Effect of Excipients on the In vitro Permeation of Drugs from Topical Products

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Session Description and Objectives

- The objective of the presentation is to discuss the influence of inactive ingredients in the formulation on the in vitro permeation of therapeutic agents.
- To understand the importance of physicochemical characteristics of inactive ingredients on the performance of topical products.

Biography and Contact Information

- **Area of Research:** Topical and Transdermal Drug Delivery, Intranasal Drug Delivery, Trans-ungual drug delivery
- **Publications**: Over 100 research papers, Two books, 15 review papers.
- **Grants and Funding**: NIH, USFDA, DOD, Pharma Industry
- **Contact information**:

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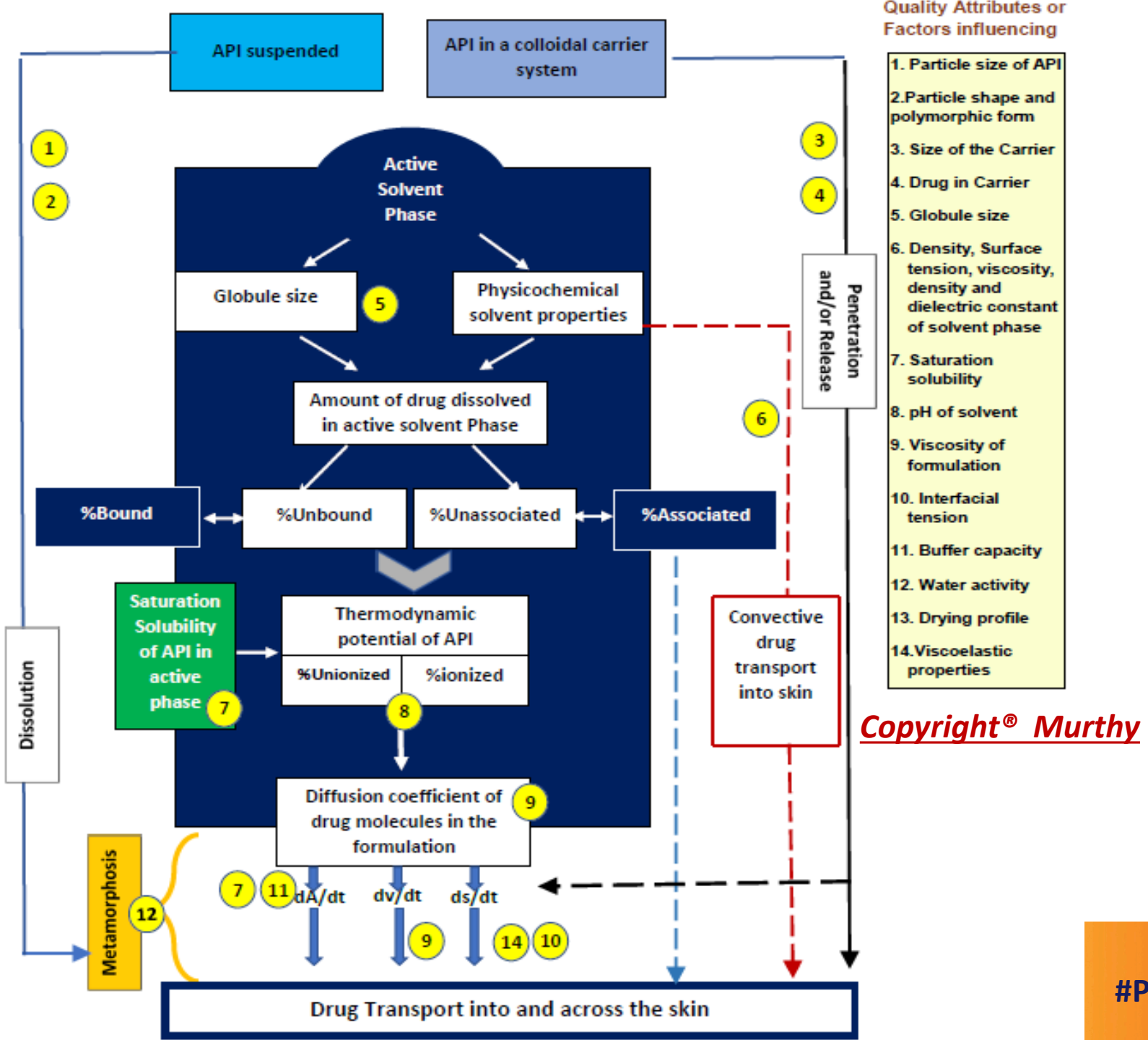
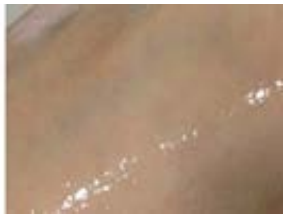


In Vitro Permeation Testing

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.

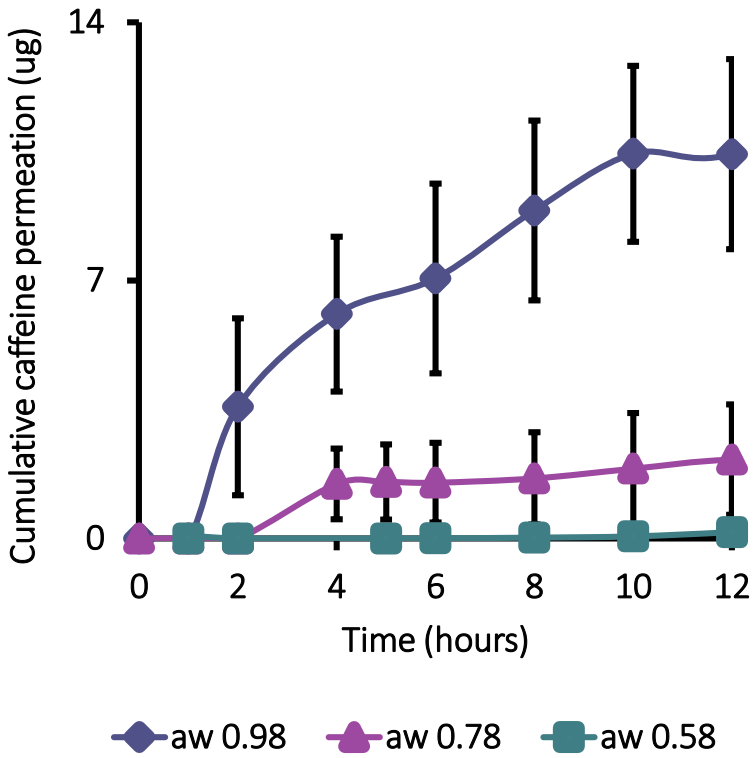
Human Skin: Cadaver or abdominoplasty 200-500 um thickness.

Integrity testing: TEWL or ER

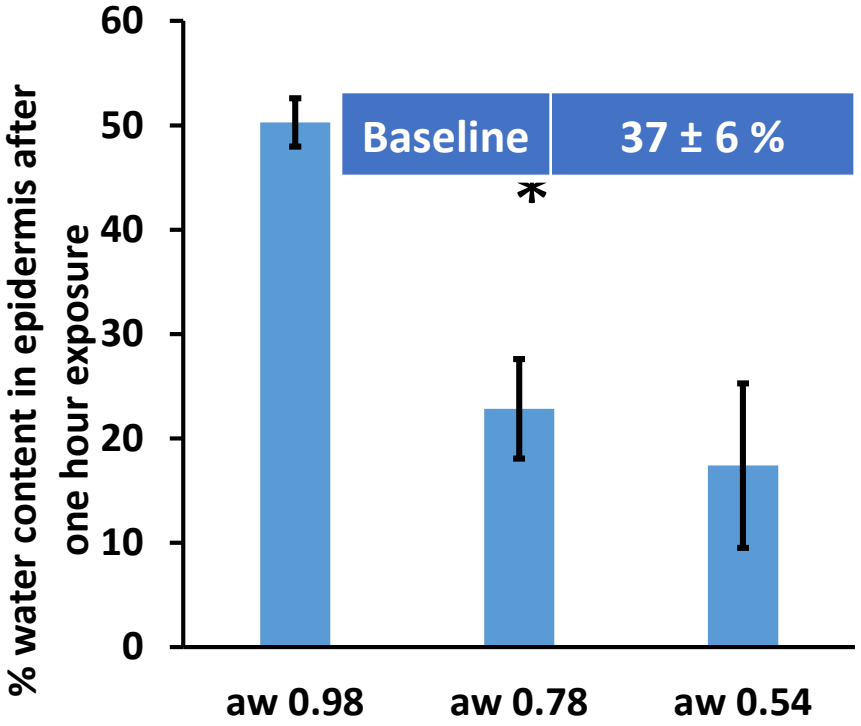
Sampling: Partial or complete.

