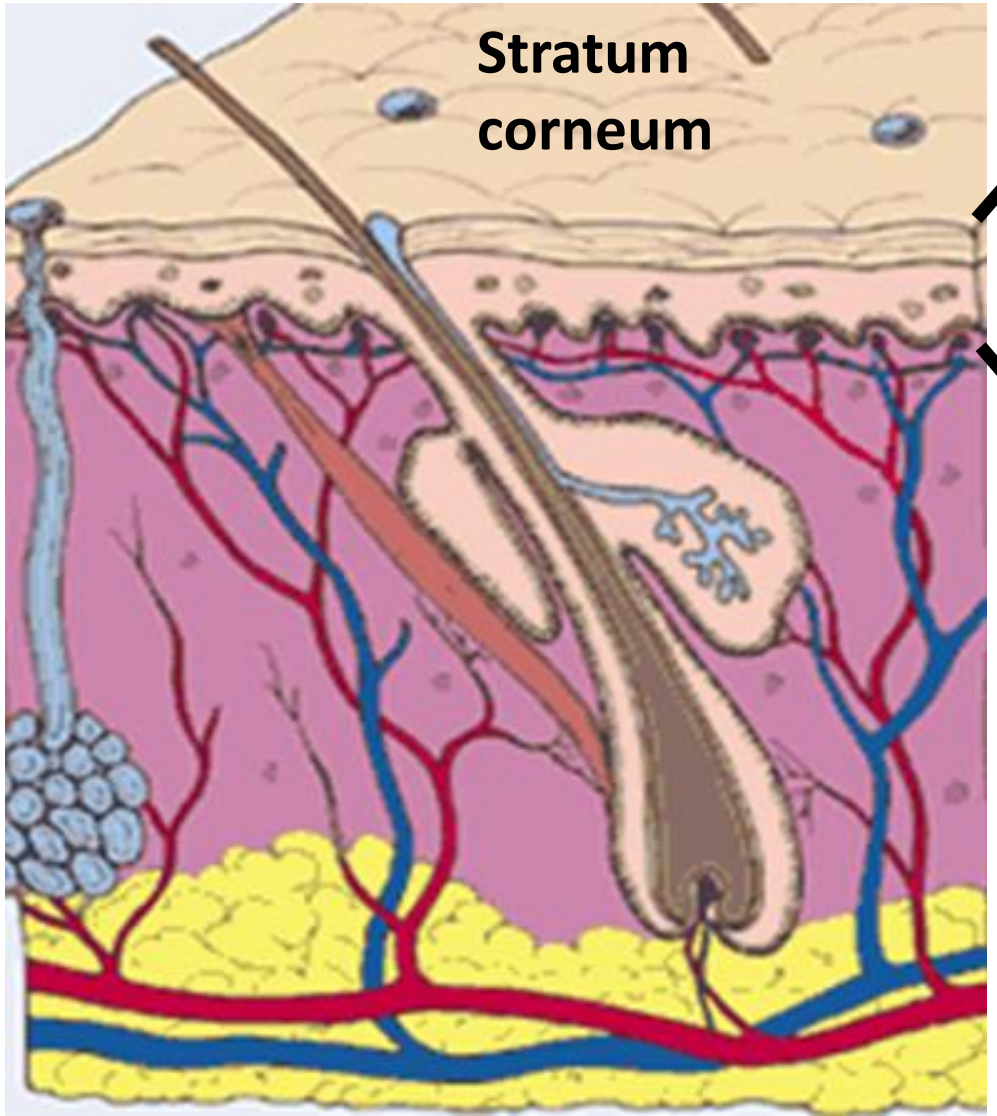
Skin Layers



Epidermis

Dermis

Skin Layers



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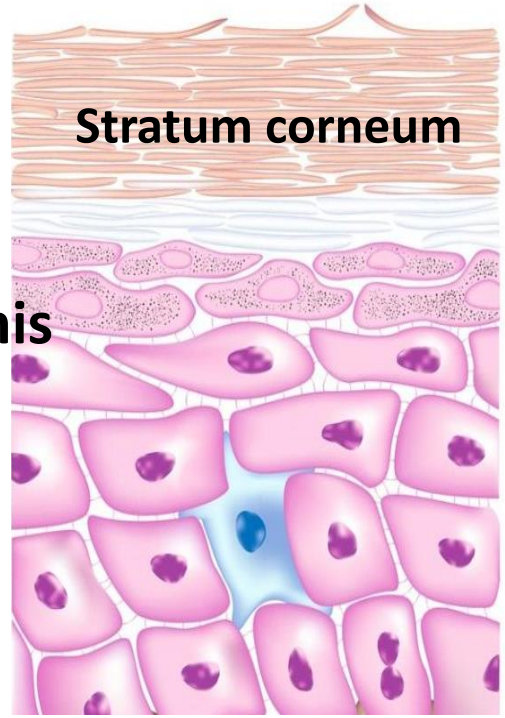
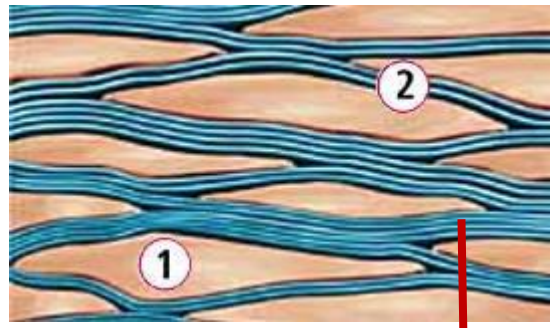
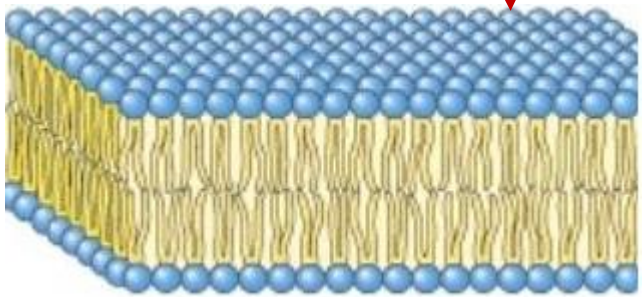




