Role of Excipients in Dermal and Transdermal Delivery of Drugs

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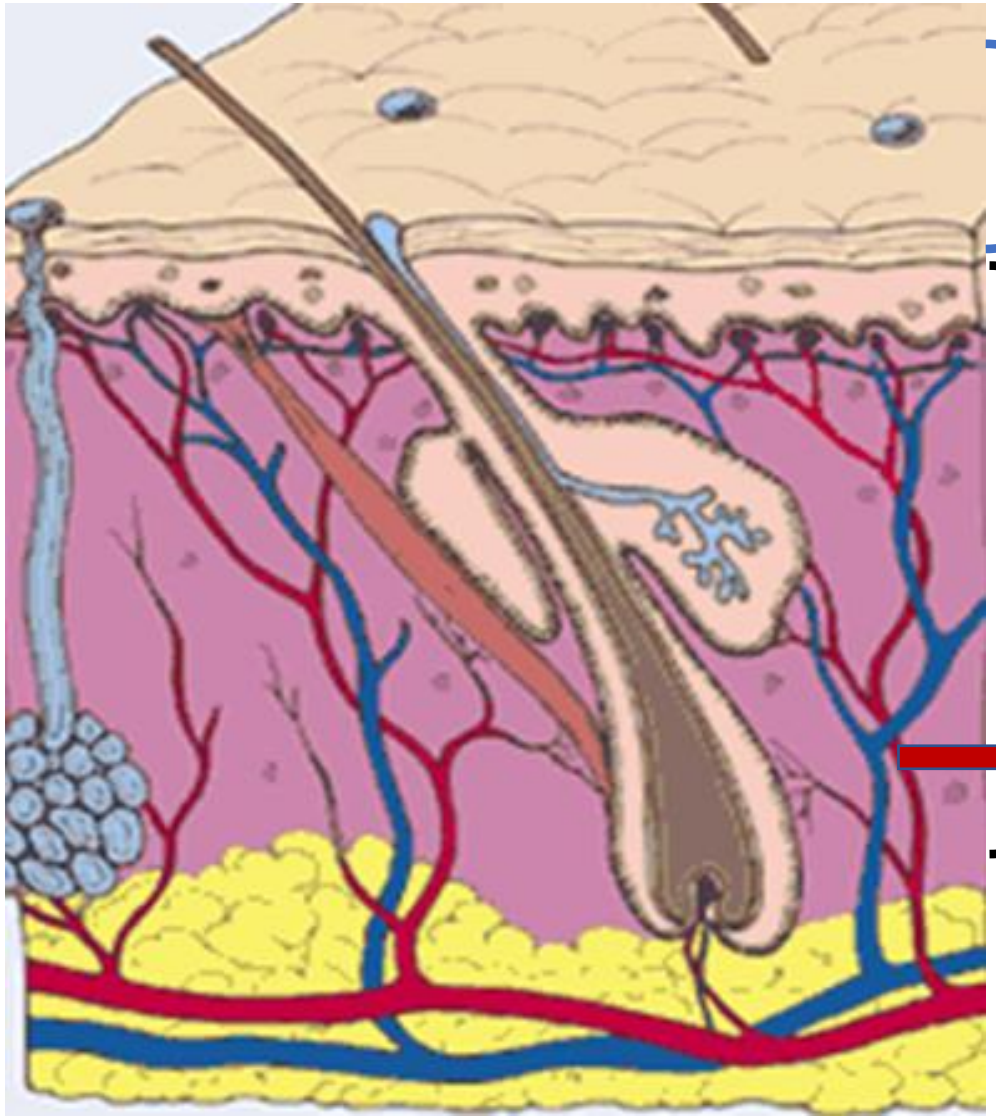
Dermal versus Transdermal Delivery



Skin Protectants
Antifungals
Antiseptics
Emollients

Local Delivery

Anti-inflammatory
Local Anesthetic
Antiviral
Corticosteroids

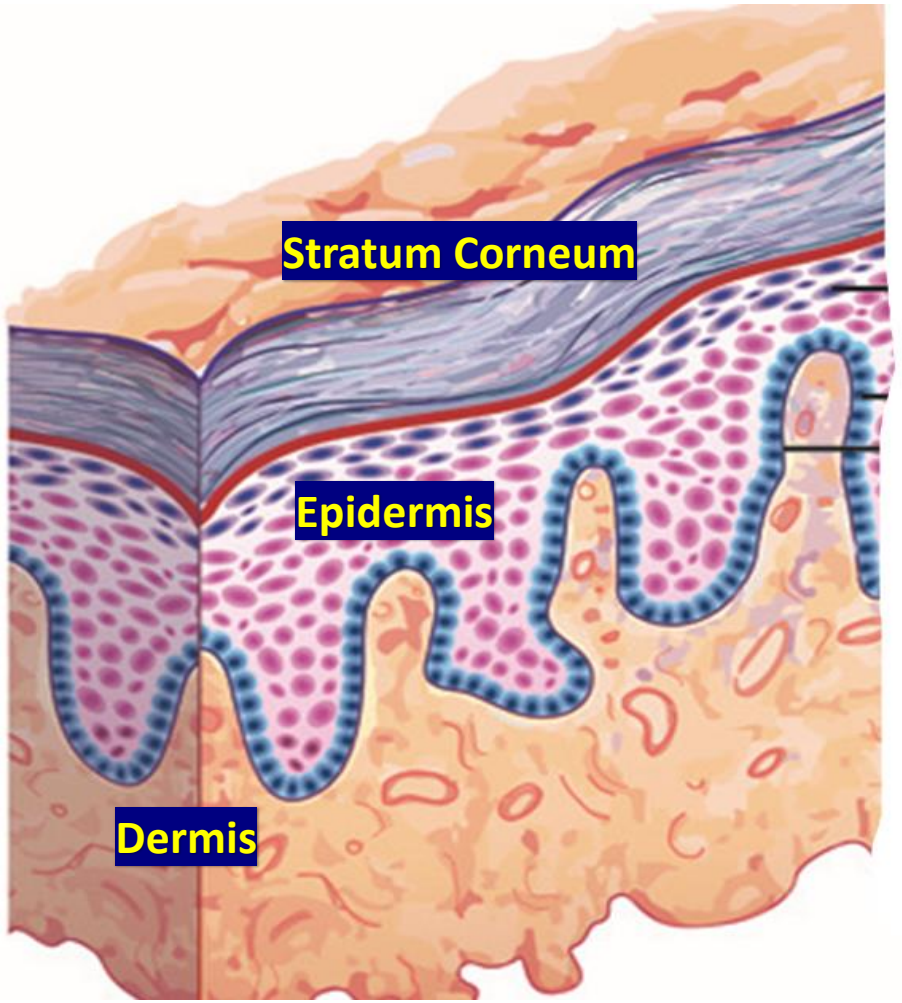
Intradermal Delivery

Fentanyl
Hormones
Nitroglycerin
Nicotine

Transdermal Delivery
(Semisolids or patches)

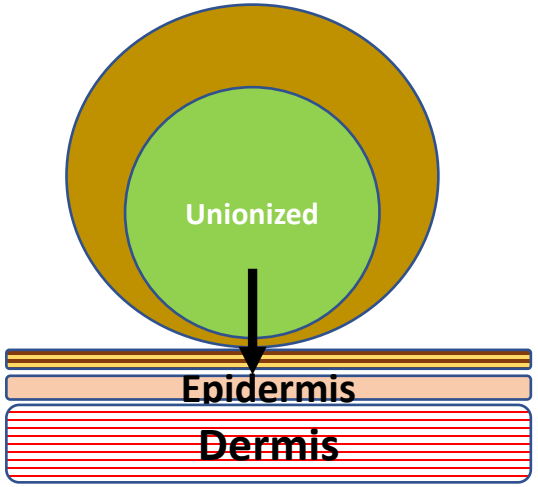
What do we know so far about Topical drug delivery?

- Stratum corneum is the topmost layer and consists of lipids and keratinocytes.
- <500Da, Log P 1-3, low melting, molecules permeate well.
- The stratum corneum is poorly permeable to macromolecules and highly polar molecules
- The drug that makes its way across the stratum corneum and epidermis will eventually end up in systemic circulation.

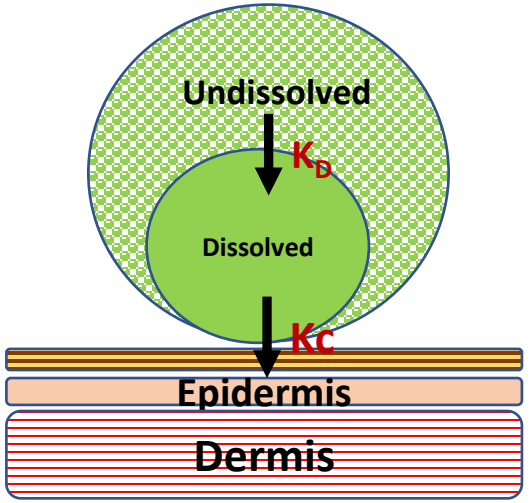


Critical Quality Attributes Products

pH of the formulation



Dissolved/Undissolved drug



Solvent Activity (a_w)

$a_w = \rho/\rho_0$

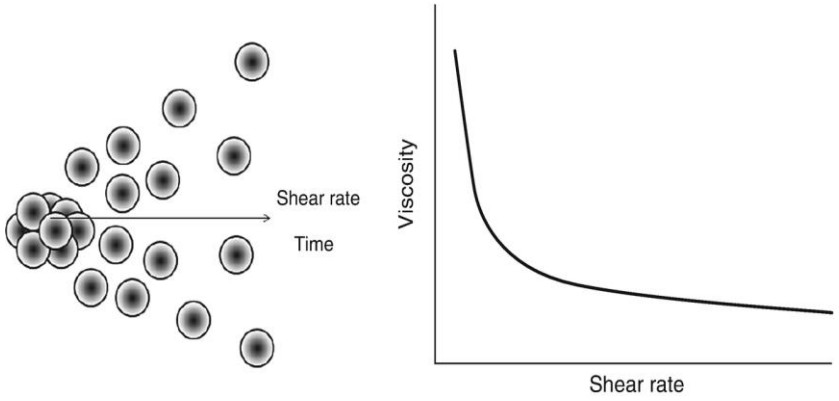
ρ = Partial vapor pressure of solvent in the product

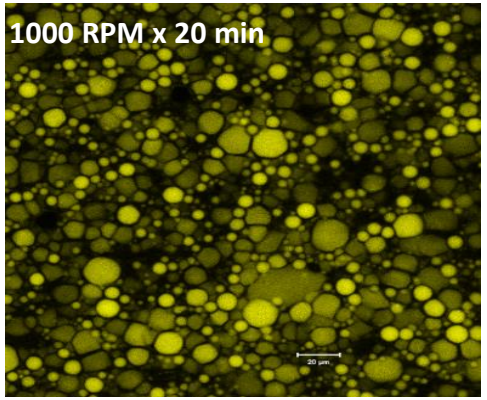
ρ_0 = Vapor pressure of pure water

Rate of dissolution of drug

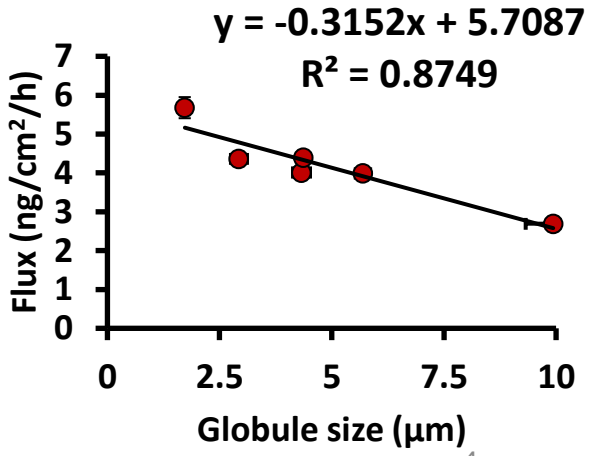
- Particle Size
- Polymorphic form
- Morphology of particles

Rheological Behavior





Globule Size



Metamorphosis and Excipients

Application induced changes in the formulation characteristics

Evaporative metamorphosis

Drug penetration from remnant vehicle of drug

Primary Phase

Secondary Phase

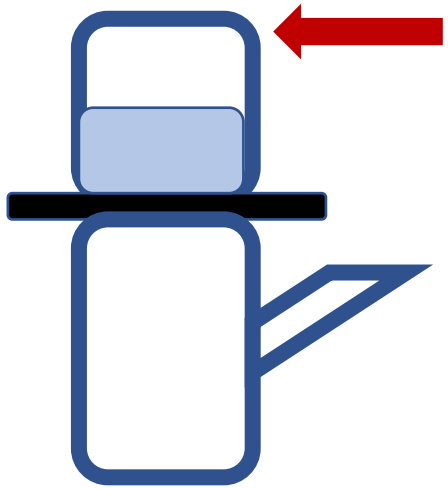
Changes in the formulation due to mode of application.