Temp: 32 C

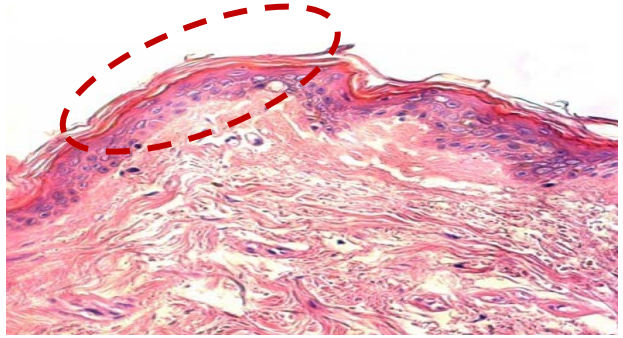
Effect of Salt Concentration on the Permeation of Drugs



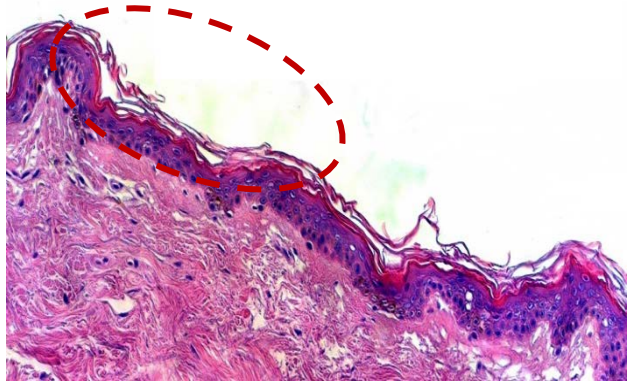
Permeation of caffeine from solutions with different amounts of salt



Amount of Moisture in the Epidermis after exposure to salt solutions

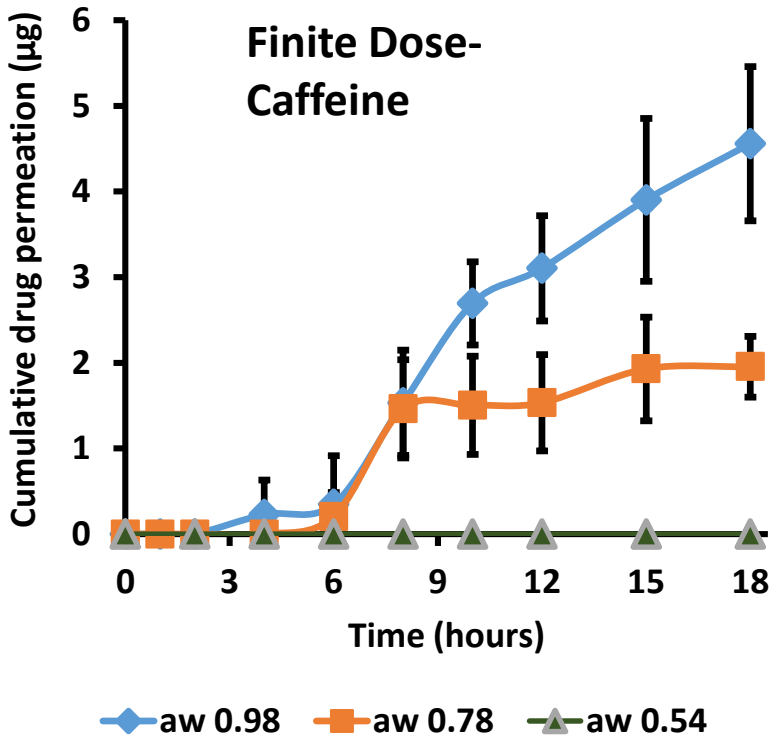


Histological evaluation of human cadaver skin treated with control vehicle (a_w 0.98)

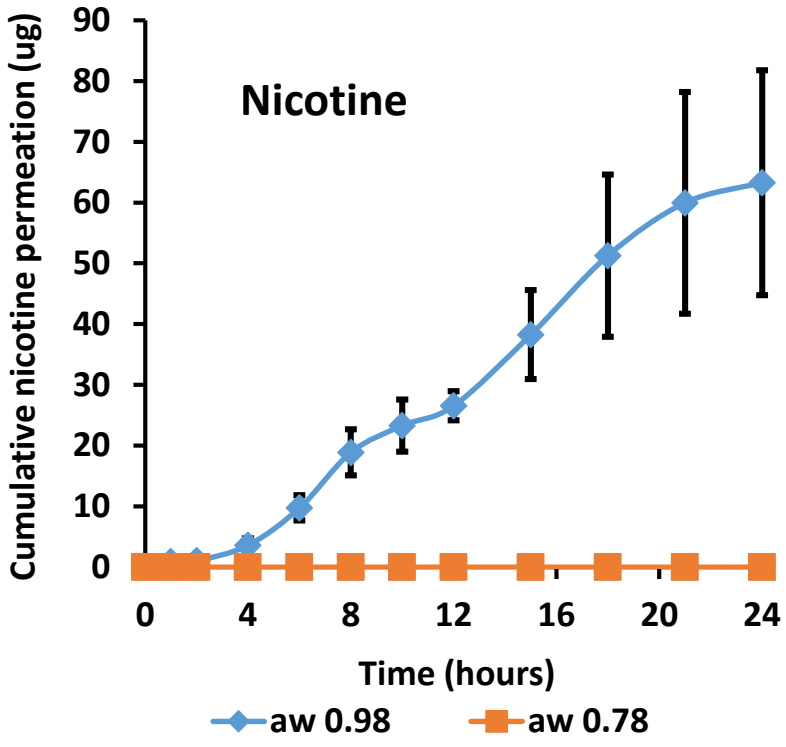


Histological evaluation of human cadaver skin treated with test vehicle (a_w 0.78)

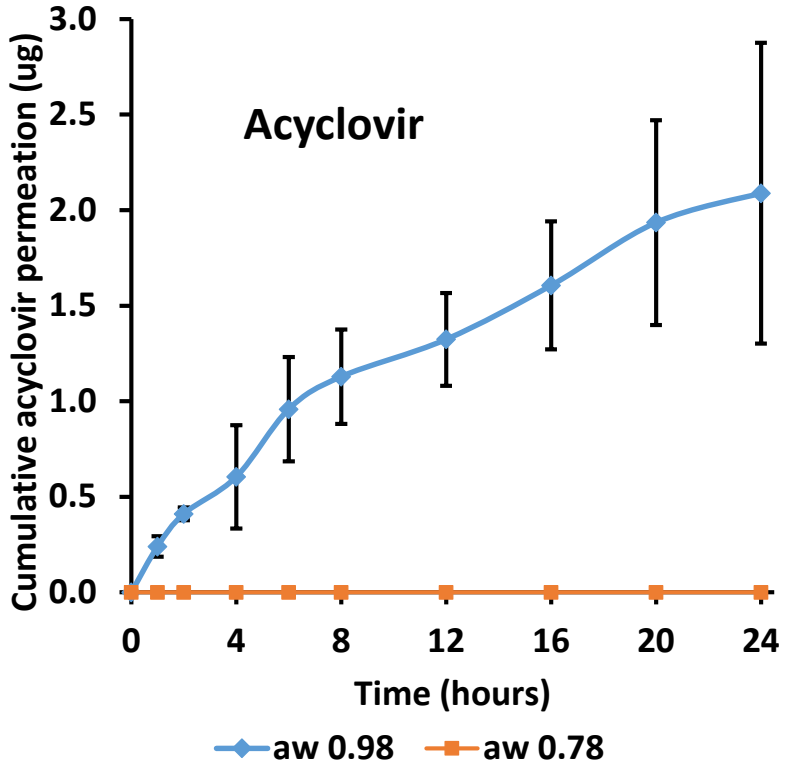
Effect of Salt Concentration on the Permeation of Drugs