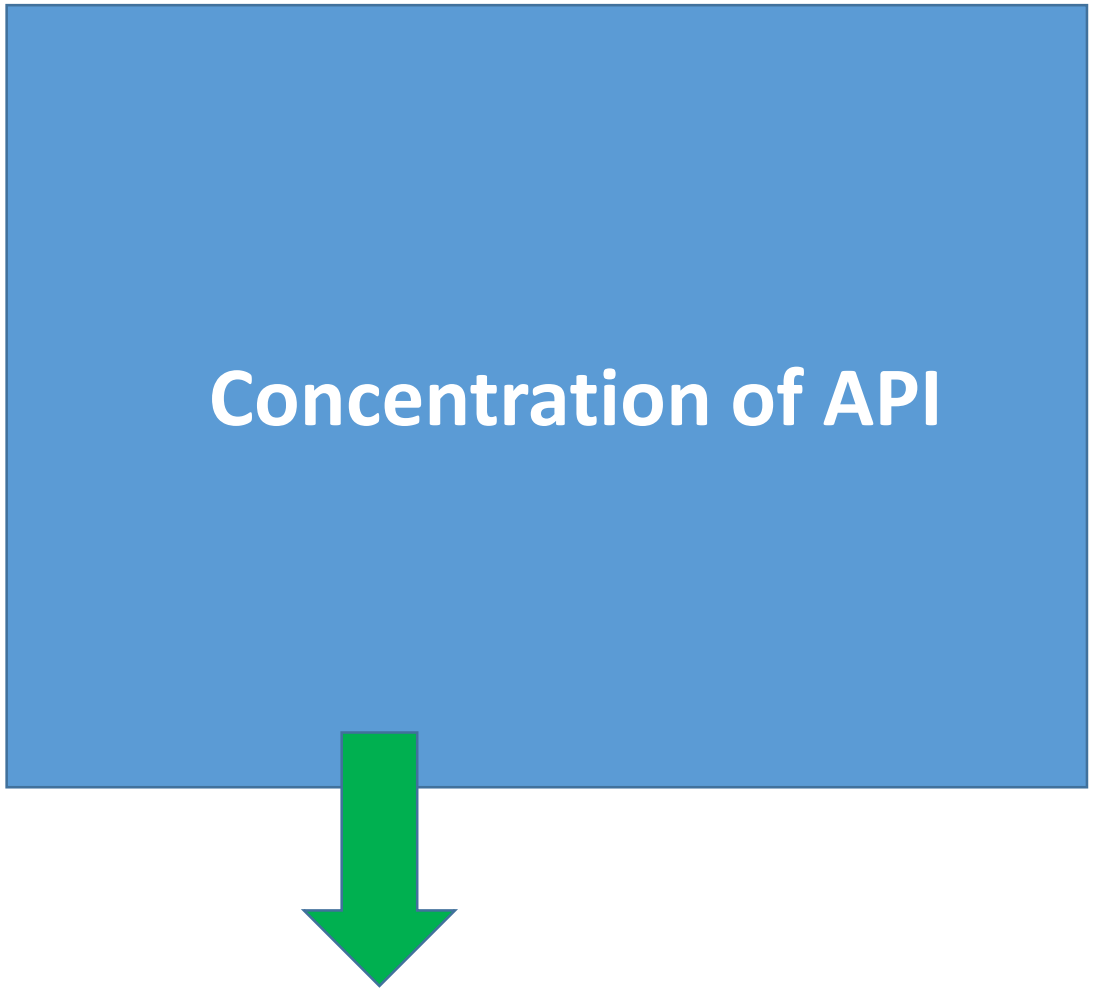


Ceramides, Fatty acids and Cholesterol

Topical Pain Products

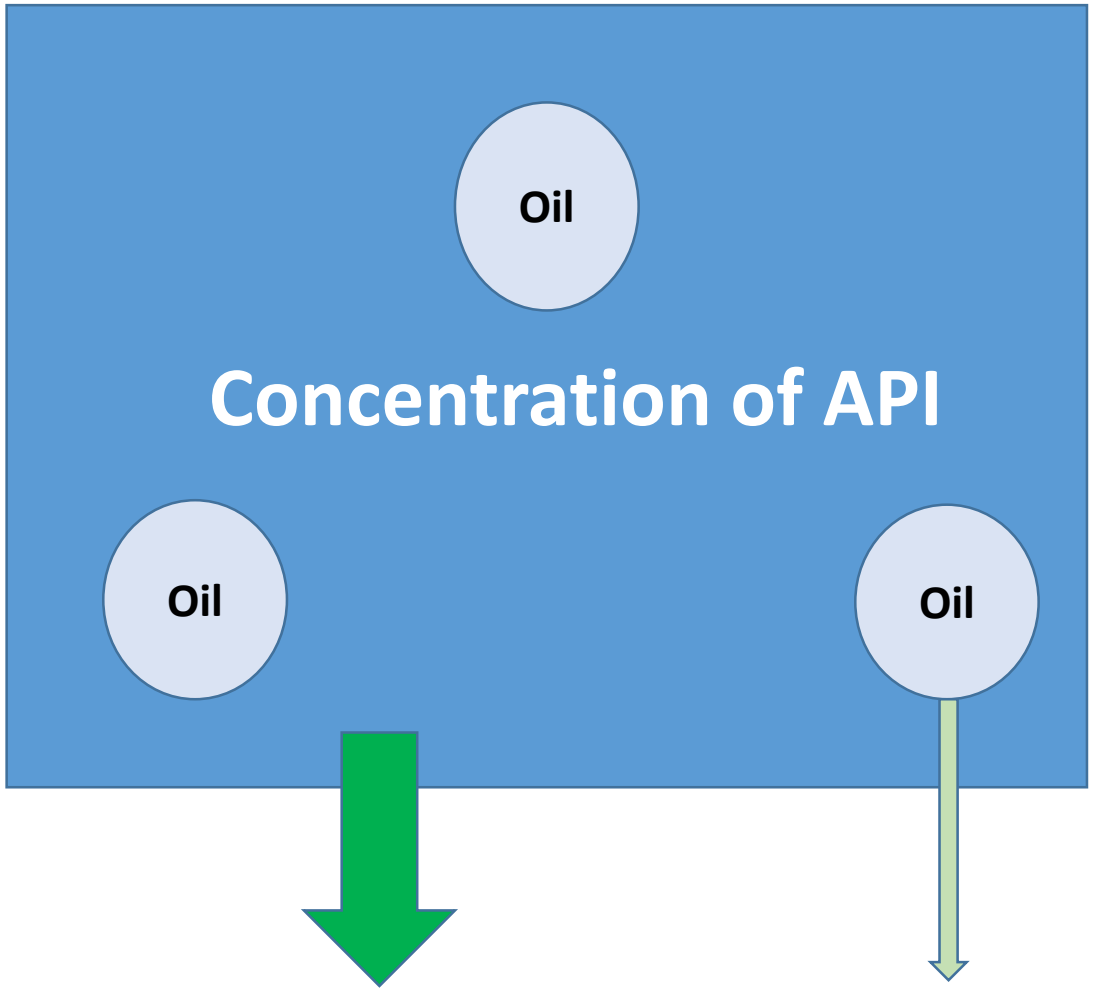
API	Log P	MP (°C)	pKa	% Unionized at pH 5
Lidocaine Hydrochloride	≤ 0	76-79	7.9	0.13
Diclofenac sodium	1.1-1.3	283-285	4.0	9.09
Ketoprofen	2.94	94	4.76	36.50
Gabapentin	-1.10	164-167	3.68 and 10.70	-
Ketamine	3.12	92-93	7.5	0.32
Cyclobenzaprine	4.9	217	8.47	0.03
Baclofen	0.46	189-191	5.4 and 9.5	-
Clonidine	0.83	140	8.2	0.06

Factors Influencing Dermal Drug Penetration



Drug concentration in the formulation determines the rate of drug release and skin penetration.

Factors Influencing Dermal Drug Penetration



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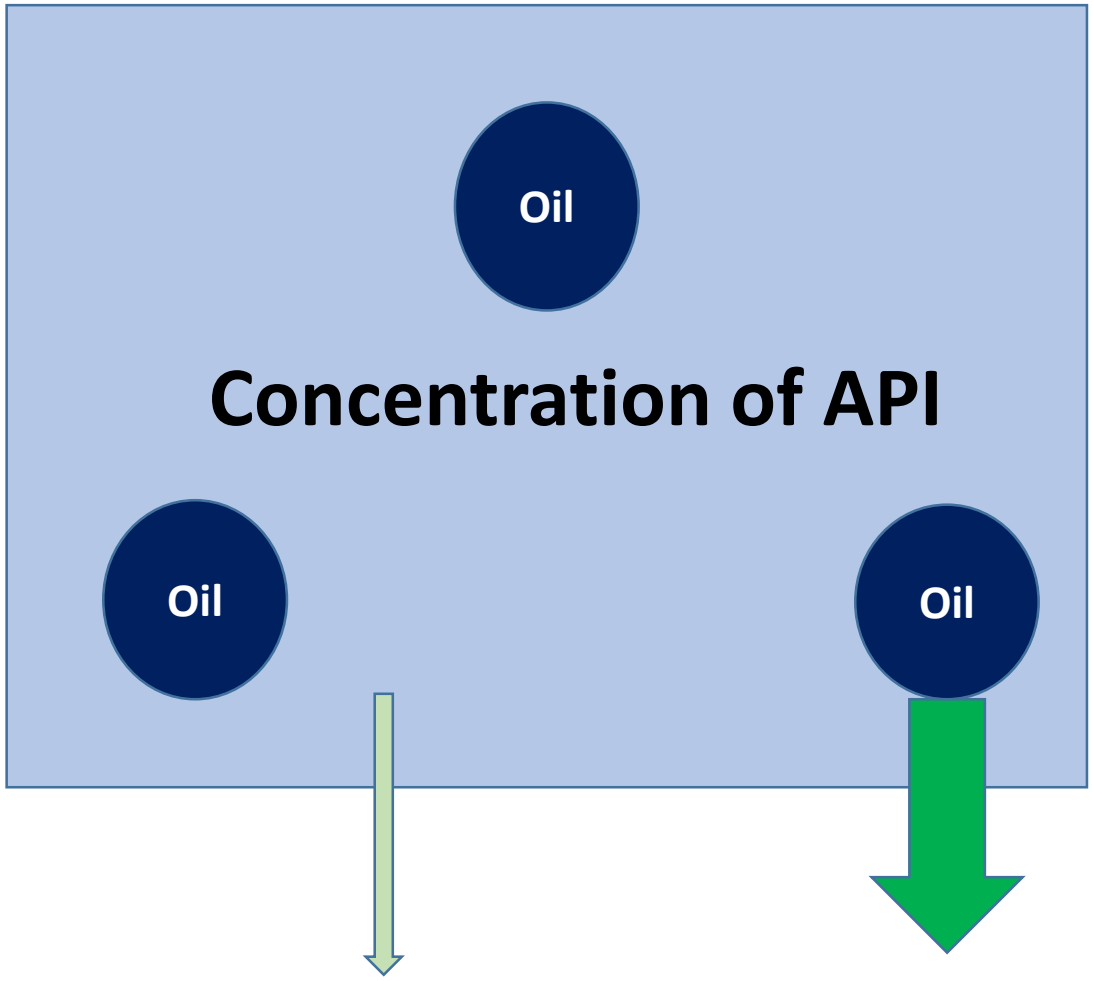