Changes predominantly due to evaporation of solvents

No major changes in the composition

In vitro Permeation Testing

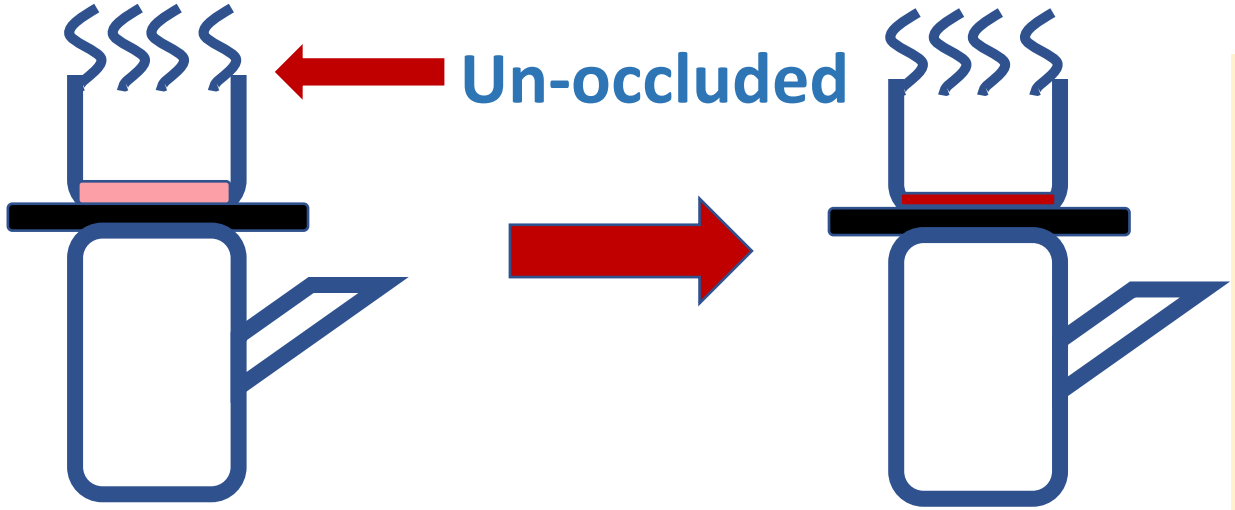
Infinite Dose



- No evaporation
- No change in composition
- Drug concentration change is negligible
- No change in CQA

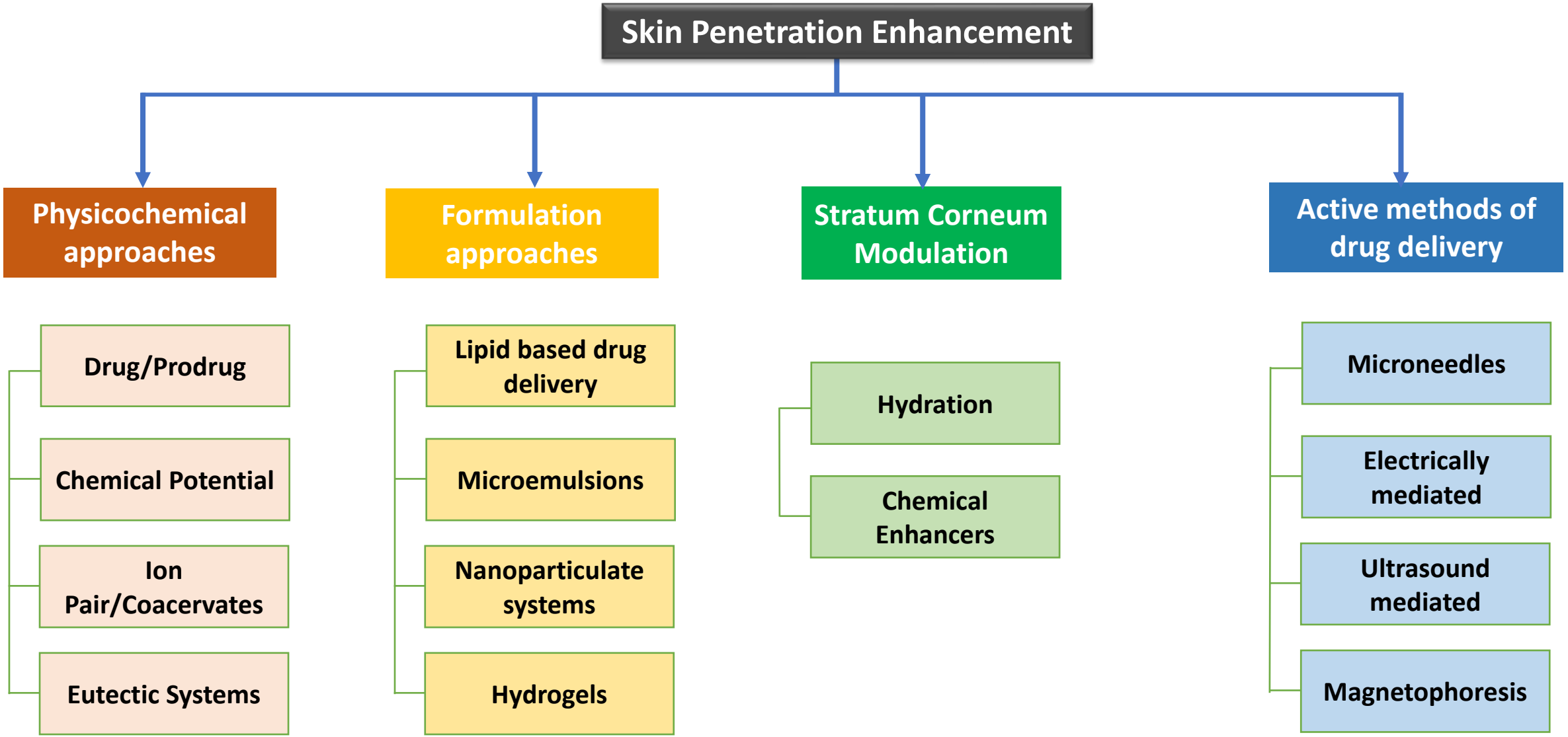
Finite Dose

- Evaporation of solvents
- Mimics in vivo condition



- Change in composition
- Change in conc. of drug is significant
- Change in CQA

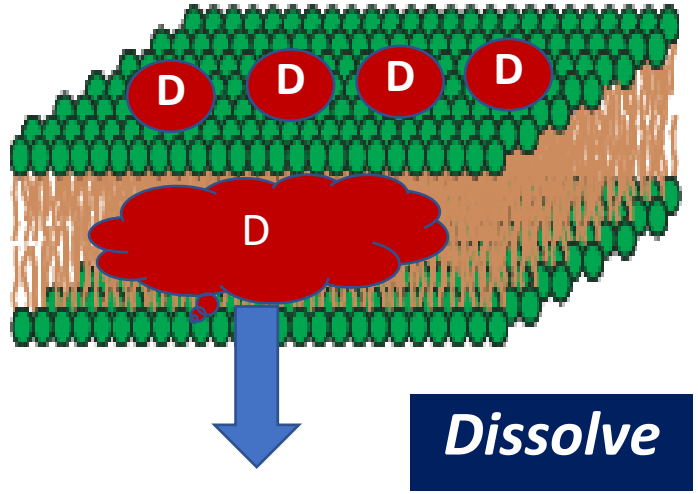
Approaches to Enhance the Dermal Drug Absorption