Effect of water activity of topical vehicle on caffeine transport across porcine epidermis (n=6)



Effect of water activity of topical vehicle on nicotine transport across porcine epidermis (n=6)



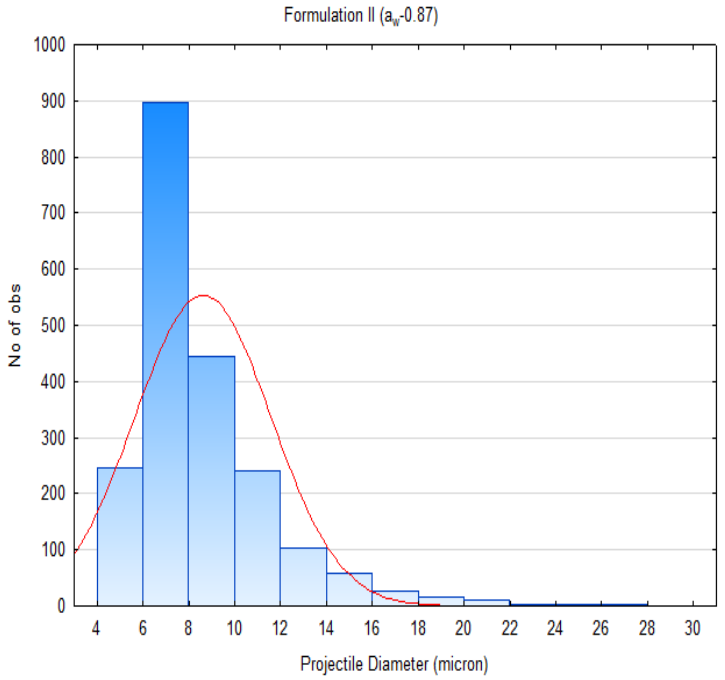
Effect of water activity of topical vehicle on acyclovir transport across porcine epidermis (n=6)

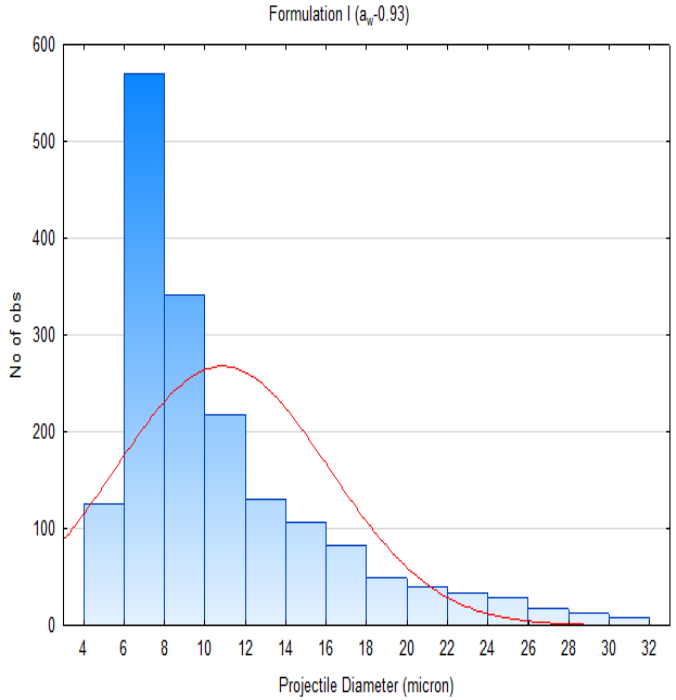
Q1 & Q2 Identical W/O Creams

Composition of a model w/o type cream formulation.

Ingredients (W/O)	Quantity (%)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100