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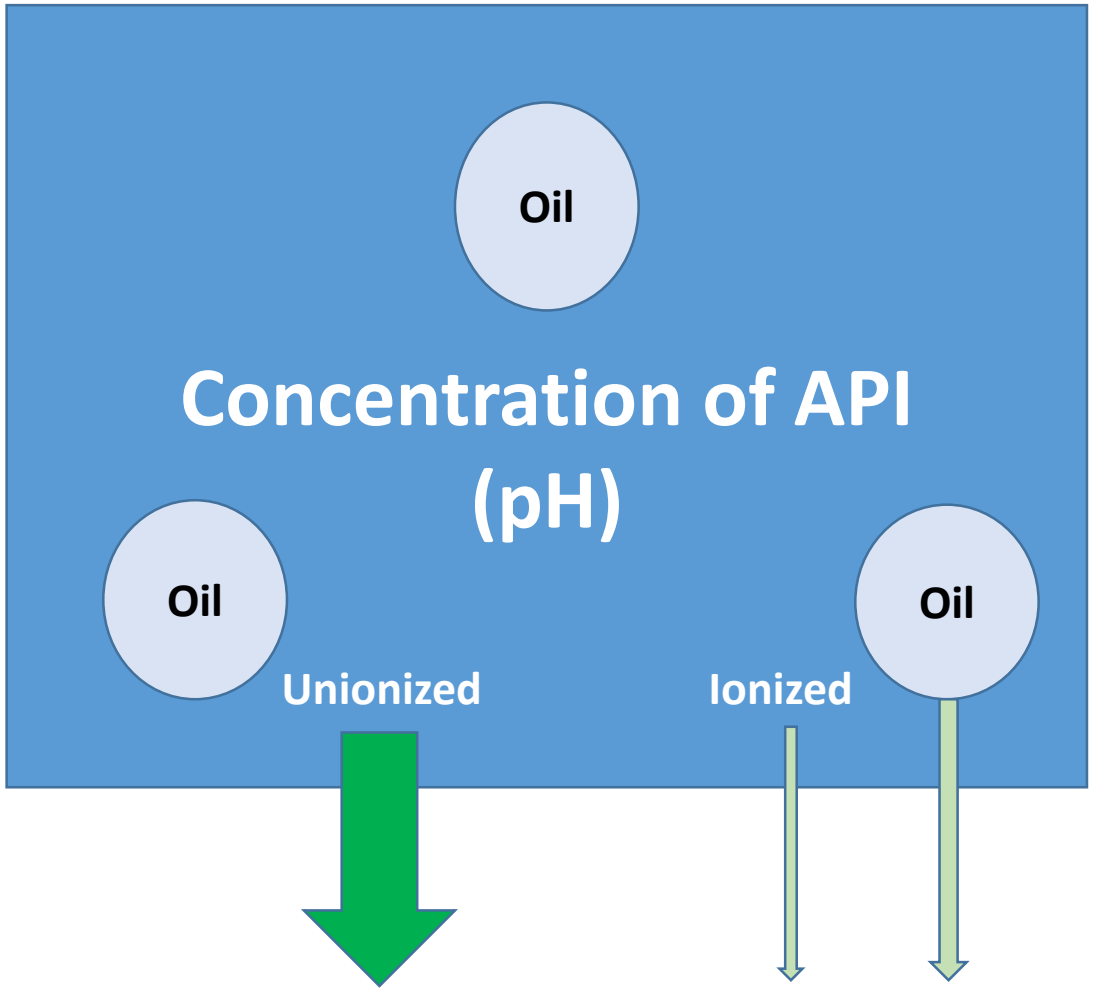

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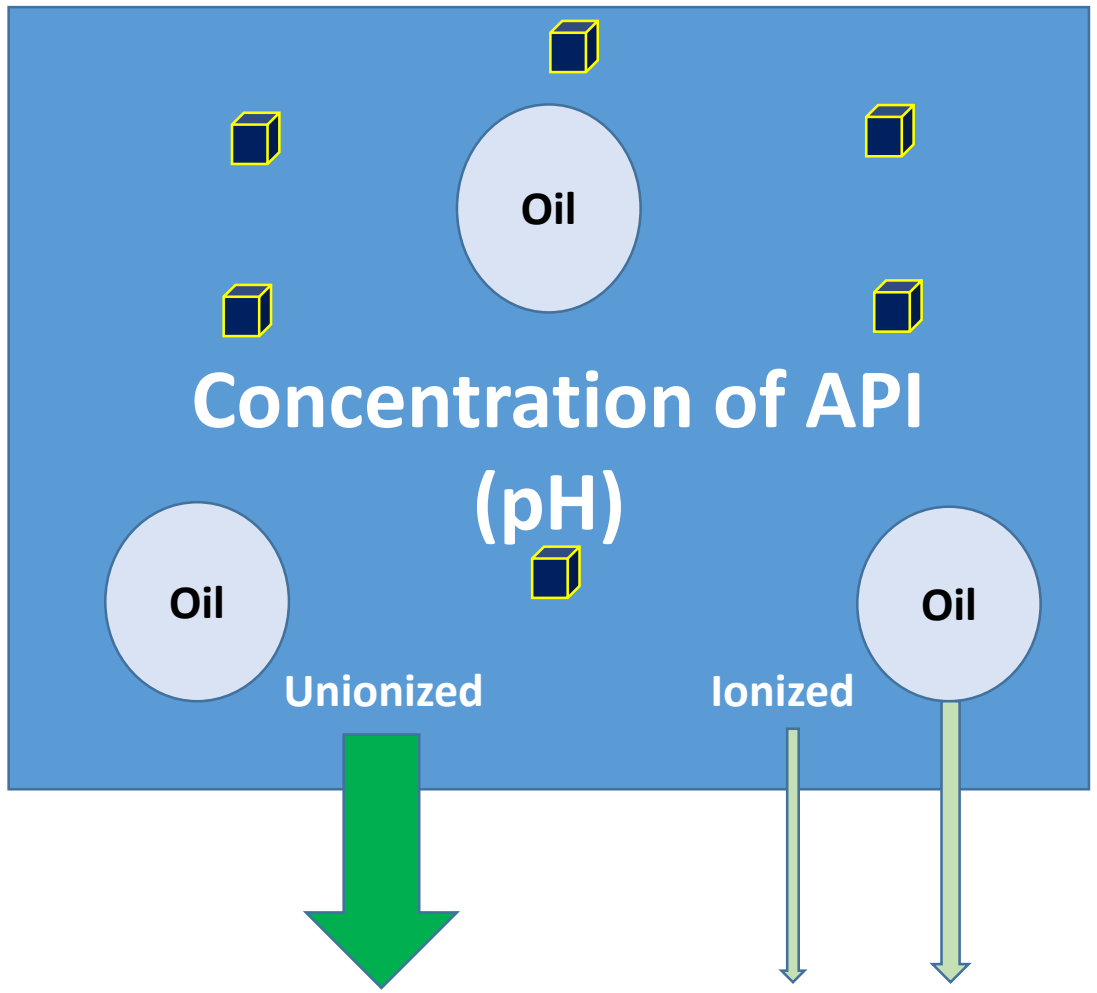