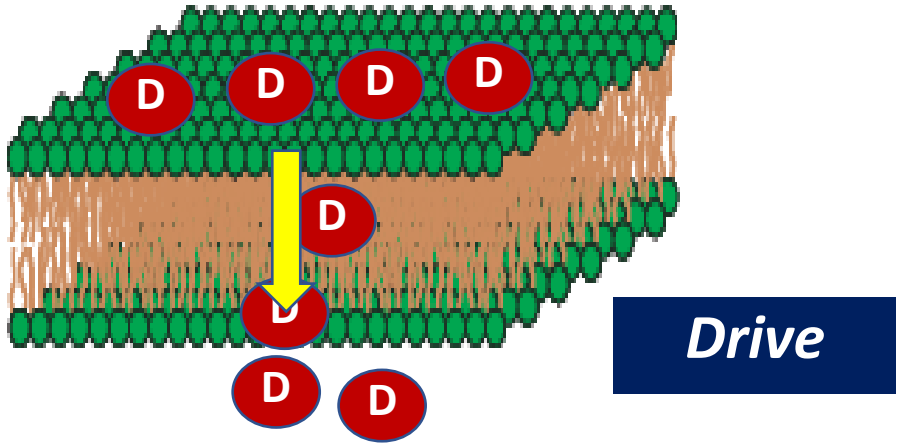


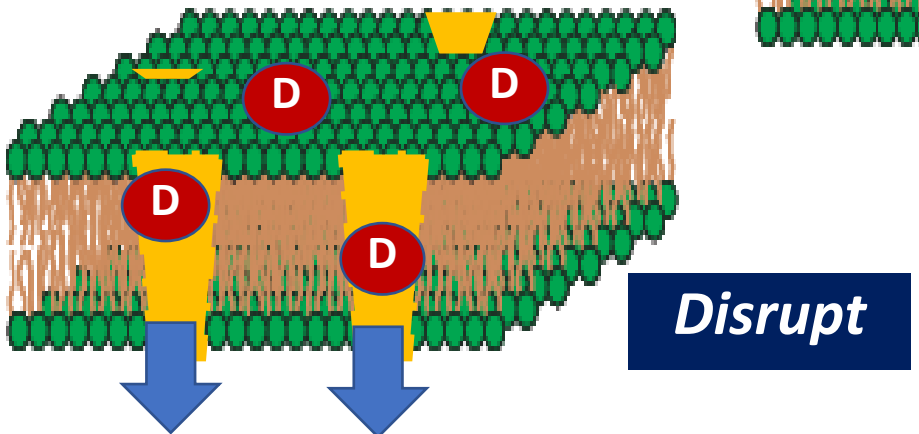
Chemical Permeation Enhancers

Chemical Permeation Enhancers

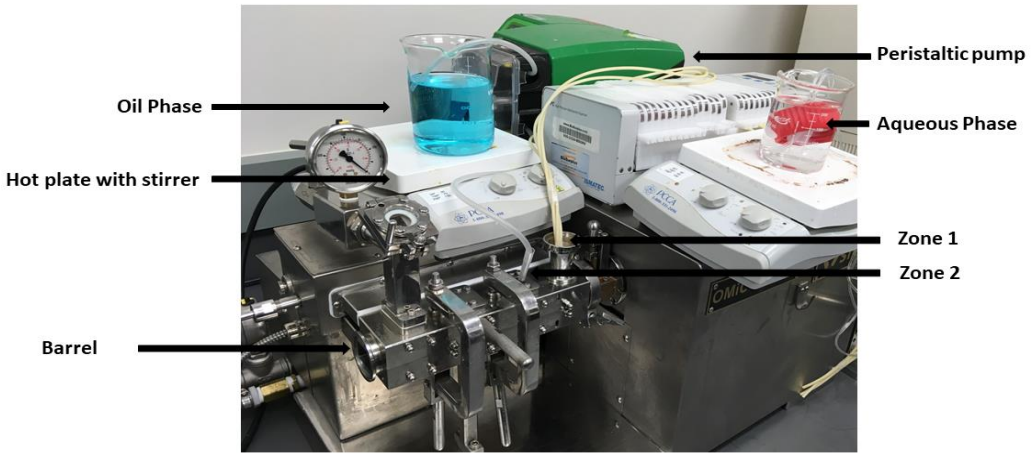
- Solvents
- lipids
- Surfactants
- Terpenes





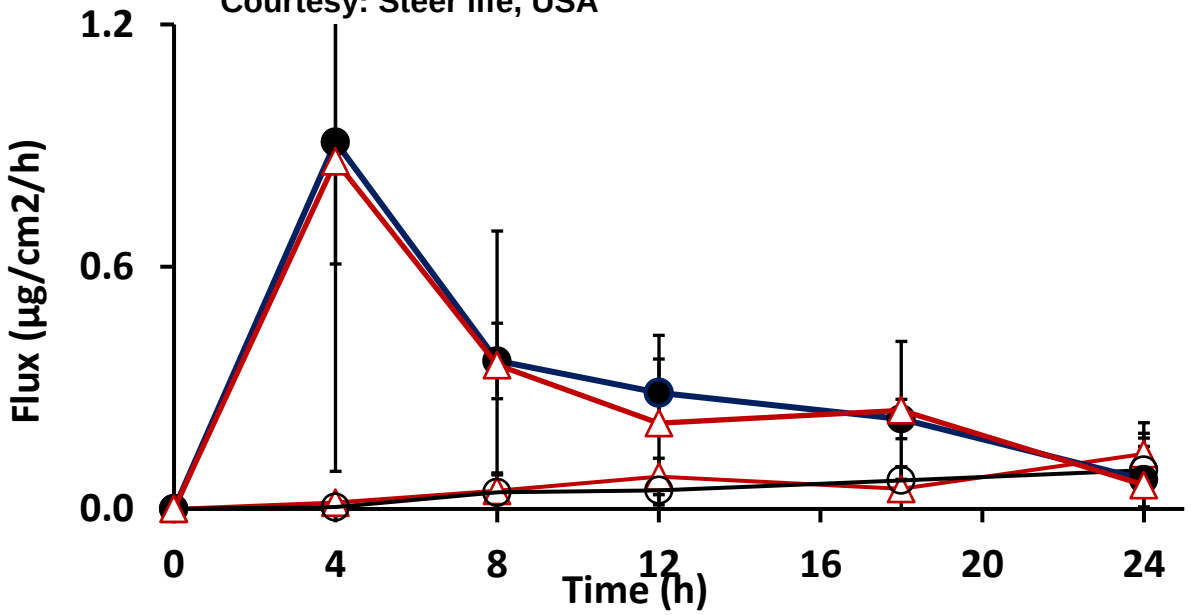


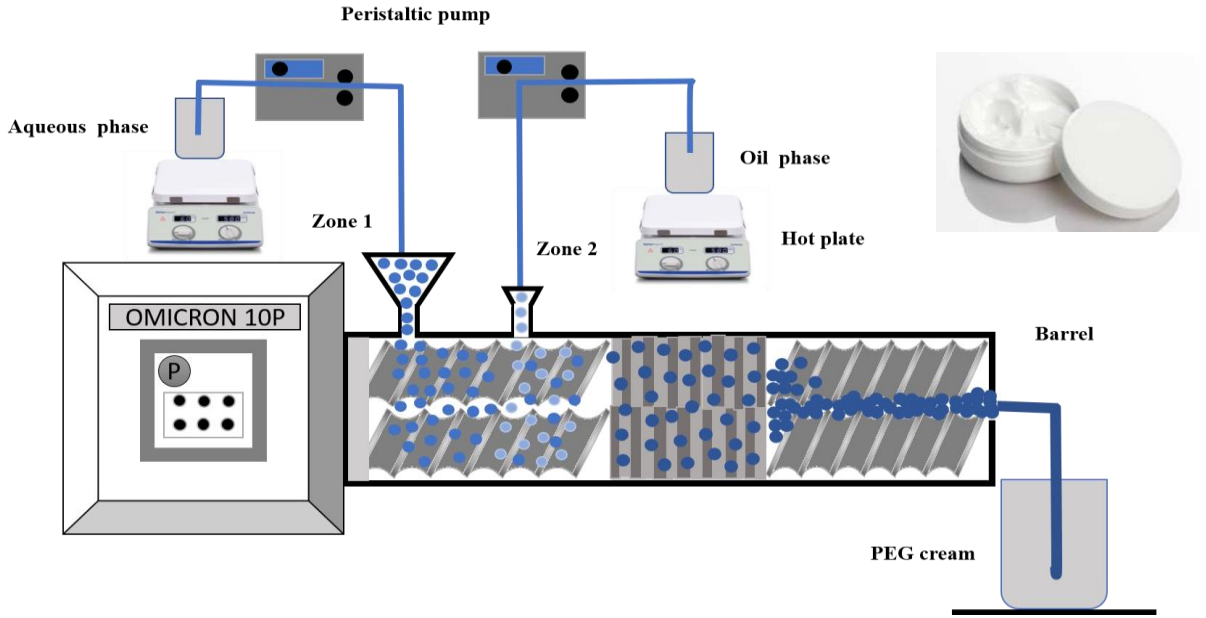
Continuous Manufacturing of Creams using HME



Omicron 10 [Mini] with Do/Di ratio 1.71 for manufacturing of the cream formulation.

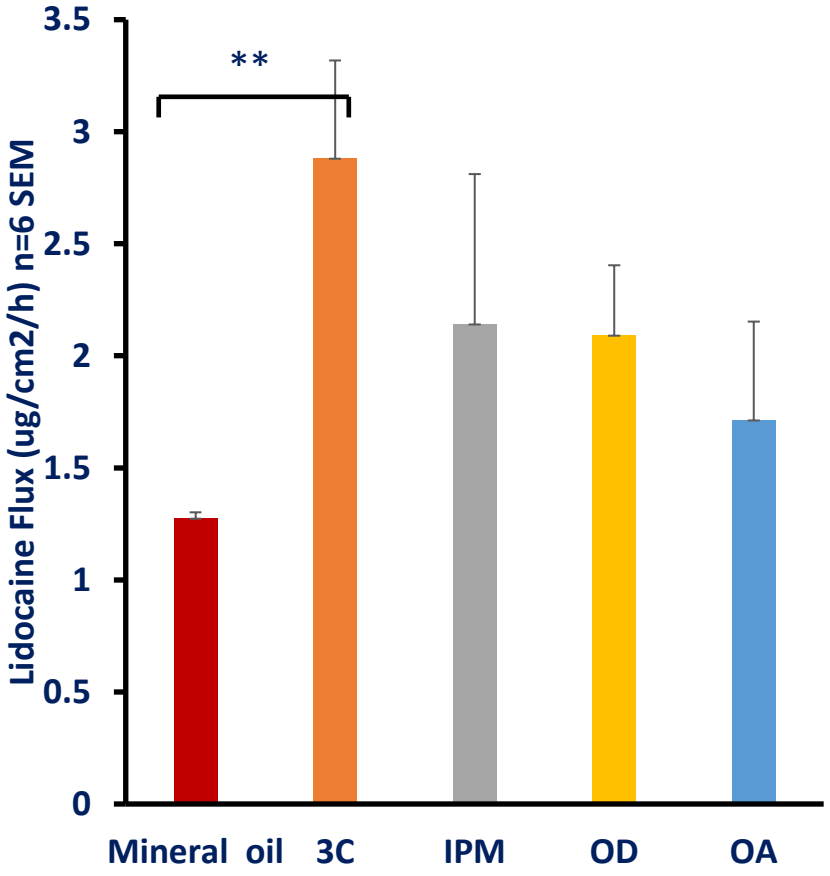
Courtesy: Steer life, USA



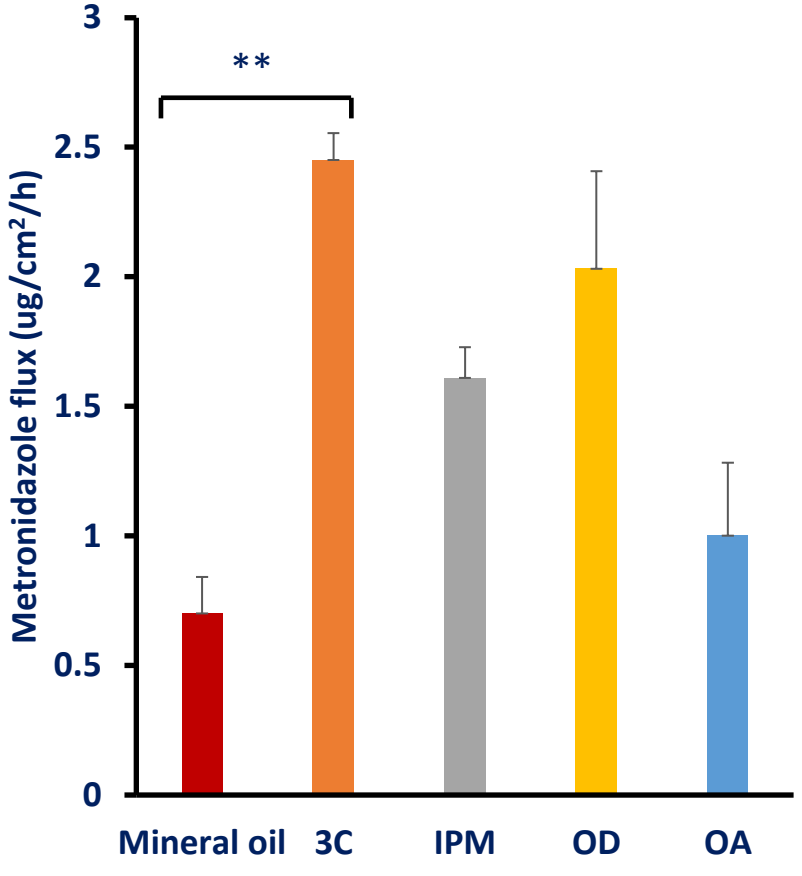


Composition	AUC (ug/cm²)	Jmax (µg/cm²/h)
Labrafil M 1944 CS.	0.81 ± 0.02	0.18 ± 0.10
Light Mineral oil	0.56 ± 0.05	0.12 ± 0.08
Labrafil M 1944 CS +Transcutol P	9.31 ± 0.89	0.91 ± 0.30
Light mineral oil+ Transcutol P	8.75 ± 2.46	0.87 ± 0.75