Code	Homogenization Speed (RPM)	Duration (minutes)
F1	3500	15
F2	7000	45

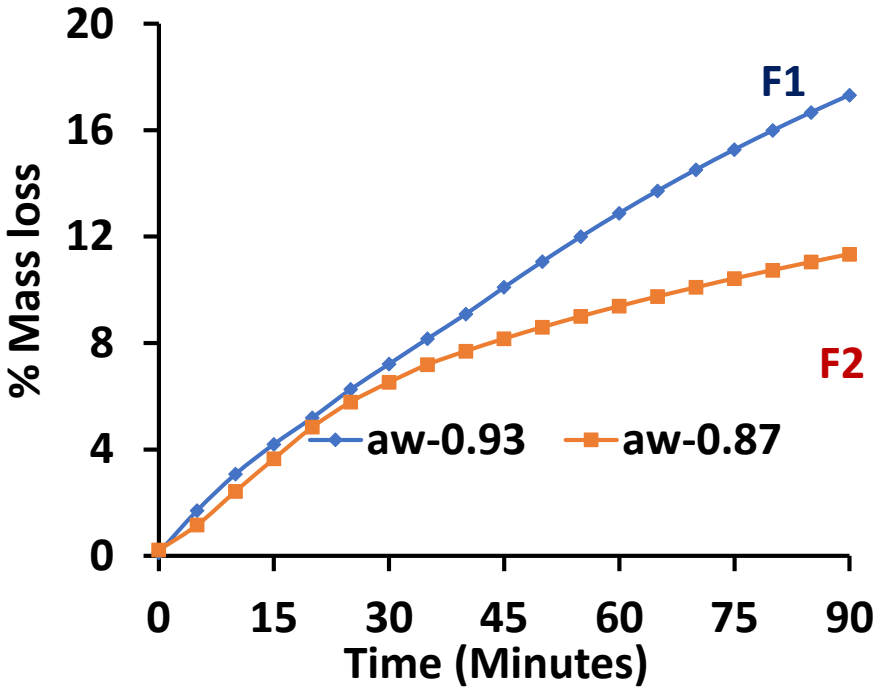


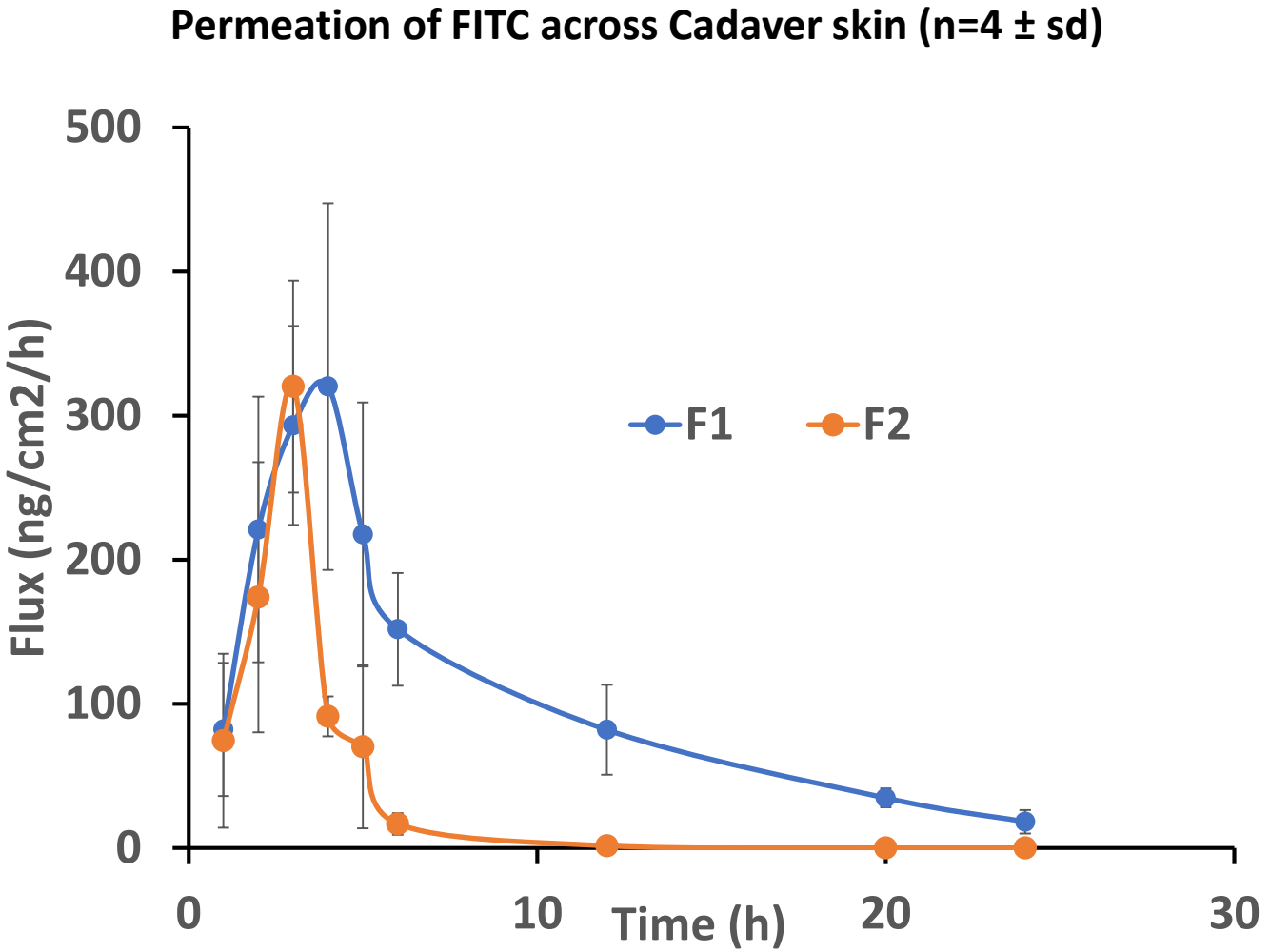


Formulation Code	Loss on Drying(%)	Water Content(%)
F1	84.32 ± 1.15	~15-16
F2	83.75 ± 1.39	~15-16

Q1 & Q2 Identical W/O Creams

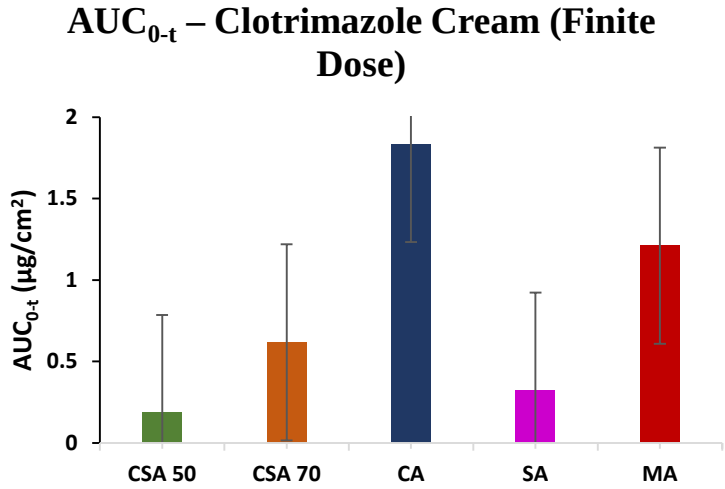
Formulation Code	Water Activity (aw)	% Mass loss at 90min
F1	0.93	16.67%
F2	0.87	11.34%

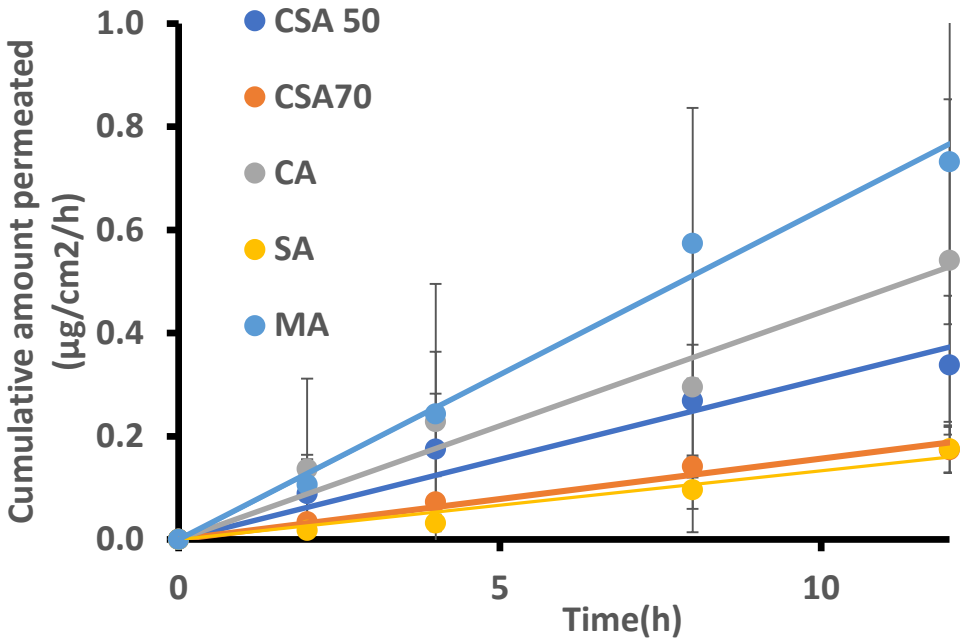


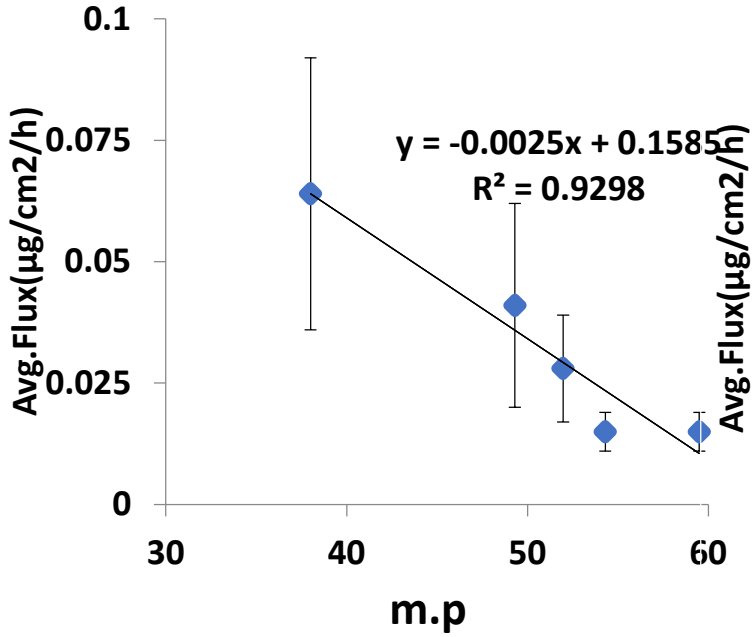


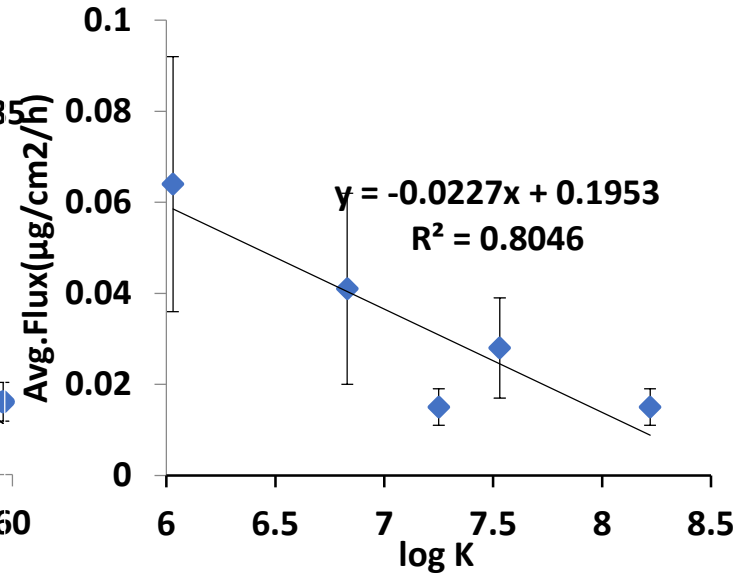
Influence of Fatty alcohols on Permeation of Clotrimazole