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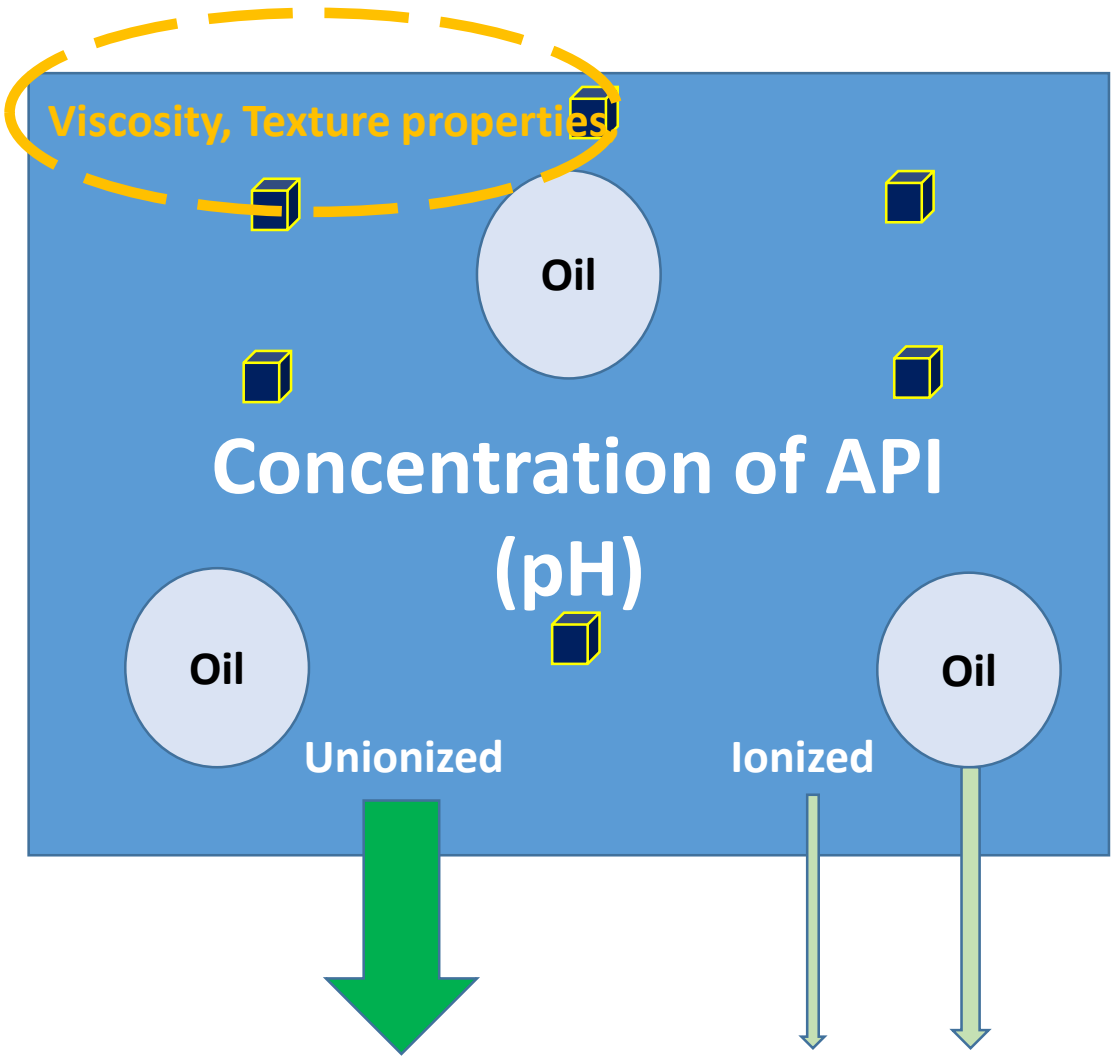

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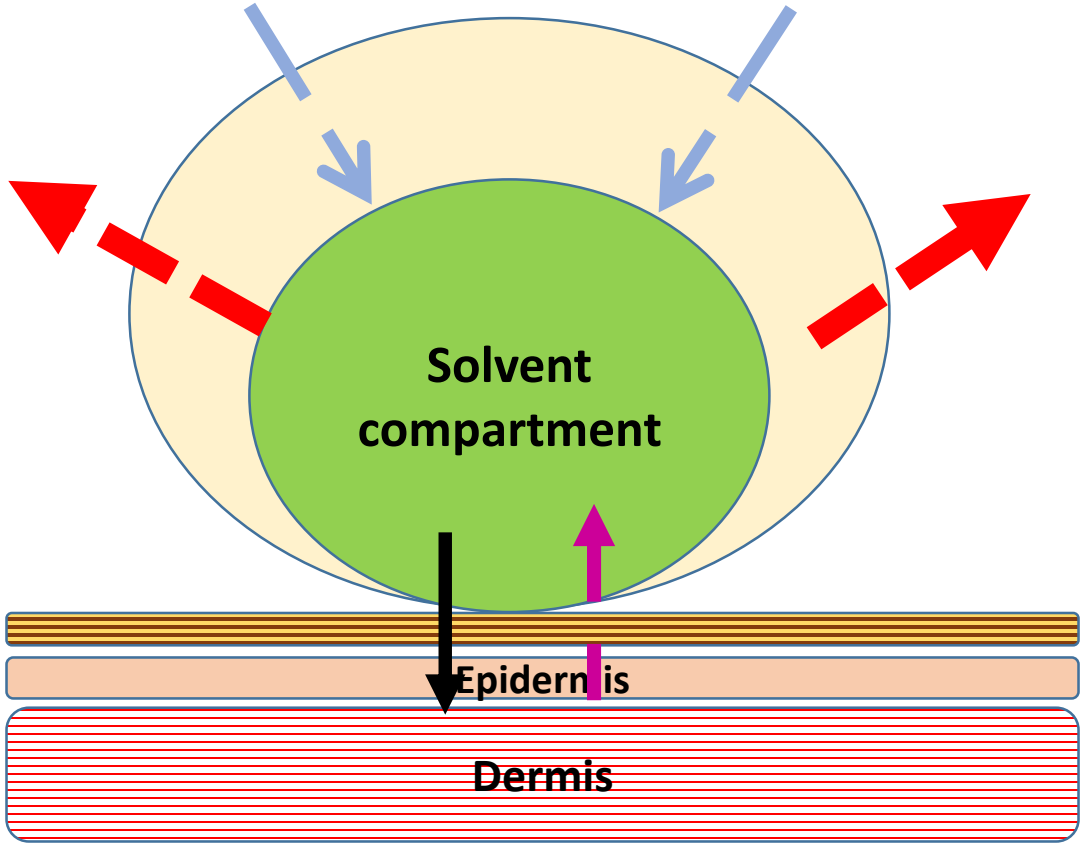
Role of Solvents on Dermal Drug Delivery



- Evaporative metamorphosis
- Solvent penetration into the skin
- Solvent that is absorbed from the atmosphere
- Formulation dehydrates the skin

Process Variables and Product Microstructure

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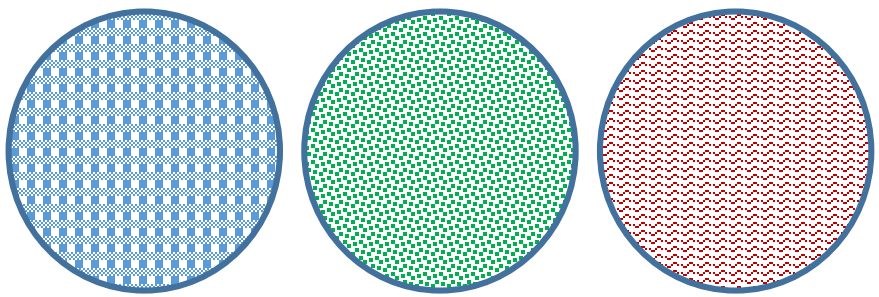