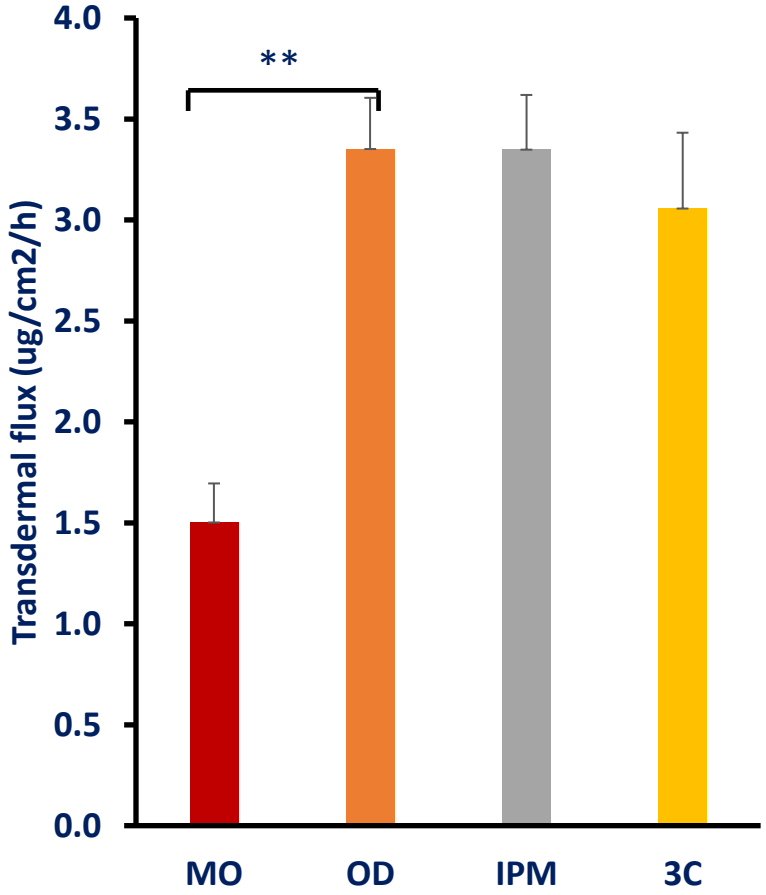
Dermal Delivery of Drugs-Role of Emollients



Metronidazole



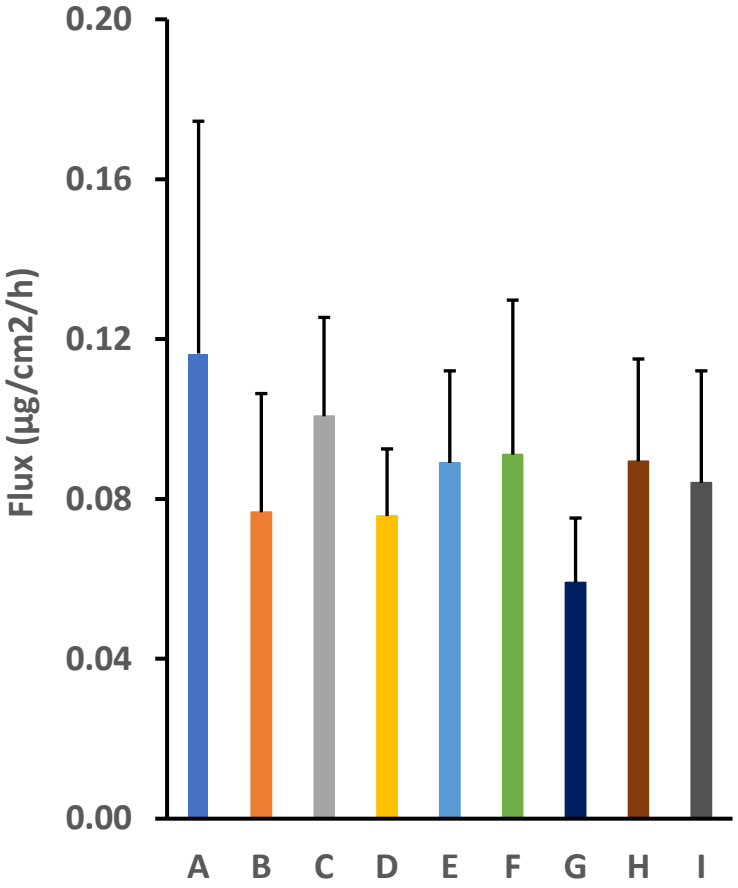
Lidocaine

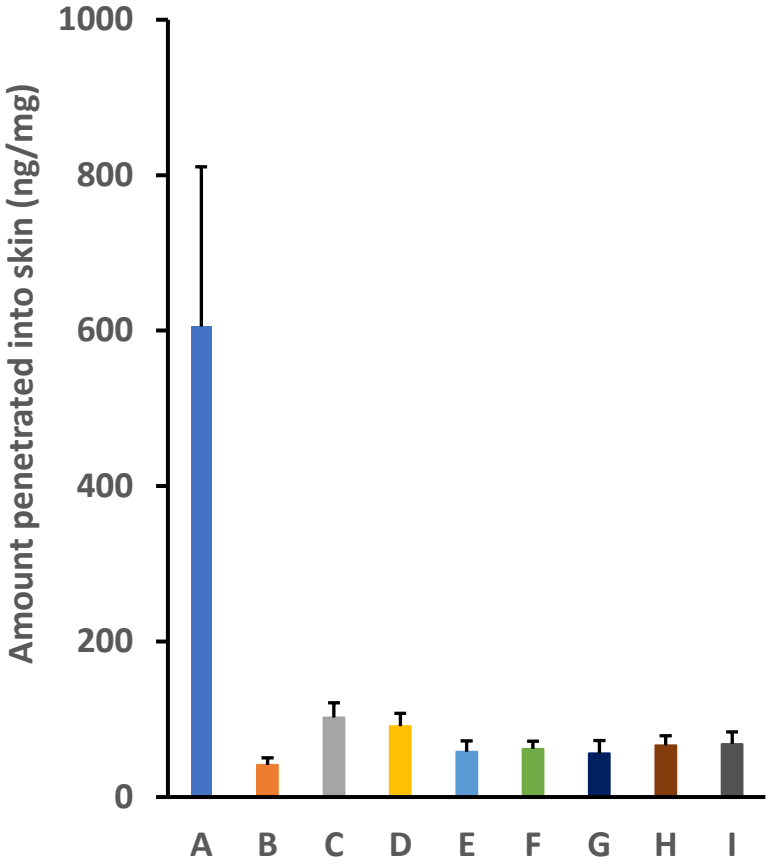


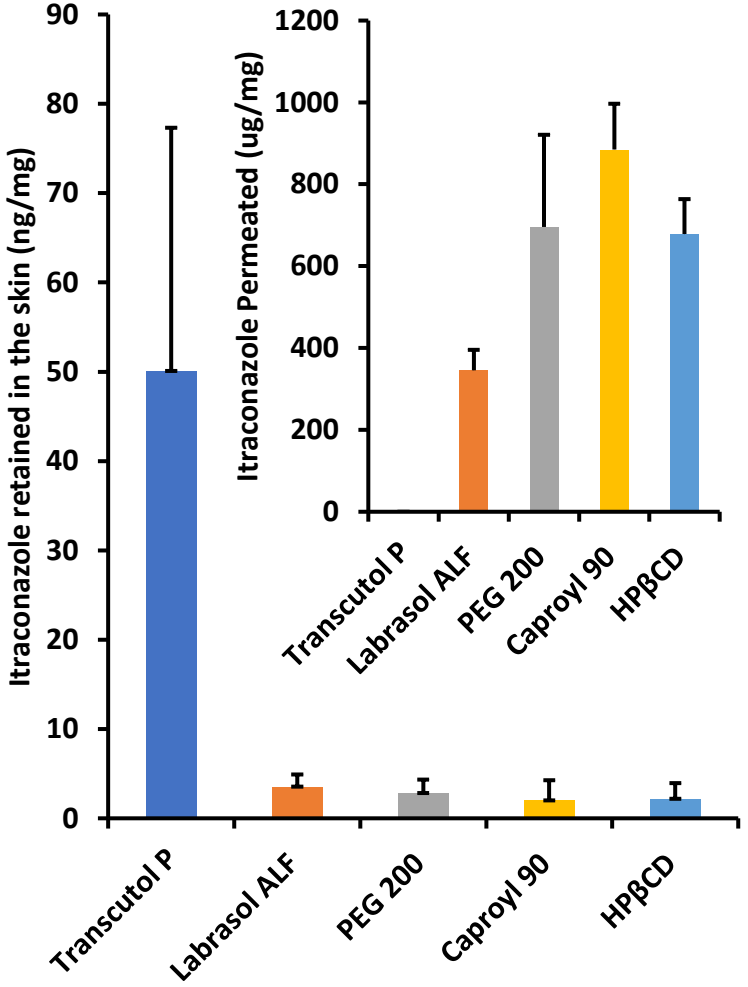
Ketoprofen

Source of Emollients: BASF, Kollicream® 3C, Kollicream® IPM, Kollicream® OD and Kollicream® OA

Dermal Delivery of Drugs-Role of Enhancers



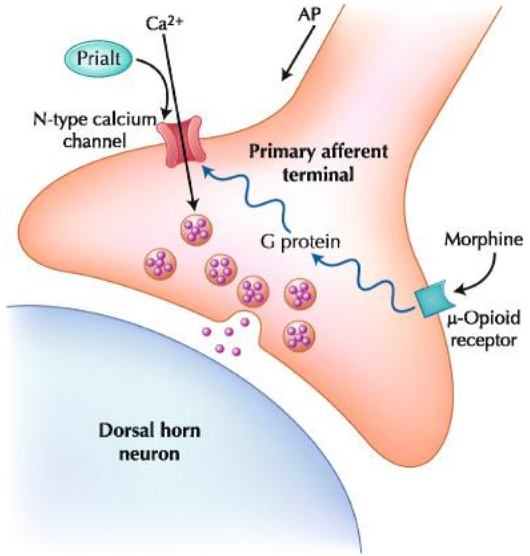




(A) Transcutol P: water (1:1), (B) Transcutol P: Labrasol (1:1), (C) Transcutol P: Labrasol: water (2:1:1), (D) Transcutol P:Lauroglycol FCC (1:1), (E) Transcutol P:Plurol Oleique CC 497 (1:1), (F) Transcutol P:Labrafil M 1944 CS (1:1), (G) Transcutol P:Capryol PGMC (1:1), (H) Transcutol P: Labrafac Lipophile WL (1:1), (I) Transcutol P