Fatty alcohol		Avg. Flux (µg/cm²/h)	M.P.	log K o/w	AUC
CSA 50	Kolliwax®CSA 50	0.028 ± 0.011	51.97	7.53	0.184 ± 0.132
CSA 70	Kolliwax® CSA 70	0.015 ± 0.004	54.3	7.25	0.618 ± 0.443
CA	Kolliwax® CA	0.041 ± 0.021	49.3	6.83	1.835 ± 1.122
SA	Kolliwax® SA	0.015 ± 0.004	59.5	8.22	0.321 ± 0.176
MA	Kolliwax®MA	0.064 ± 0.028	38	6.03	1.211 ± 0.602









Surfactant Concentration and Product Performance

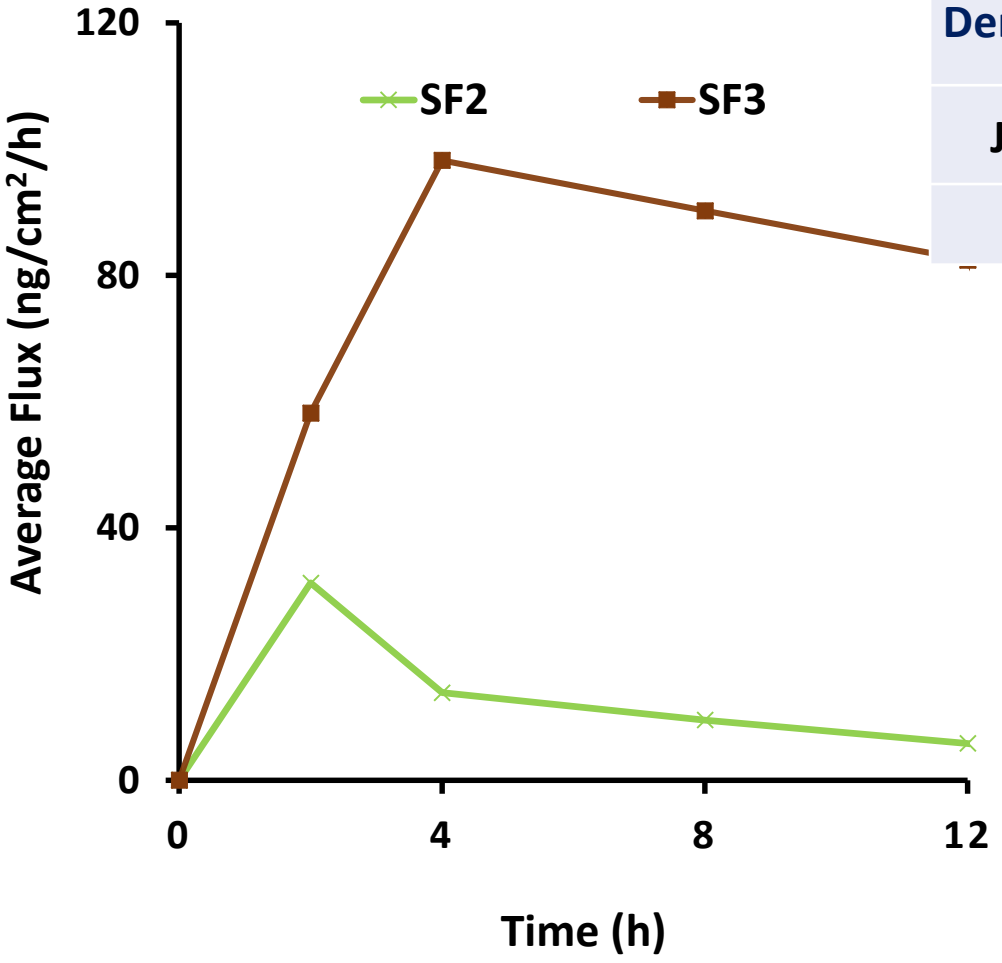
Cream Formulation

Ingredients	SF1 (% w/w)	SF2 (% w/w)	SF3 (% w/w)	SF4 (% w/w)
Mineral oil	15	15	15	15
Cremophor® A6	1.5	1.5	1.5	1.5
Cremophor® A25	1.5	1.5	1.5	1.5
Cetostearyl alcohol 70	7	7	7	7
Isopropyl myristate	3	3	3	3
Tefose® 63	1	1	1	1
Labrafil® M 1944 CS	1	1	1	1
PEG 400	5	5	5	5
TPGS	1.2	1.2	1.2	1.2
Tween 80	1.21	1.27	1.33	1.40
Span 60	2	2	2	2
Propylene glycol	10	10	10	10
Drug (Metronidazole)	0.75	0.75	0.75	0.75
Water (q.s.to 100%)	49.84	49.78	49.72	49.65

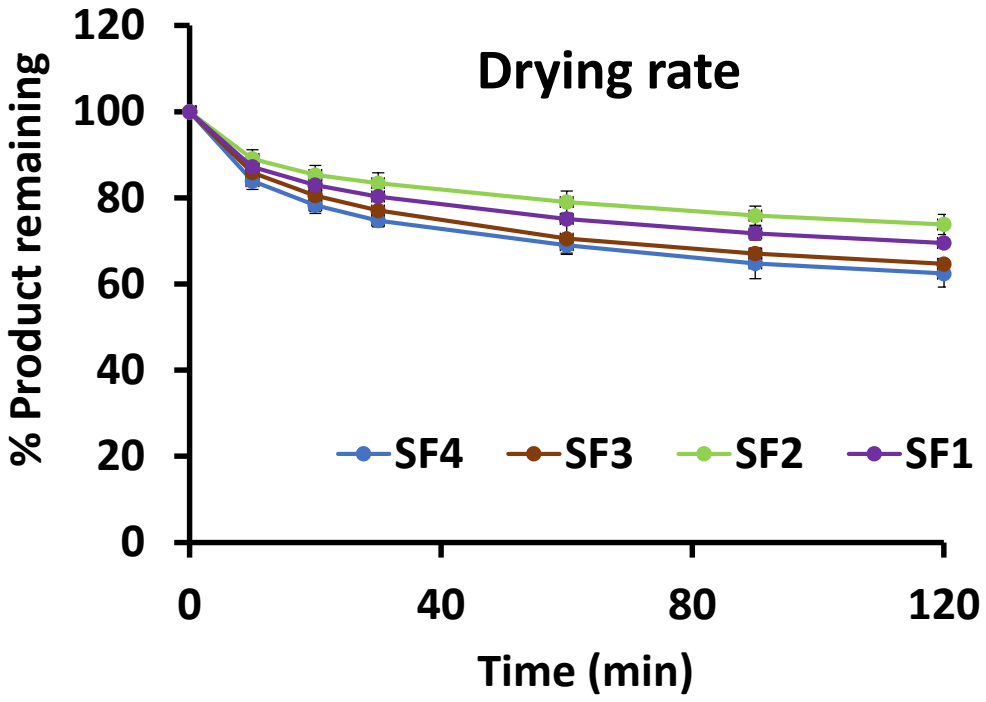
Critical Quality Attributes

Code	Amount of surfactant (% w/w)	Average globule size (µm)	Cream pH	Amount in Aqueous phase (mg/g)	Water activity (a_w)	IVRT slope (ug/cm2/h)	Work of adhesion (g.sec)	Viscosity (Pa.s) at Shear rate 100 1/s	Yield stress (Pa)
SF1	1.21	20.7± 16.54	5.60± 0.15	5.17	0.894± 0.025	245.2± 36.3	214.4± 14.45	3.37	190
SF2	1.27	19.3± 14.81	5.49± 0.08	5.54	0.890± 0.008	258.1± 32.9	217.1± 13.03	3.40	132
SF3	1.33	19.1± 16.79	5.54± 0.04	6.09	0.894± 0.003	266.1± 40.9	221.8± 13.90	2.95	132
SF4	1.40	14.4± 10.98	5.57± 0.04	4.42	0.917± 0.007	233.8± 27.4	244.3± 26.48	3.56	122