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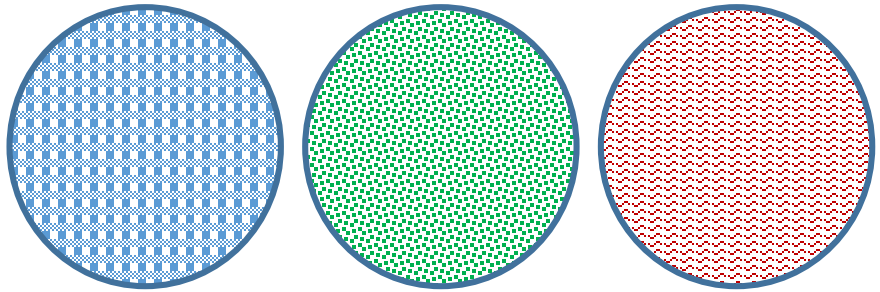
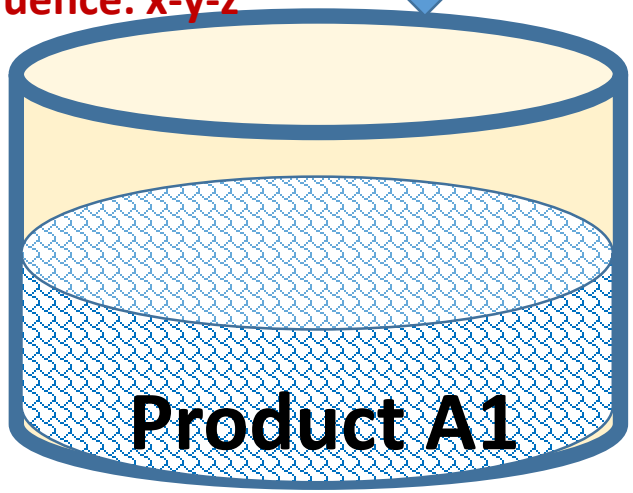
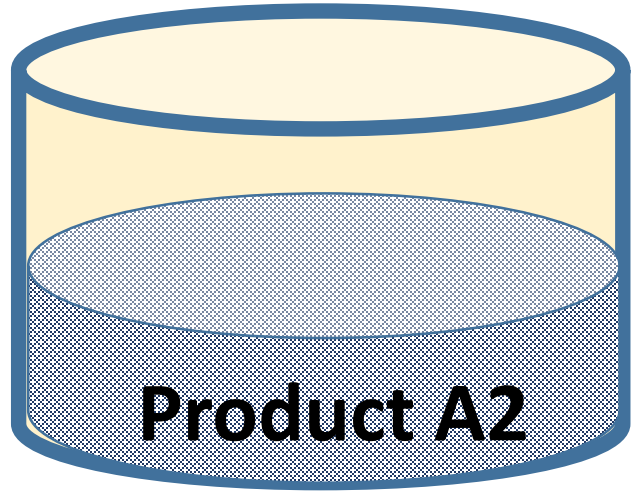


Homogenization at T1 degree at speed R1 for M1 minutes.
Sequence: x-y-z



Homogenization at T2 degree at speed R2 for M2 minutes.
Sequence: x-z-y



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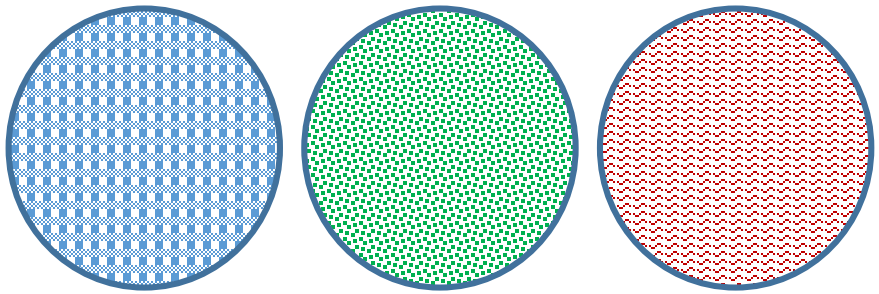

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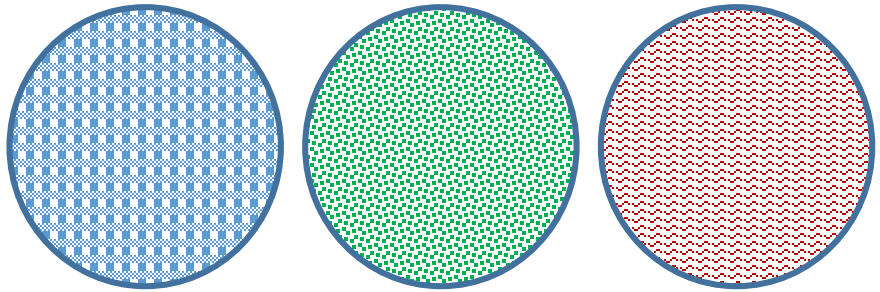
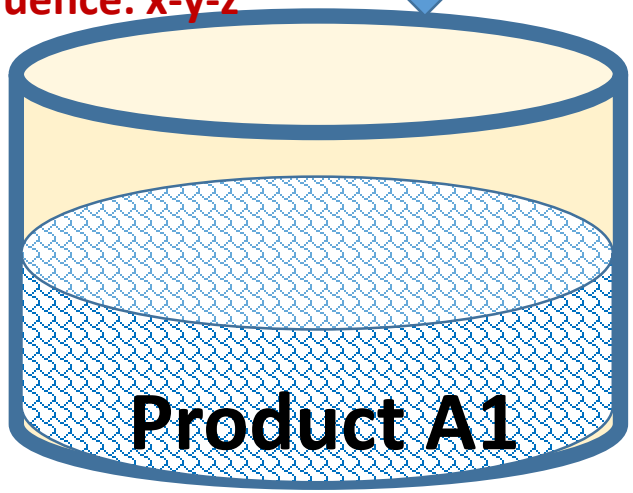


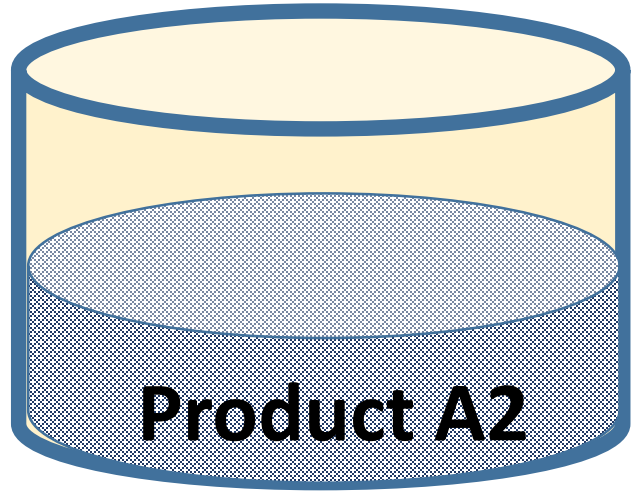
Homogenization at T1 degree at speed R1 for M1 minutes. Sequence: x-y-z

Homogenization at T2 degree at speed R2 for M2 minutes. Sequence: x-z-y

Quality Attributes

- pH
- Particle size and shape
- Globule size
- Water activity
- Phase distribution of drug
- Density
- Rheology
- Texture properties
- Appearance