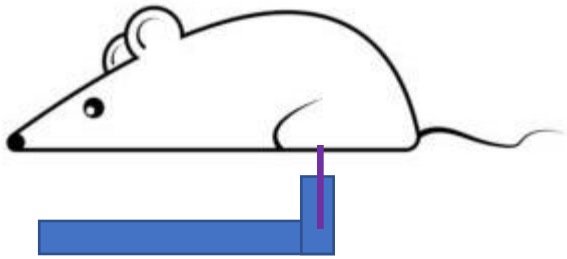
Source of Lipid excipients: Gattefosse

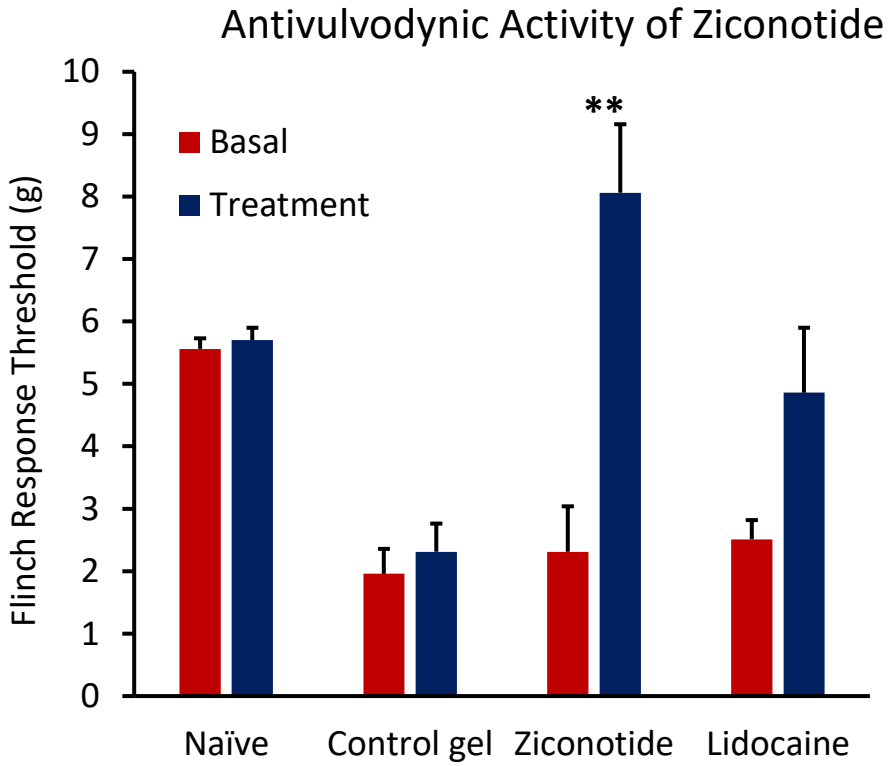
Passive Delivery of Peptide- Topical Treatment for Vulvodynia



(*Courtesy of* Elan Corporation)

Induction of candidiasis fungal infection



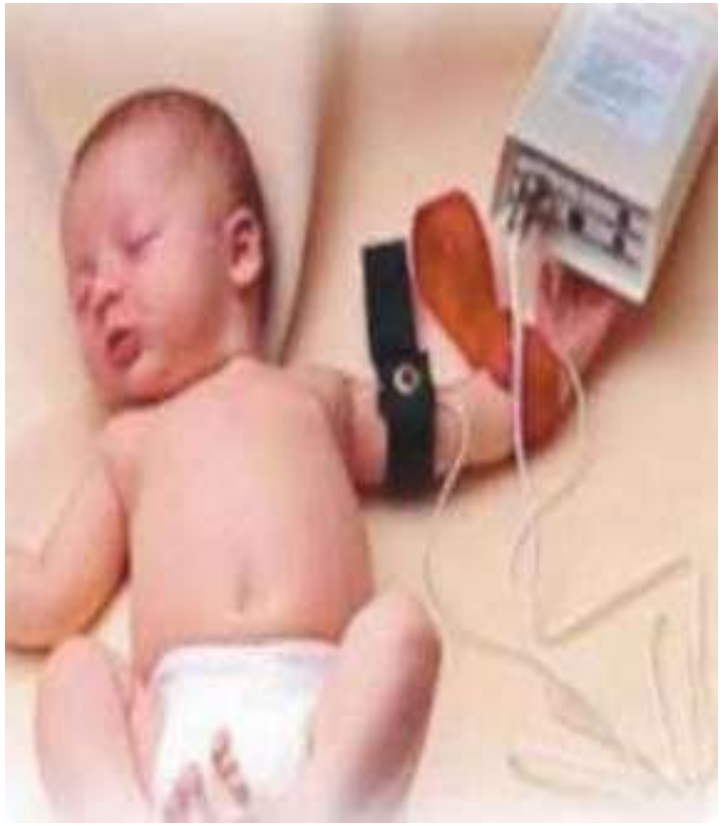


- Intraplantar administration of ziconotide in rats demonstrated significant antinociception.
- Ziconotide is shown to act on CaV.2.2 receptors to produce its locoregional analgesia.
- Ziconotide in the mouse model of vulvodynia exhibited significantly potentiated the flinch response threshold.

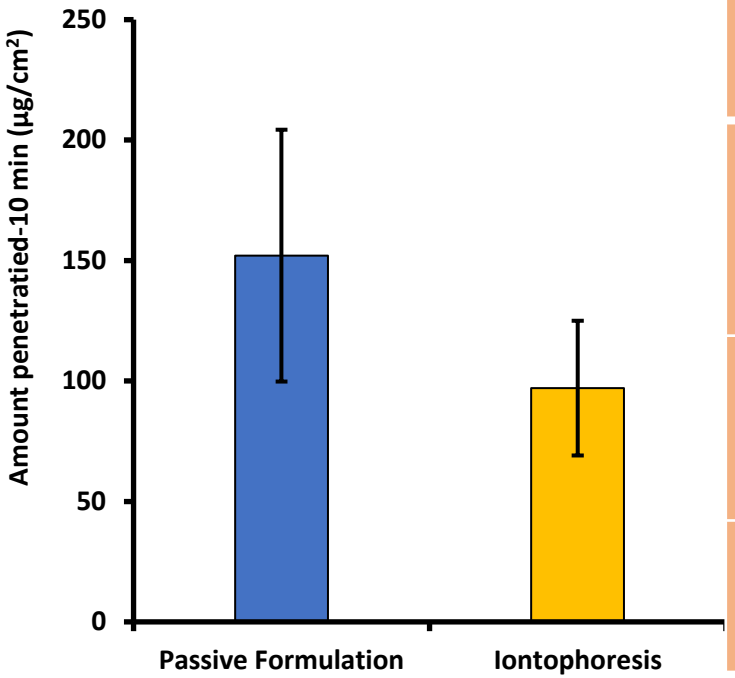
After 6h , ziconotide significantly potentiated the flinch response threshold compared to the lidocaine group($p<0.01$)

Topical Pilocarpine Formulation for Diagnosis of Cystic Fibrosis

Formulation	Penetration enhancer	Enhancer concentration (%w/w)	Amount Permeated after 10 min (ug/cm2)
S12	PMS10:4:10	PEG 200 - 10% Menthol - 4% Salicylic acid - 10%	105.45 ± 41.58



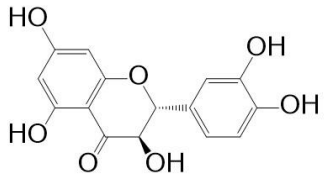
Sweat test- Diagnosis of cystic fibrosis
Pilocarpine iontophoresis



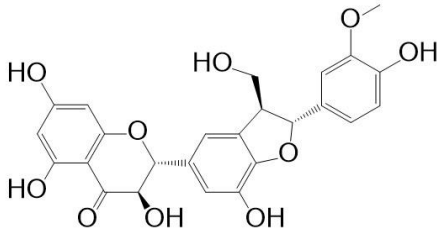
Human Subject n=20 in each group		
Formulation	Sweat Collected (mg)	Chloride Concentration (mMol/L)
Test formulation	77.28 ± 18.97	11.67 ± 6.22
Control	16.75 ± 9.71	-

Fatima et al., J Pharm.Sci. 2020, 109: 1747

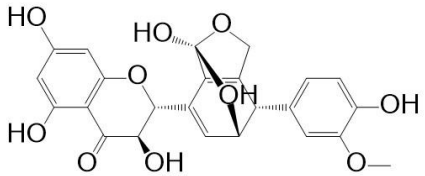
Dermal Delivery of Drugs-Role of Complexing Agents