Surfactant Concentration and Product Performance

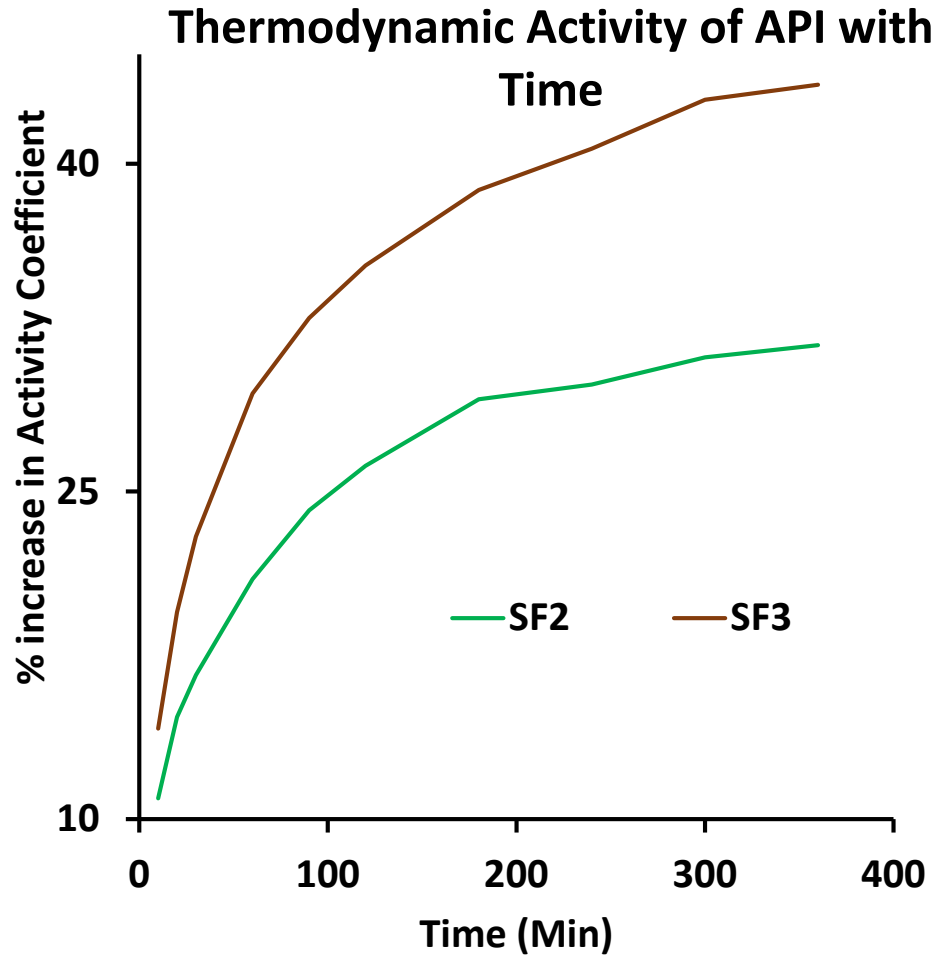


Dermatokinetics	SF1	SF2	SF3	SF4
$J_{max\ (ng/cm2/h)}$	51.2±45.53	41.2±32.71	149.4±93.96	308.0±138.89
AUC_{0-12}	289.2±258.93	154.0±117.65	936.8±669.55	1736.5±636.14



Surfactant Concentration and Product Performance

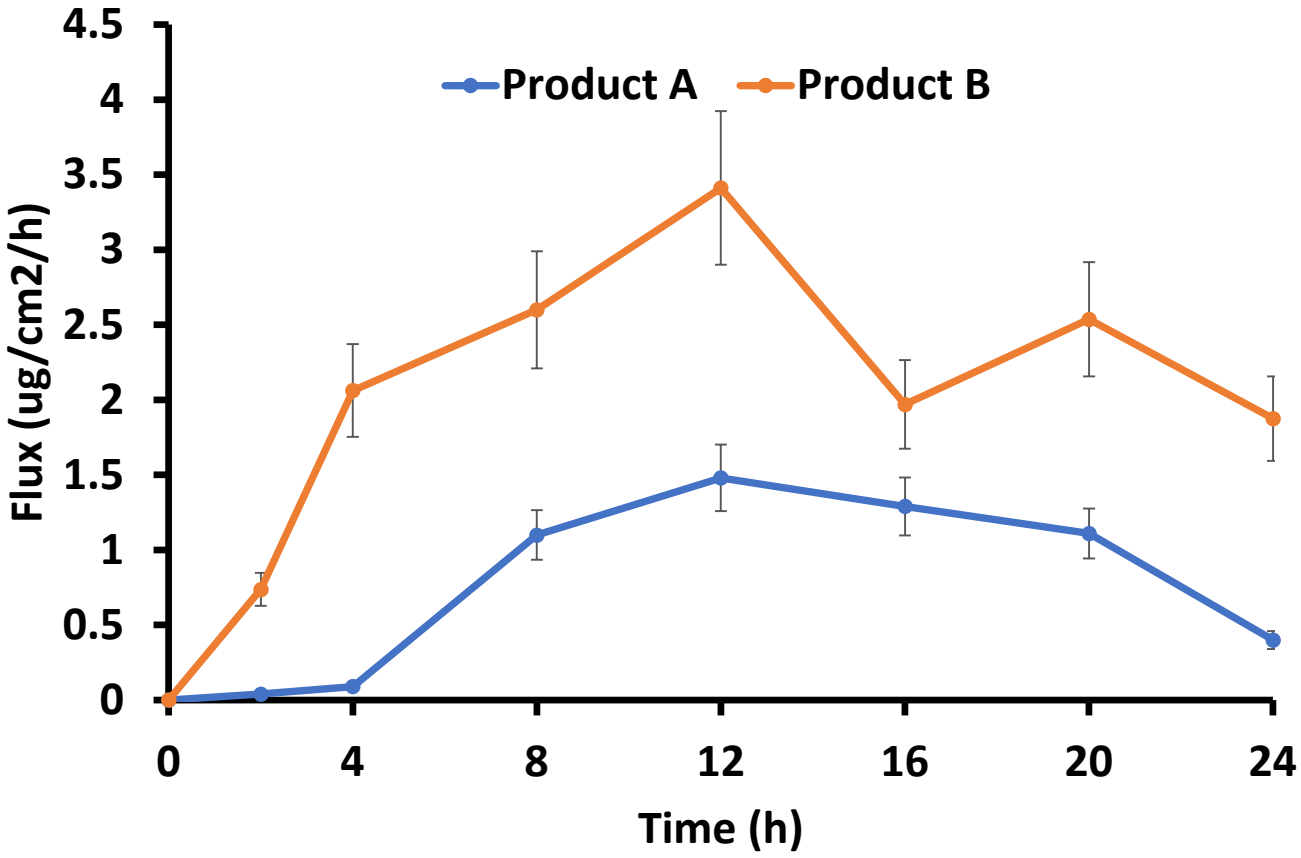
CQA	SF1	SF2	SF3	SF4
Amount of Drug in the Aqueous phase (ug/ml)	5173	5548	6099	5592
Saturation solubility of drug in the aqueous phase	6053	5650	10479	9189
Initial Thermodynamic activity	0.8542	0.9834	0.6643	0.5592



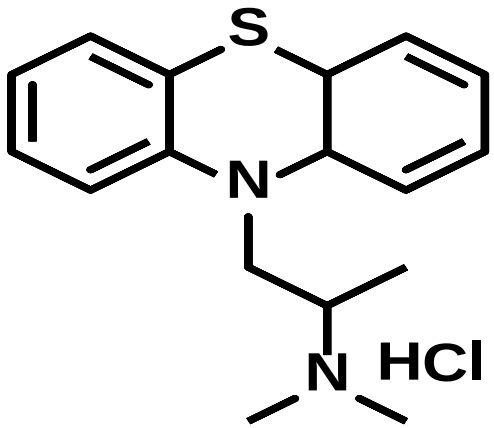
Permeation profile of Promethazine from Gels