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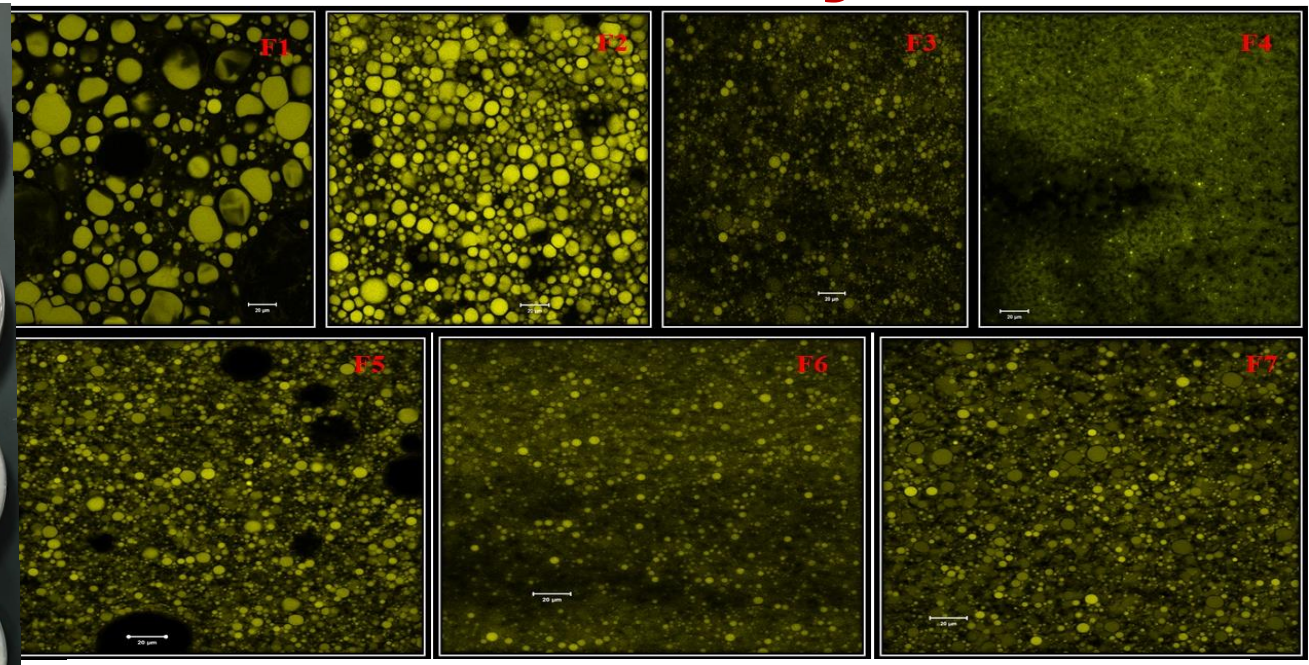
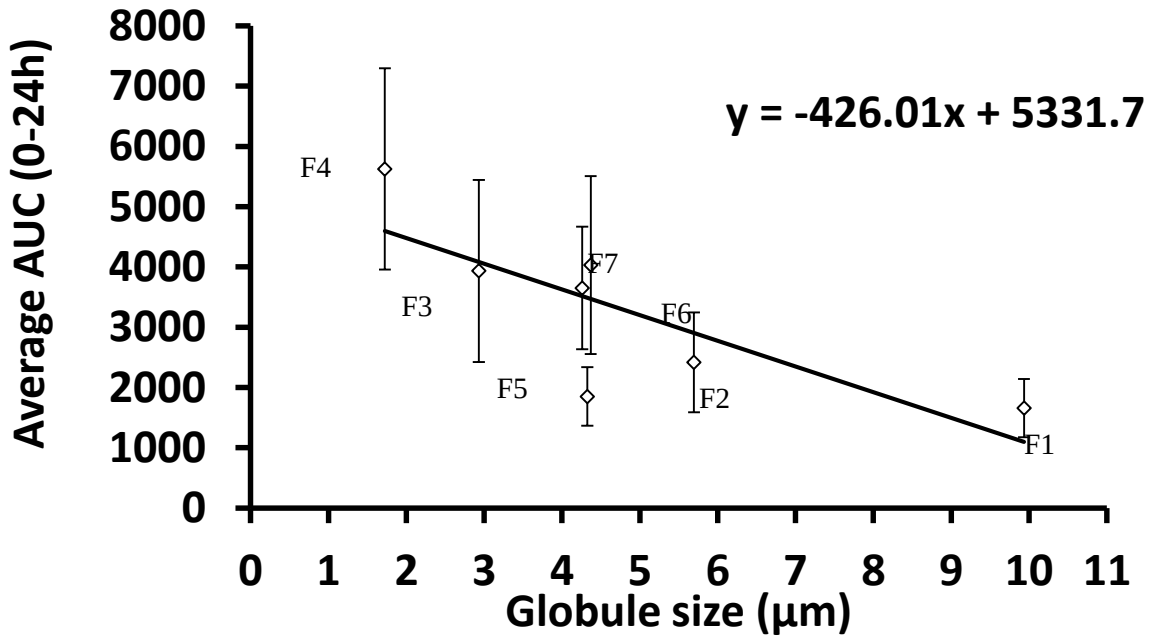
- Dermal penetration
- Therapeutic efficacy
- Sensorial Characteristics

Globule Size and Dermal Delivery

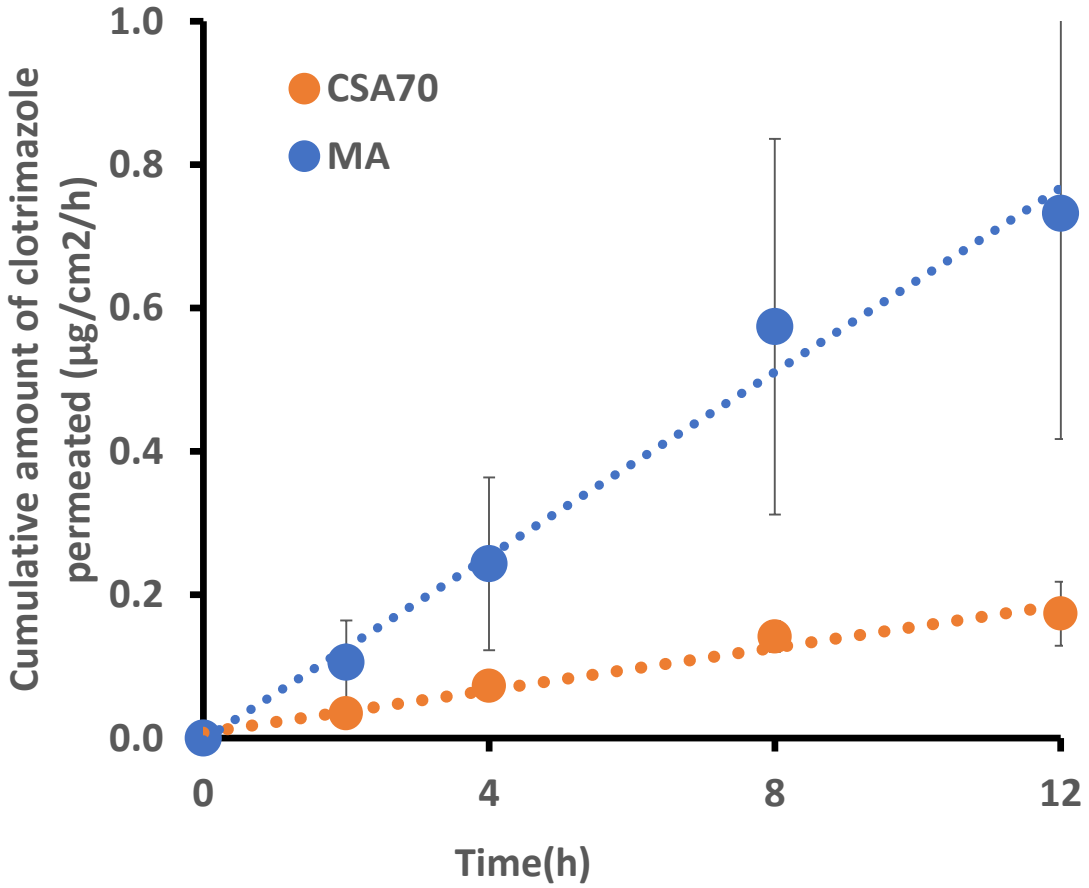
Ingredients (O/W)	Quantity (%)
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	70

Formulation Code	Variable	Globule Size (um)
F1	500 rpm -20 min	11.37 ±7.03
F2	1000 rpm - 20 min	7.41 ±2.19
F3	3000 rpm - 20 min	2.98 ±1.25
F4	5000 rpm -20 min	1.71±0.41
F5	3000 rpm - 10 min	4.30±1.33
F6	3000 rpm - 40 min	4.36±0.88
F7	3000 rpm - 20 min (GC)	4.25±0.99





Fatty alcohols on Permeation of Clotrimazole



Amount of Clotrimazole permeated across the porcine epidermis from creams containing Cetostearyl alcohol 70 or Myristyl alcohol