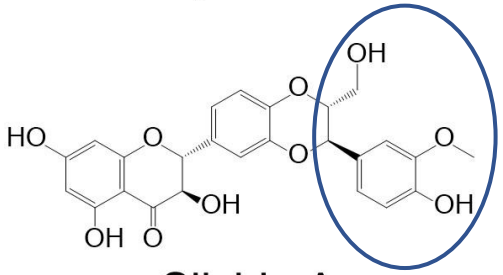
Taxifolin



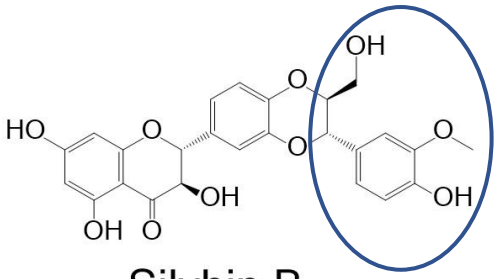
Silychristin



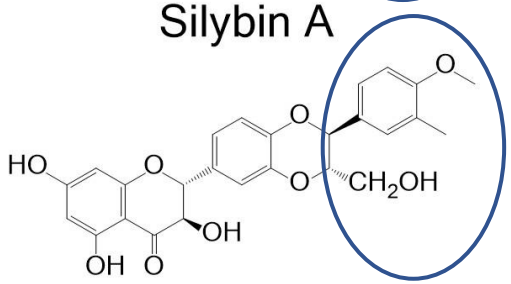
Silydianin



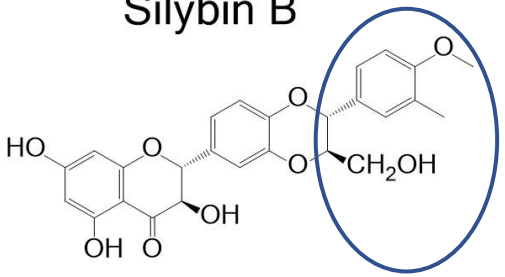
Silybin A



Silybin B



Isosilybin A



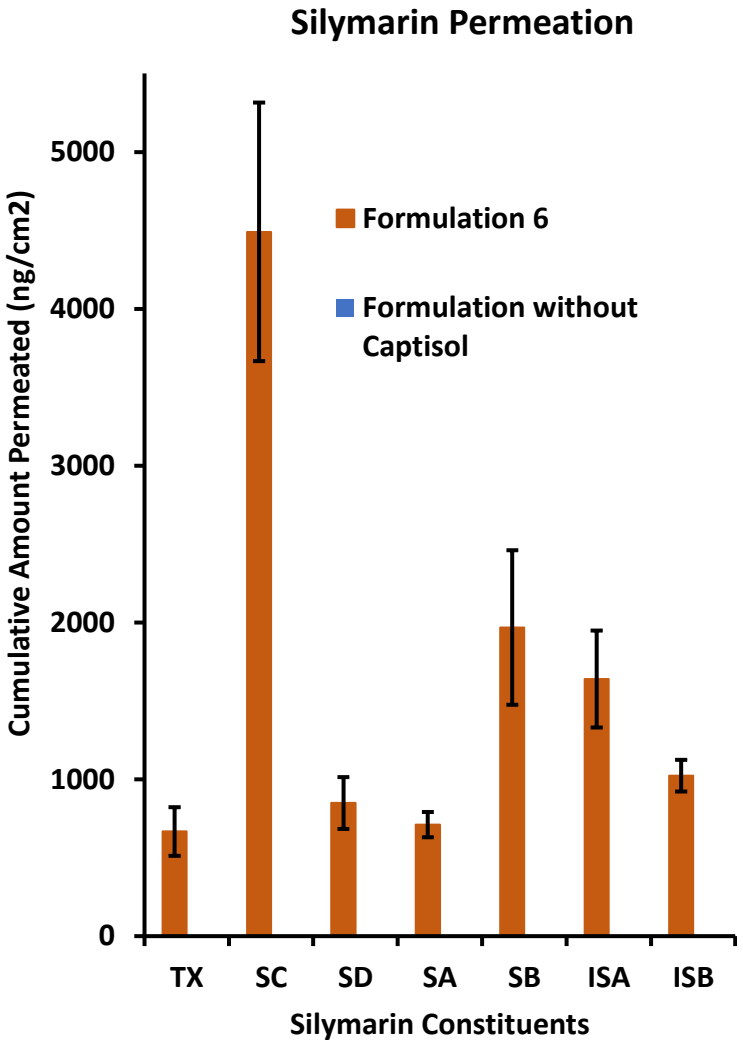
Isosilybin B

Silymarin Constituents	Silymarin constituents (mg/gm of extract)	Solubility in water (µg/mL)	Log P	Solubility in 100 mM Captisol (mg/mL)
Taxifolin	11.1 ± 0.36	135 ± 3.31	1.06 ± 0.06	2.62 ± 0.31
Silychristin	57.1 ± 1.18	145 ± 9.87	1.51 ± 0.01	5.25 ± 0.28
Silydianin	19.0 ± 0.57	55.9 ± 1.56	1.16 ± 0.05	7.71 ± 0.20
Silybin-A	21.4 ± 0.74	3.45 ± 0.45	2.29 ± 0.03	2.24 ± 0.12
Silybin-B	35.8 ± 1.08	11.0 ± 0.24	2.26 ± 0.07	4.40 ± 0.18
Isosilybin-A	28.2 ± 0.86	7.29 ± 0.20	2.55 ± 0.40	2.75 ± 0.08
Isosilybin-B	7.81 ± 0.26	1.52 ± 0.03	2.69 ± 0.27	0.79 ± 0.03

Source of Captisol®: Ligand Pharmaceuticals Inc

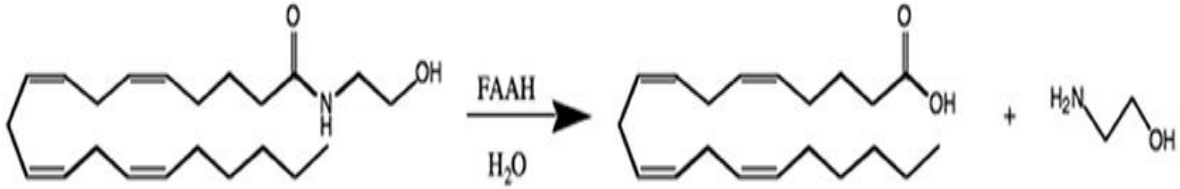
Dermal Delivery of Drugs-Role of Complexing Agents

Enhancers	Taxifolin	Silychristin	Silydianin	Silybin A	Silybin B	Isosilybin A	Isosilybin B
No Captisol	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
No enhancer	BLQ	50 ± 3.89	81.3 ± 7.41	20.4 ± 4.82	32.4 ± 6.21	31.3 ± 5.12	BLQ
TPGS (10%)	BLQ	127 ± 9.54	116 ± 9.32	69.9 ± 10.2	63.9 ± 5.87	54.2 ± 7.41	32.8 ± 4.06
Taurine (5%)	BLQ	110 ± 11.5	327 ± 76.2	48.8 ± 6.23	96.4 ± 14.8	67.6 ± 10.2	24.8 ± 4.17
Tween 80 (10%)	BLQ	56.1 ± 6.32	63.9 ± 7.61	33.0 ± 3.91	49.5 ± 7.84	27.2 ± 2.86	20.9 ± 3.67
TPGS : Tween 80 (5 : 5%)	5.22 ± 1.2	59.9 ± 4.81	78.6 ± 8.93	34.6 ± 3.47	43.2 ± 9.23	27.2 ± 5.23	22.8 ± 3.14
Phenyl piperazine (0.15%)	16.4 ± 6.83	92.6 ± 11.8	68.5 ± 5.87	36.0 ± 5.76	67.1 ± 7.95	56.9 ± 7.48	26.9 ± 1.89
PEG 400 (20%)	7.12 ± 1.75	86.3 ± 6.41	135 ± 8.89	45.6 ± 7.84	55.7 ± 6.32	69.4 ± 10.2	34.2 ± 2.32
Propylene glycol (20%)	44.8 ± 2.62	616 ± 69.1	1525 ± 182	113 ± 16.2	308 ± 45.1	216 ± 26.4	61.9 ± 3.48
Transcutol (20%)	35.8 ± 4.45	348 ± 35.7	468 ± 36.9	57.8 ± 11.9	128 ± 17.4	106 ± 17.1	26.2 ± 1.43

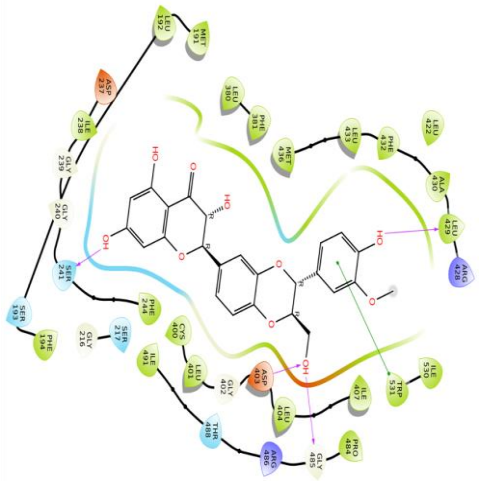


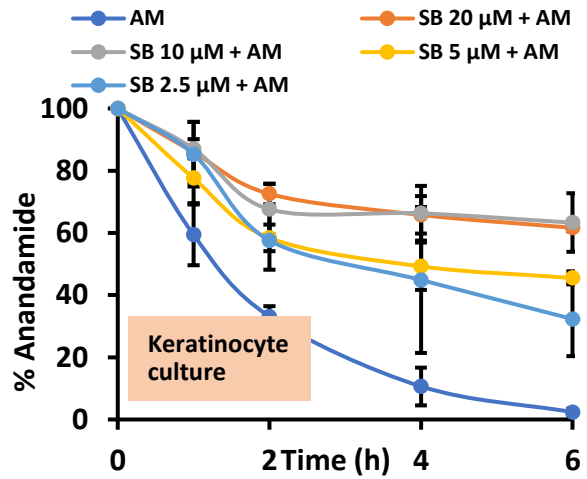
* Control (silymarin in 0.5% Brij S20), BLQ: Below limit of quantitation, NA: Not applicable

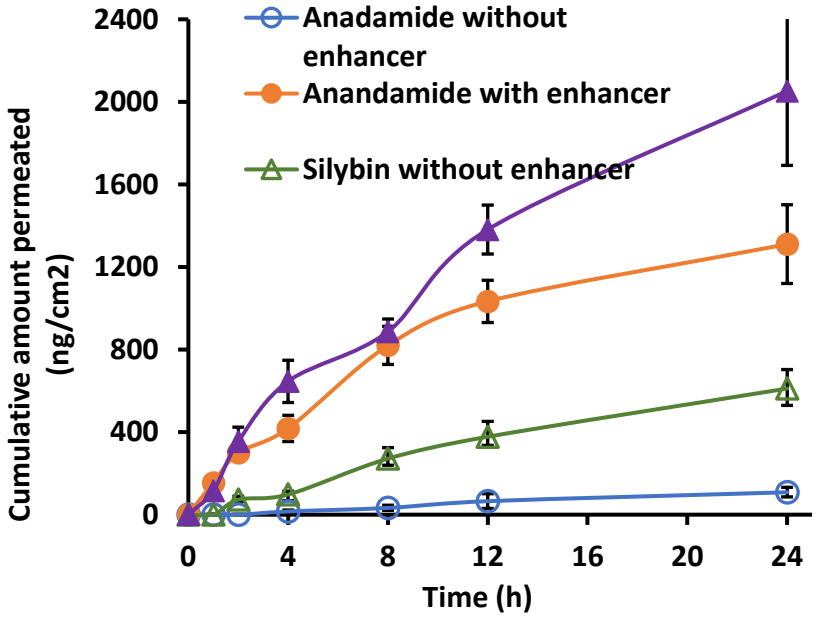
Dermal Delivery of Drugs-Role of Enzyme Inhibitors

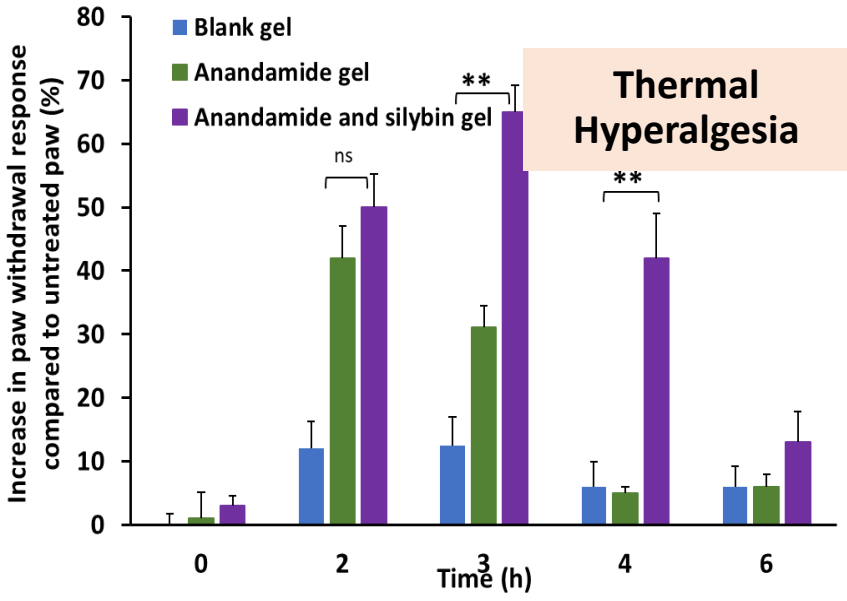


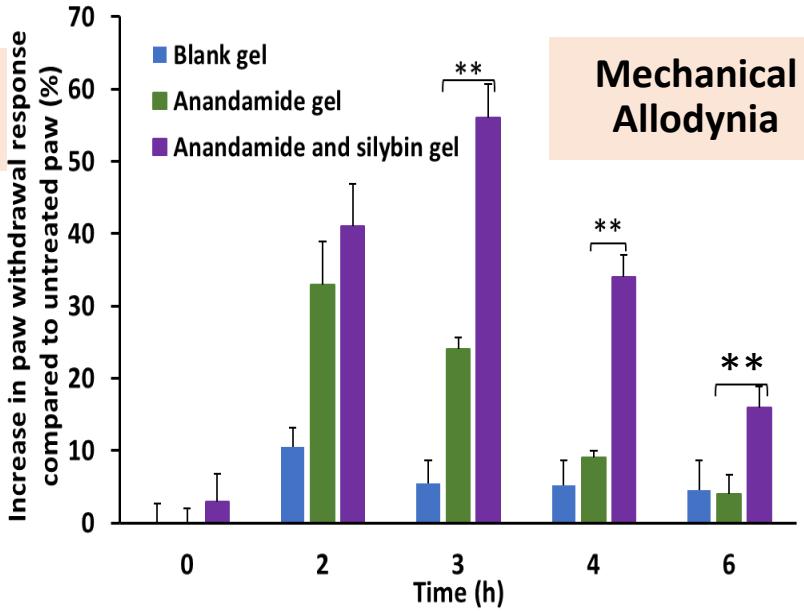
Anandamide | **Arachidonic acid** | **Ethanolamine**