Product A: API dissolved in Water (50 mg/ml)+ HPMC HV 4%
Product B: 2% HPMC in water +API dissolved in water+2% HPMC

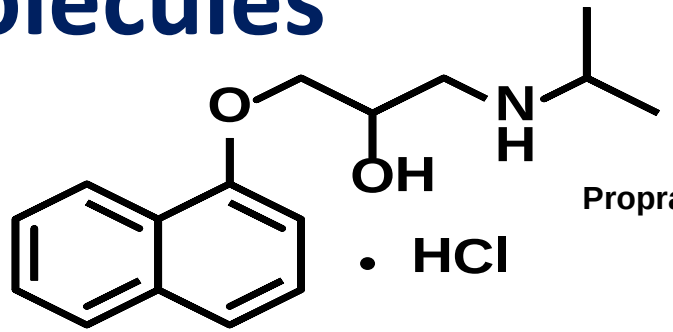
Characteristics	Product A	Product B
pH	6.0	6.0
Viscosity (0.0102 1/s)	10230 Pa.s	10,141Pa.s
Water activity	0.9976	0.9971
Drying rate (t50%)	11 min	10.5 min



Molecular Association of Surfactant like Drug Molecules

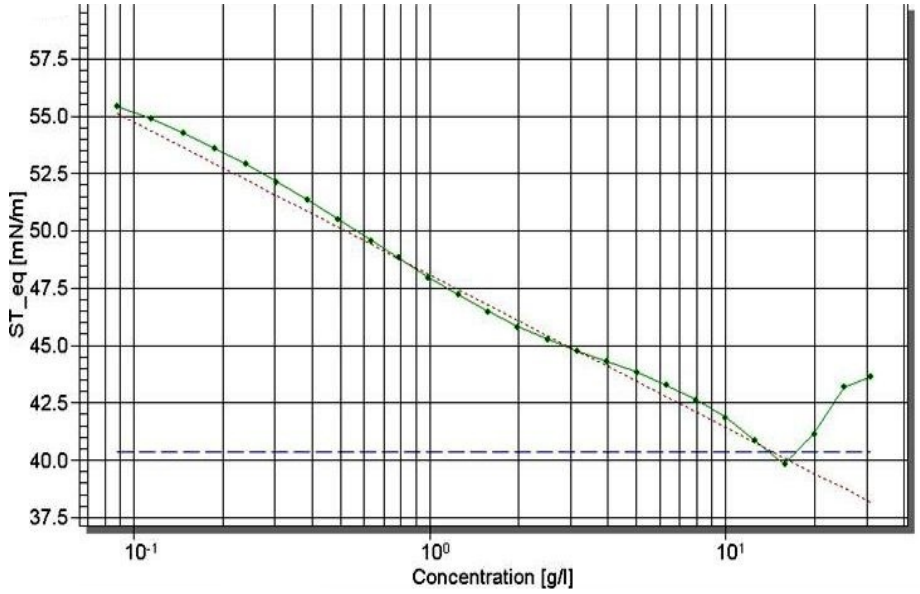


Promethazine hydrochloride structure

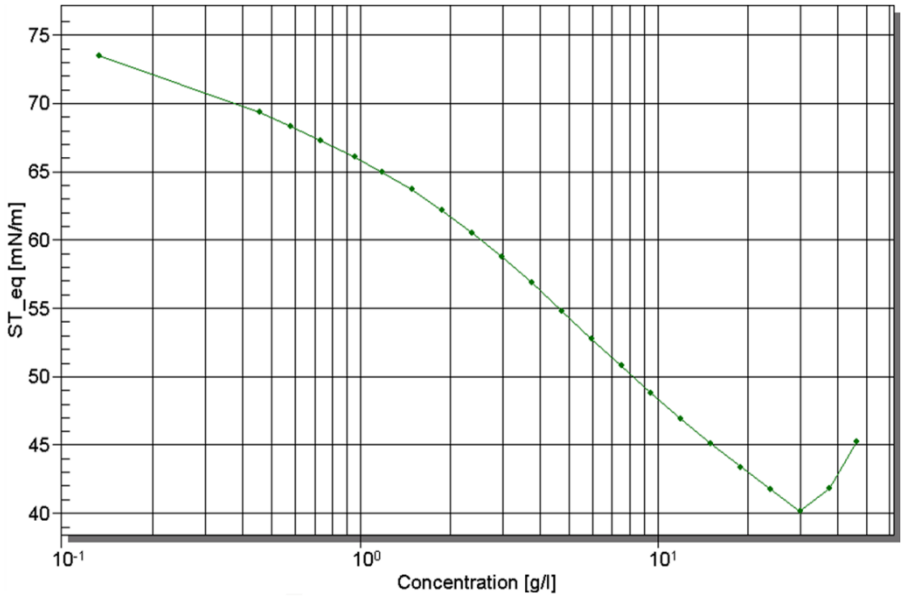


Propranolol hydrochloride structure

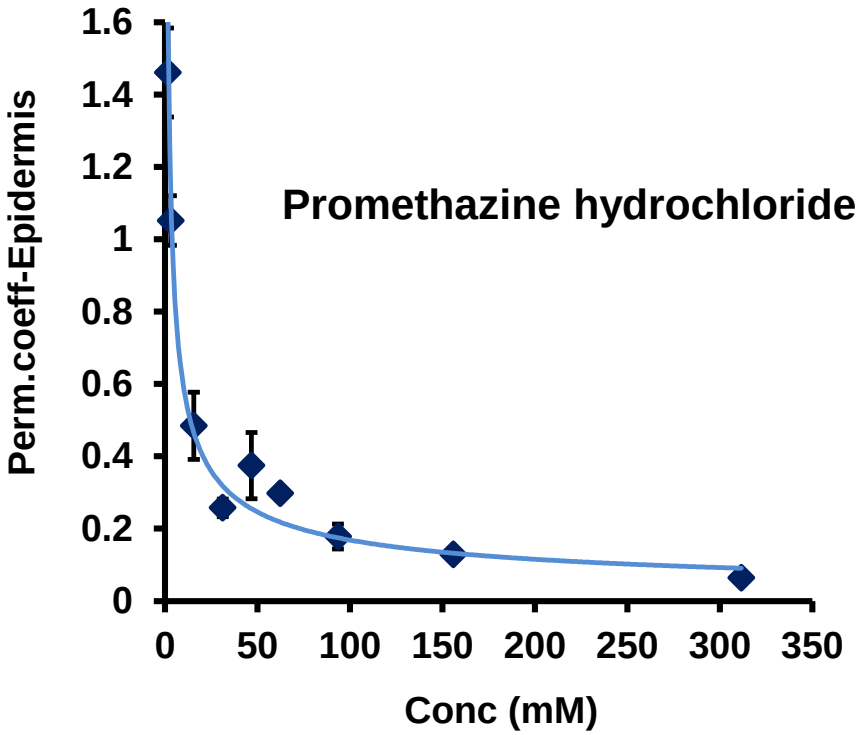
CMC = 49.2 mM

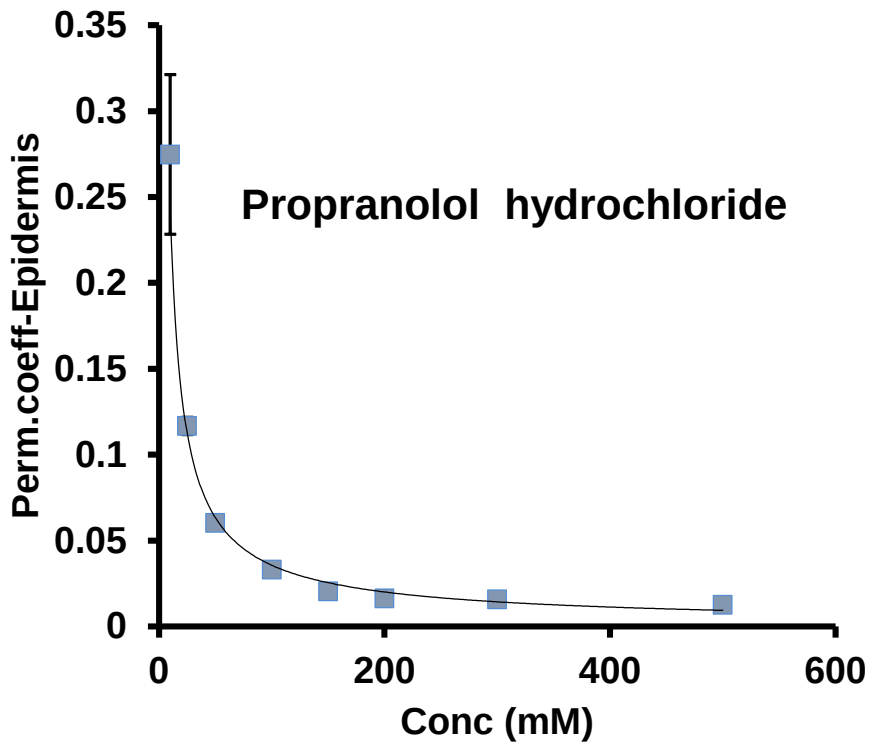


CMC = 98.4 mM

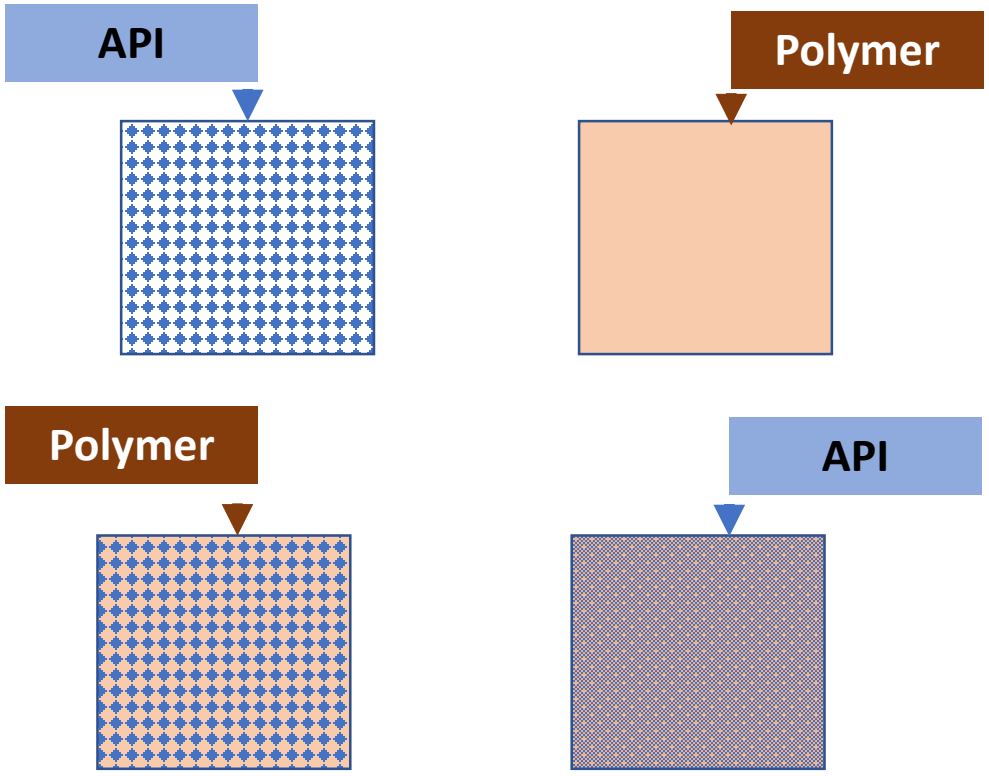


Permeability Coefficient Changes with Concentration



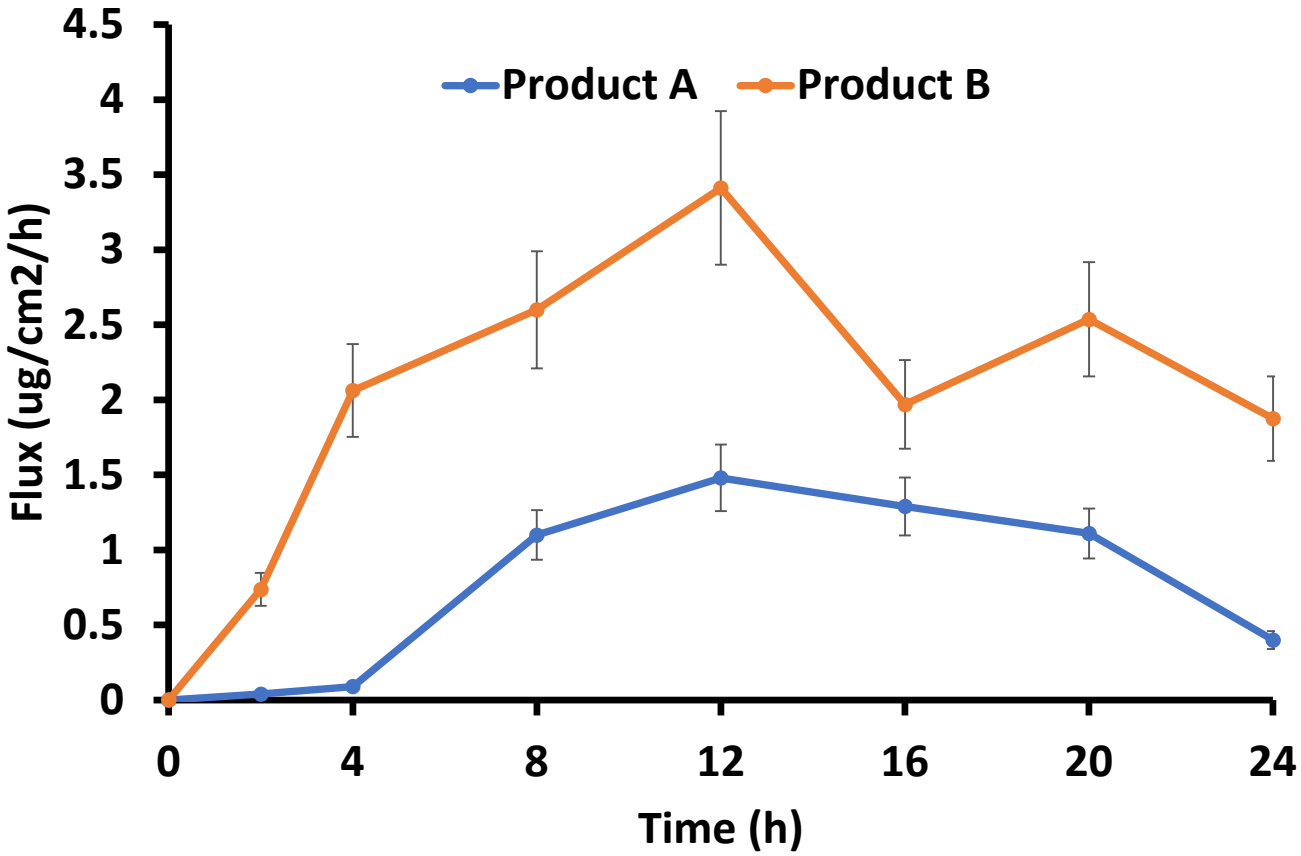


Permeation profile of Promethazine from Gels



Product A
API dissolved in Water (50 mg/ml)+ HPMC HV 4%

Product B
2% HPMC in water +API dissolved in water+2% HPMC



Conclusions

- The inactive ingredients present in the formulation could influence of the performance of topical products.
- The physicochemical nature of inactive ingredients and interaction between the inactive ingredients in the formulation would determine the net impact on the skin permeability to API.
- The inactive ingredients could change the thermodynamical characteristics of API in the formulation which in turn could influence the performance of the topical product.
- Manufacturing and Process variables of inactive ingredients could influence the microstructure of the product leading to difference in performance between RLD and Generic product (Q1/Q2 identical).

Acknowledgements

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