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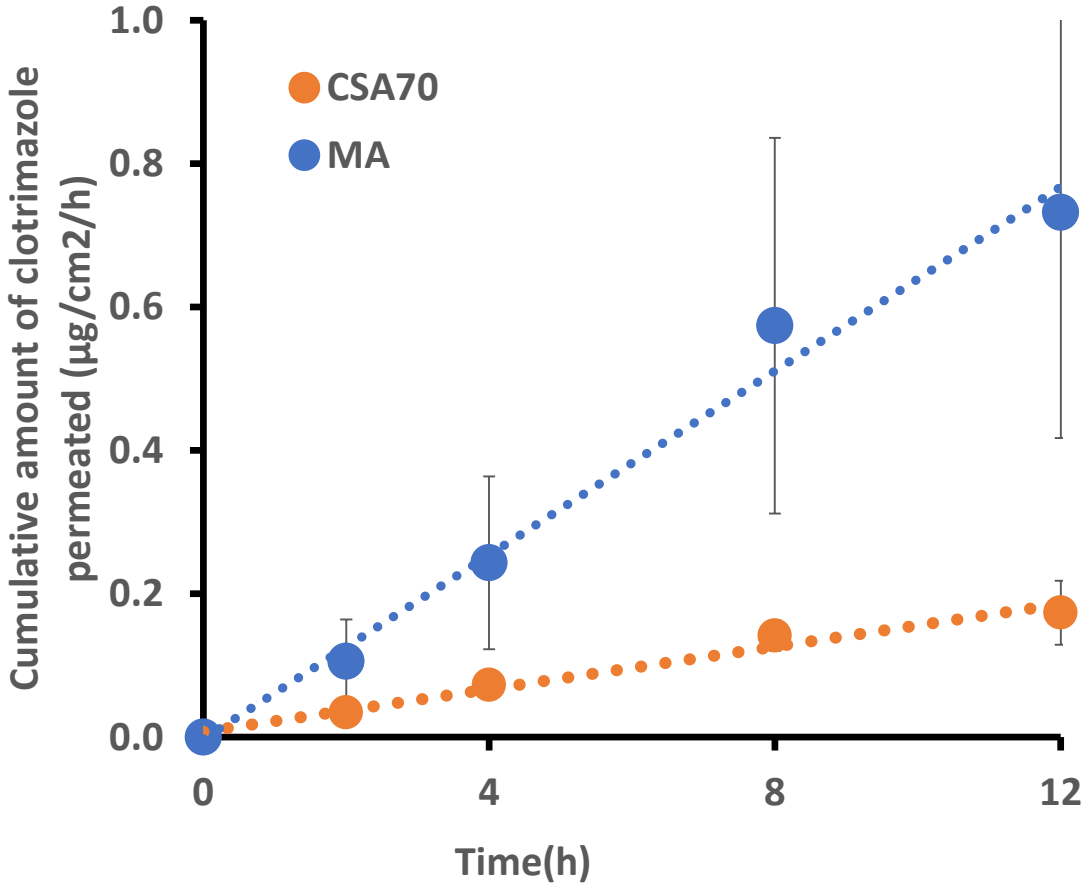

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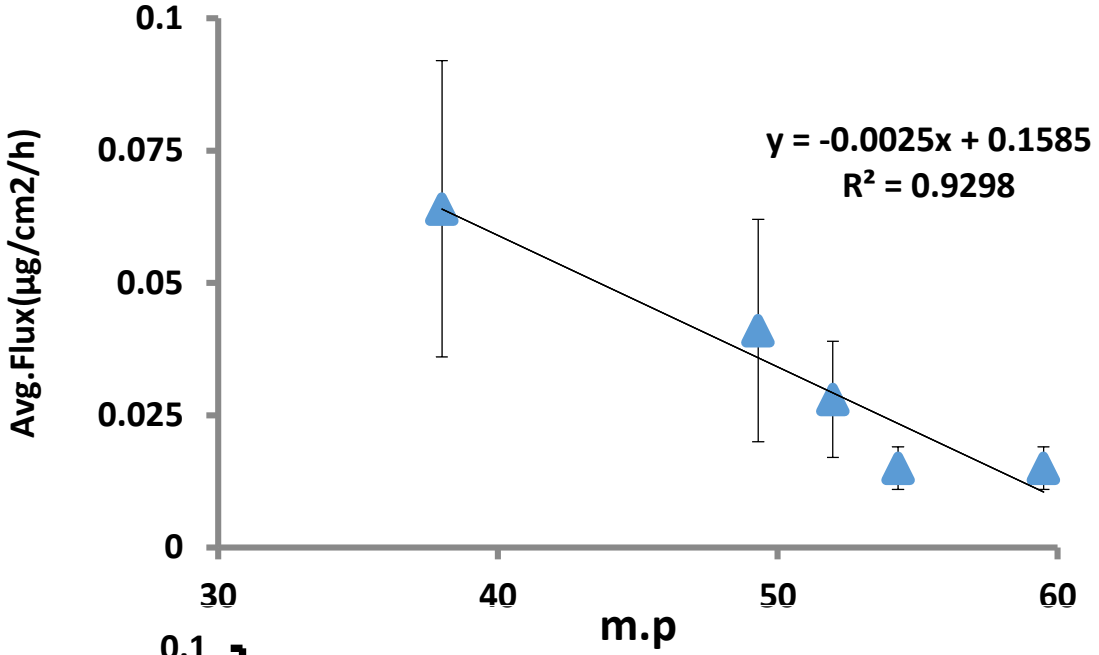
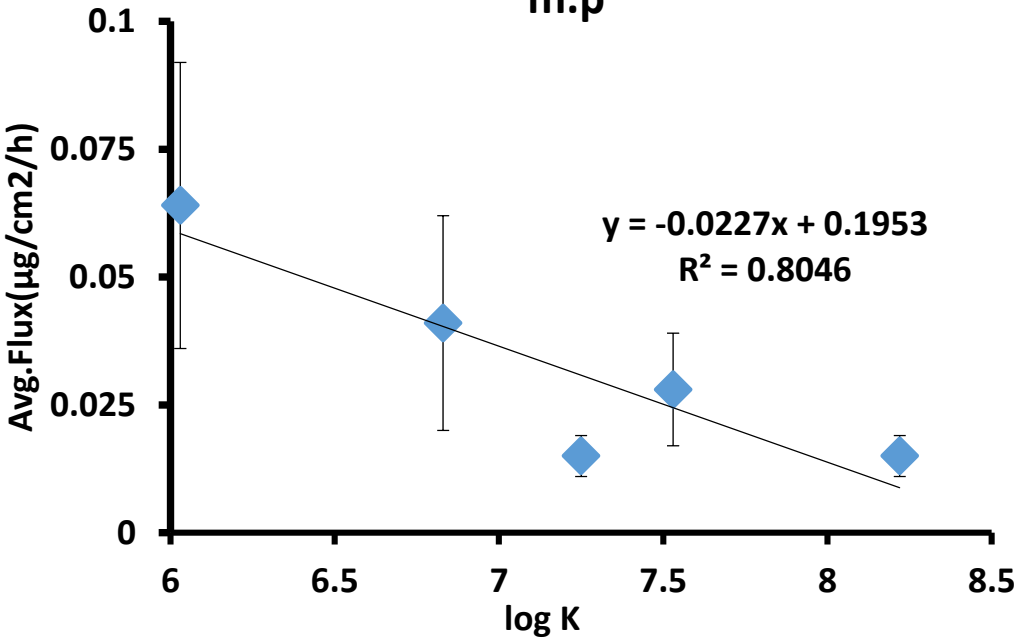
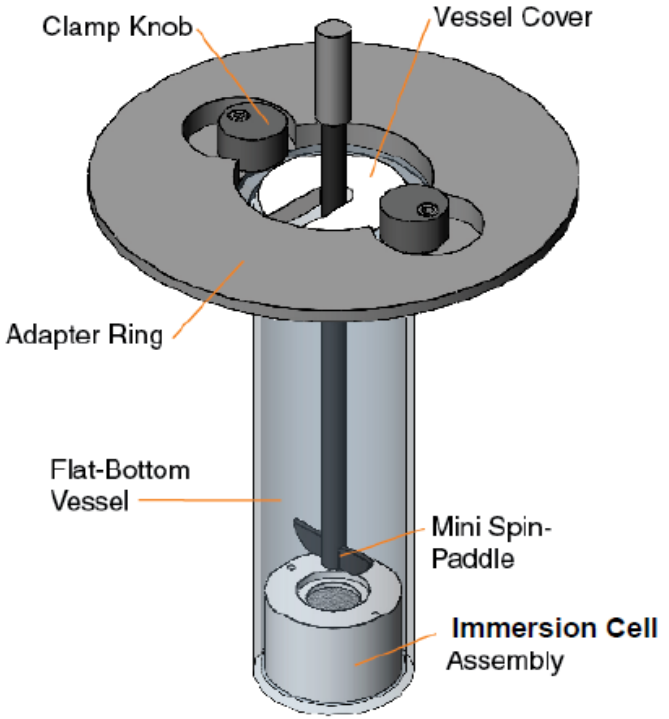