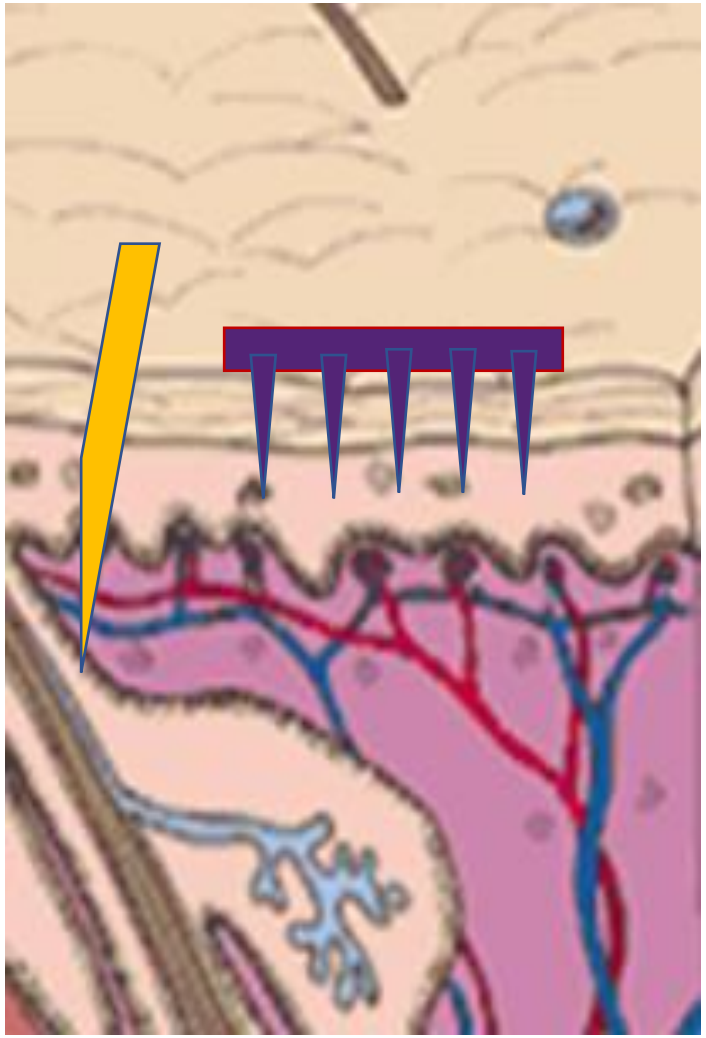




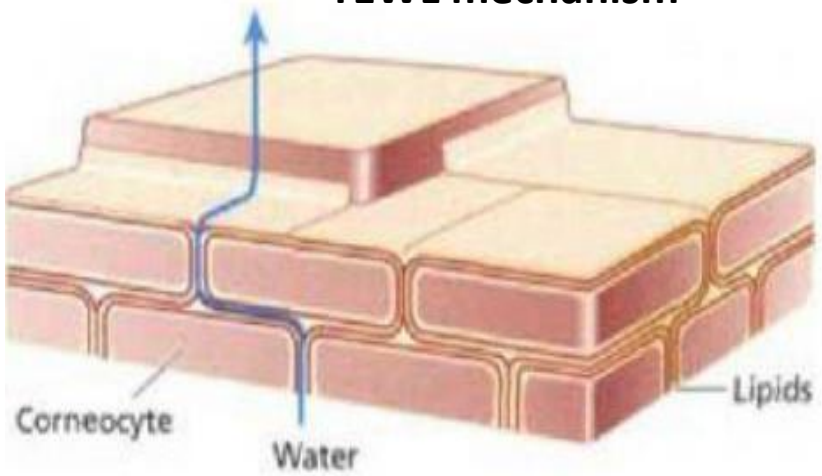


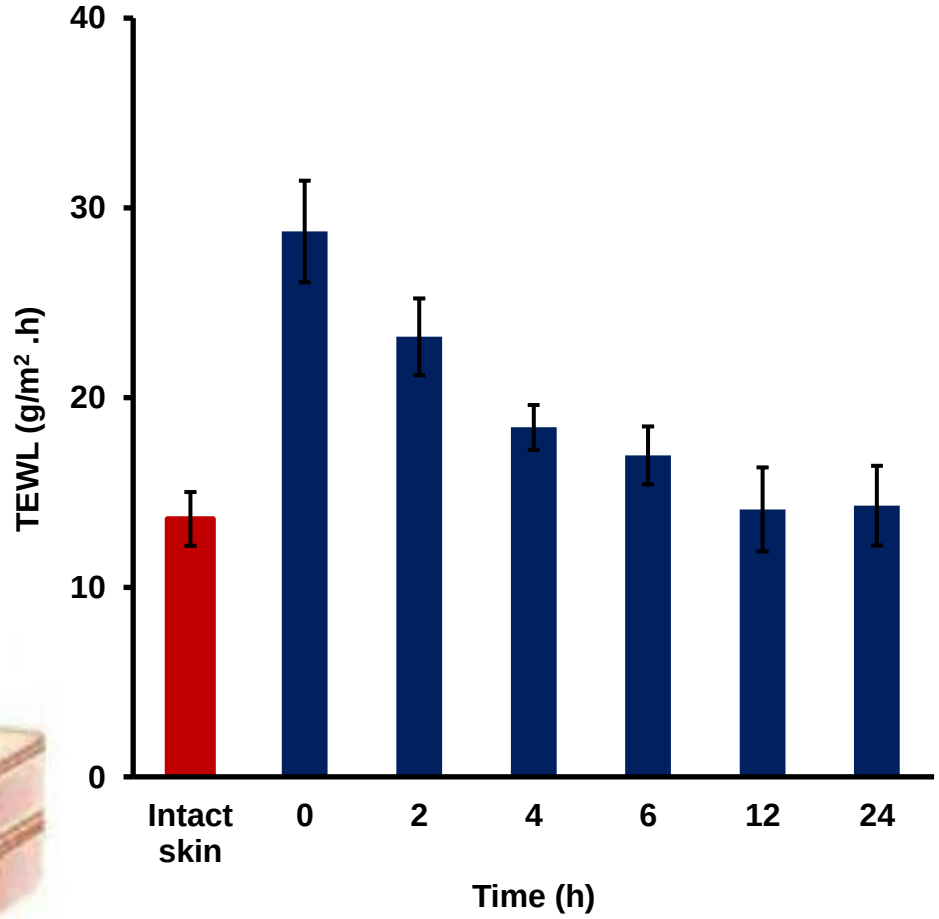
Percentage increase in paw withdrawal threshold in chemotherapy induced neuropathic rat models