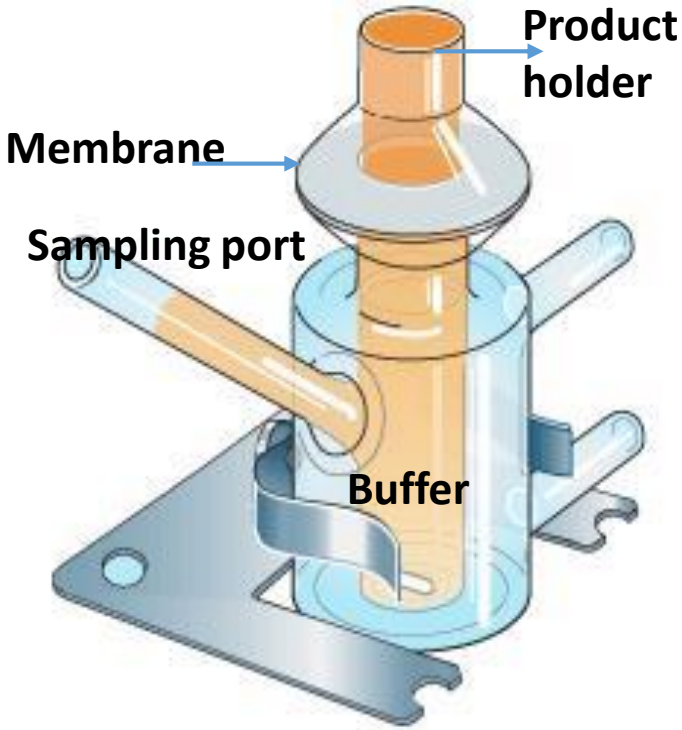


In Vitro Release Testing

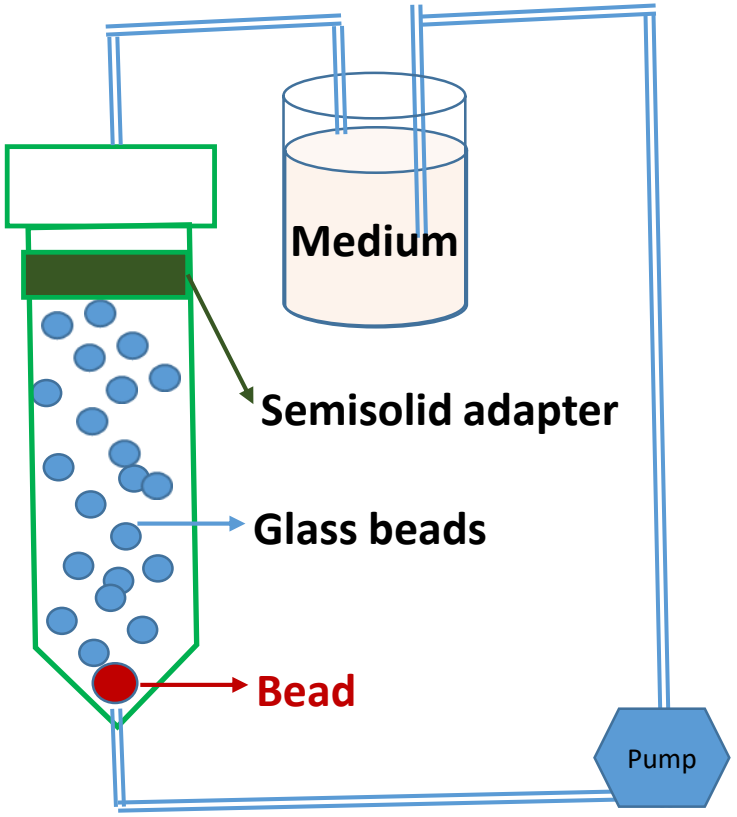
- Release Rate of Drug form the formulation depends on its quality attributes.
- Need to be performed across a non-rate controlling membrane (Filter membranes or dialysis membrane)



USP Dissolution II Apparatus with Immersion cells (semisolid holder)



Franz diffusion cell



USP Dissolution IV

In Vitro Permeation Testing

Finite Dose: 5-15 mg/ cm2 (Not occluded)

Infinite dose:>15mg/cm2

Receiver compartment

Buffer or surfactant solution that satisfies the criteria for sink condition.

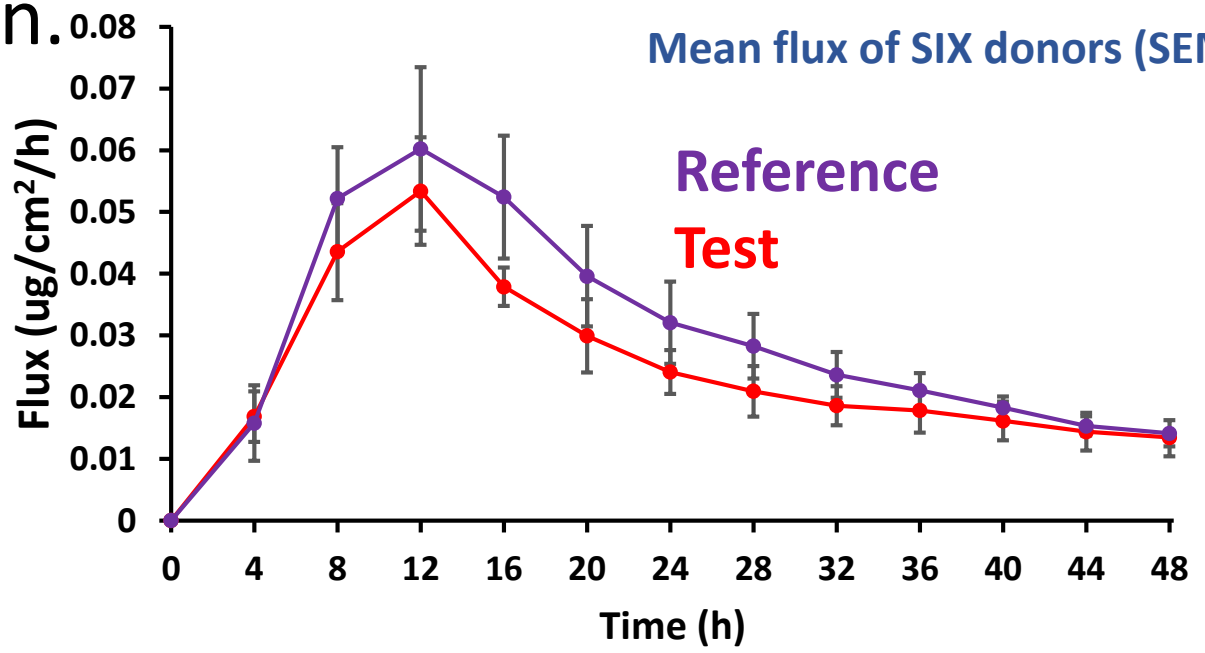
Human Skin: Cadaver or abdominoplasty

200-500 um thickness.

Integrity testing: TEWL or ER

Sampling: Partial or complete.

Temp: 32 C



Summary Points

- Physicochemical properties of the API, formulation and excipients are known to influence the drug penetration into the skin.
- The development of a product that is stable, safe and effective involves systematic screening of ingredients and process variables and testing process.
- Comparison of performance of test products(release and/or permeation) with a reference product would help in compounding a clinically efficacious formulation.


Thanks!