Microneedles-Barrier Perturbation and Recovery

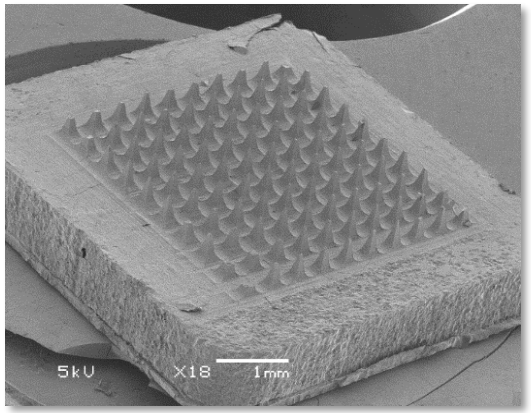


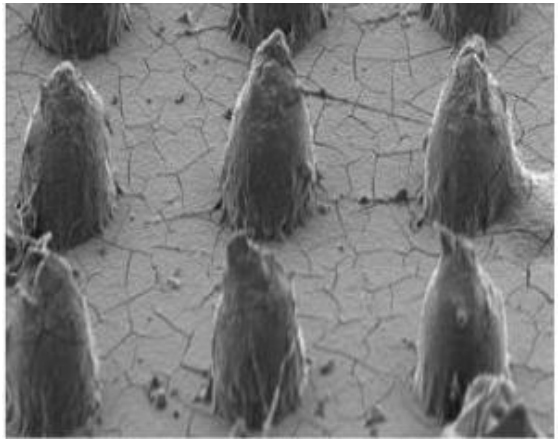
TEWL mechanism

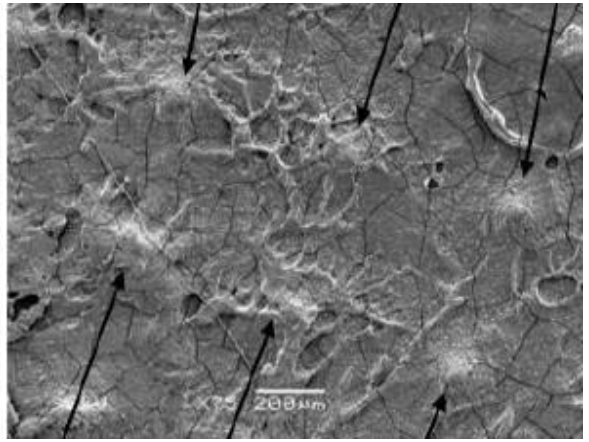


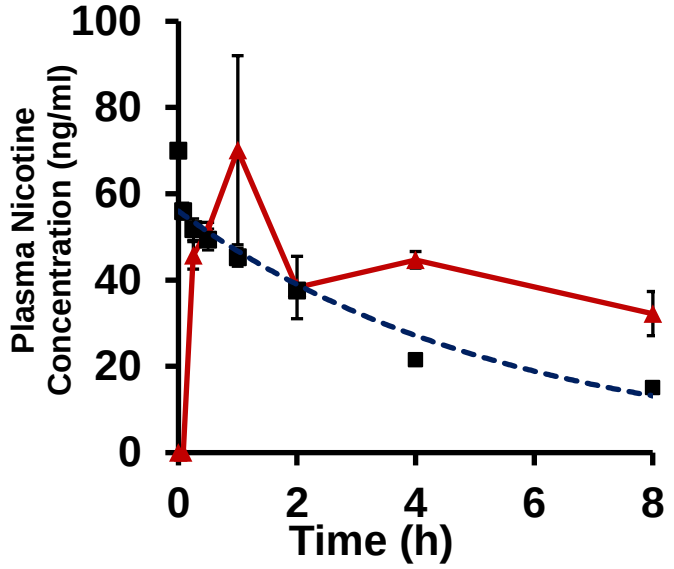


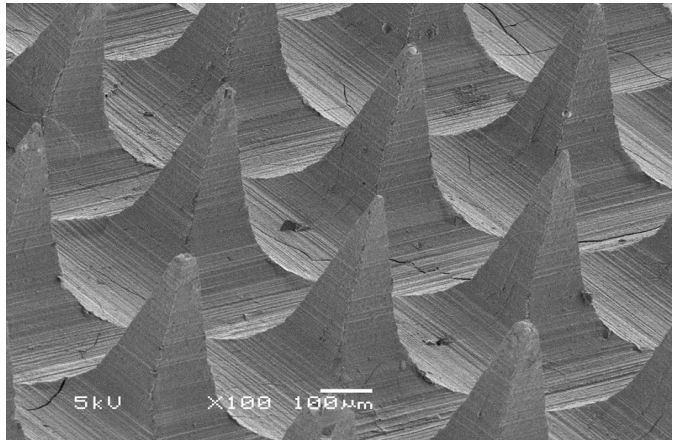
Dissolving Polymeric Microneedles

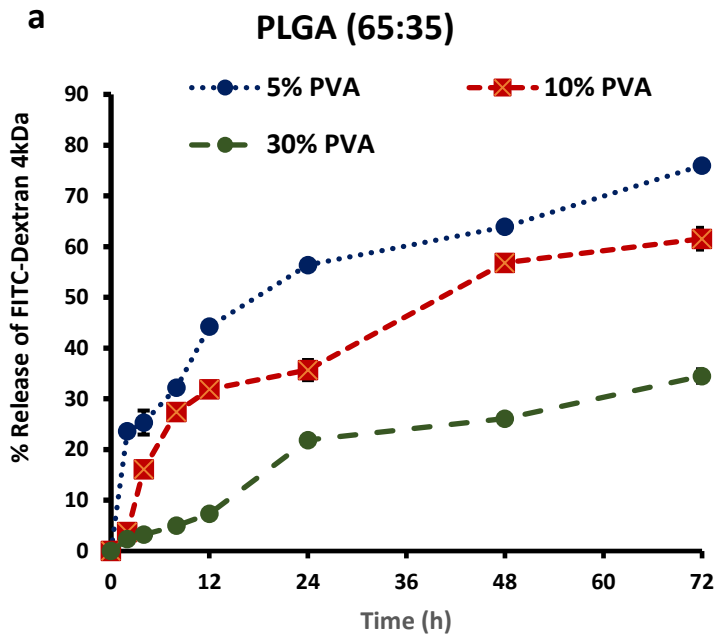


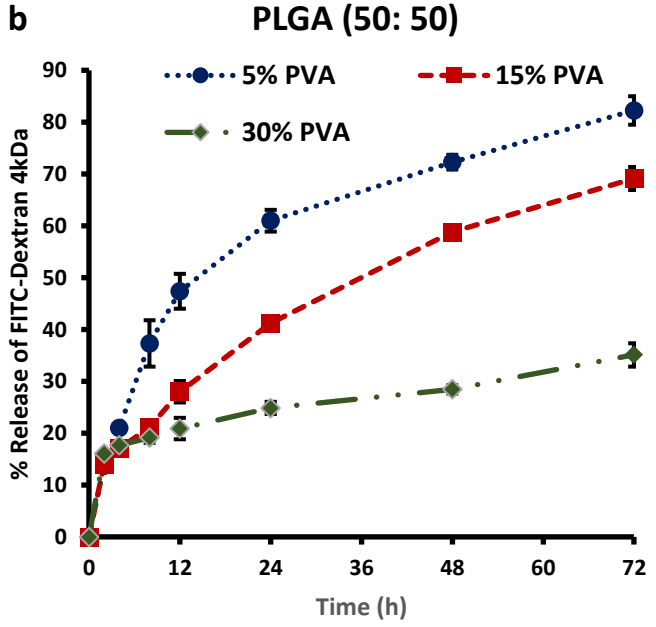












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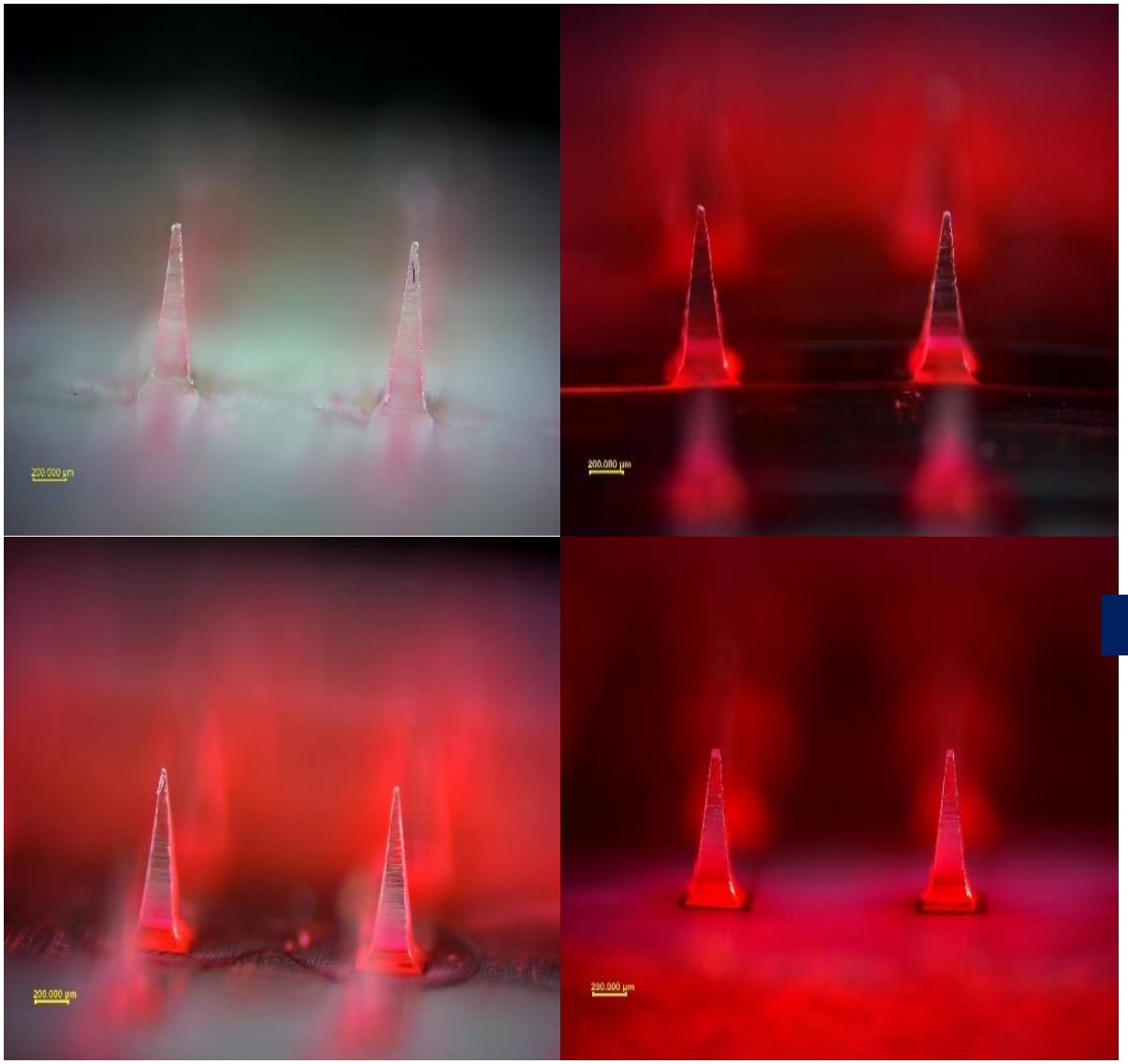
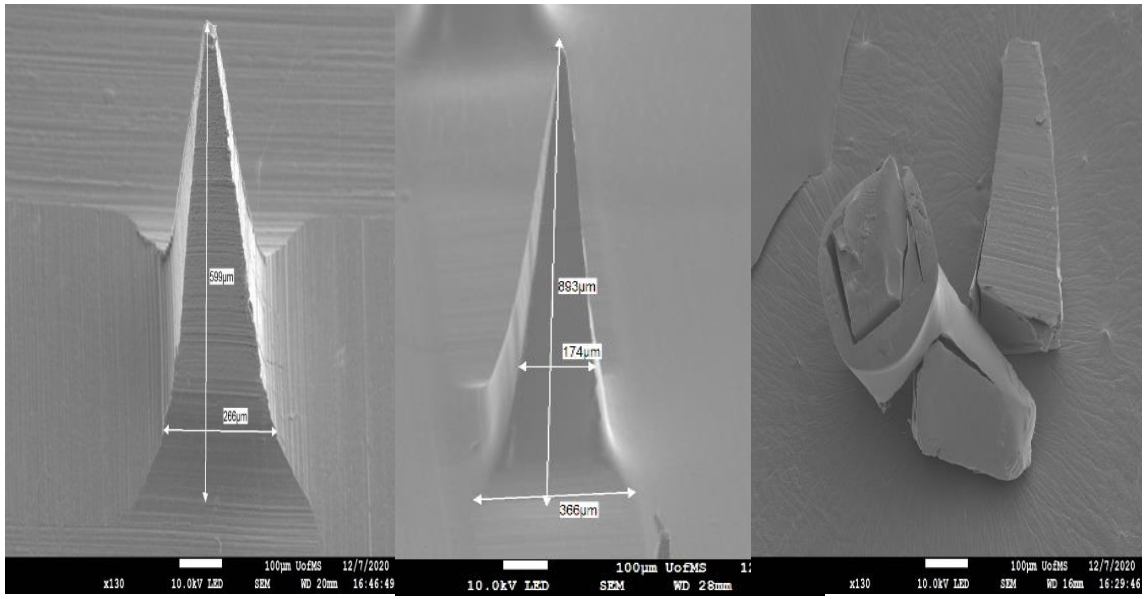
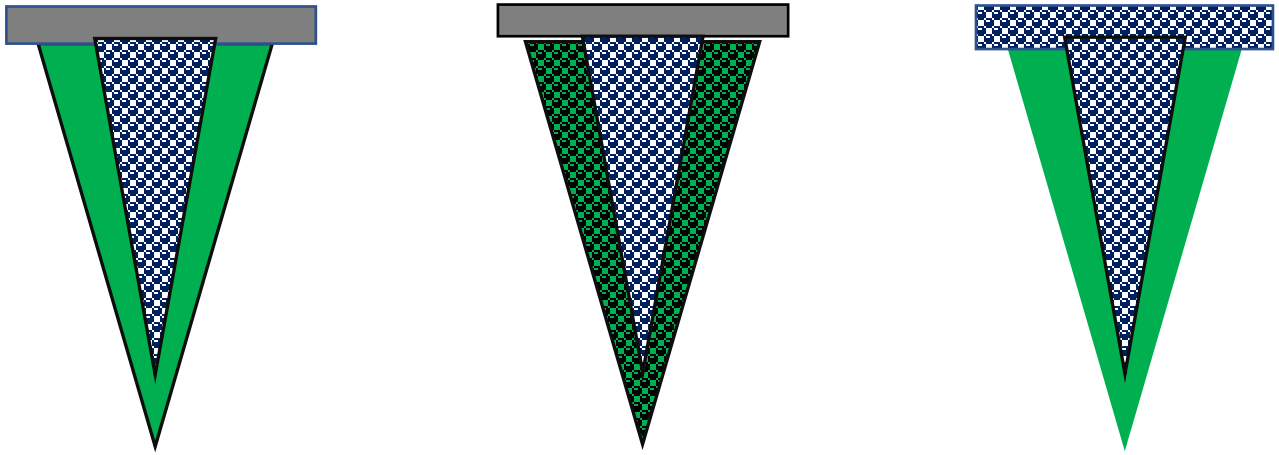
Polymer Coated Polymeric Microneedles



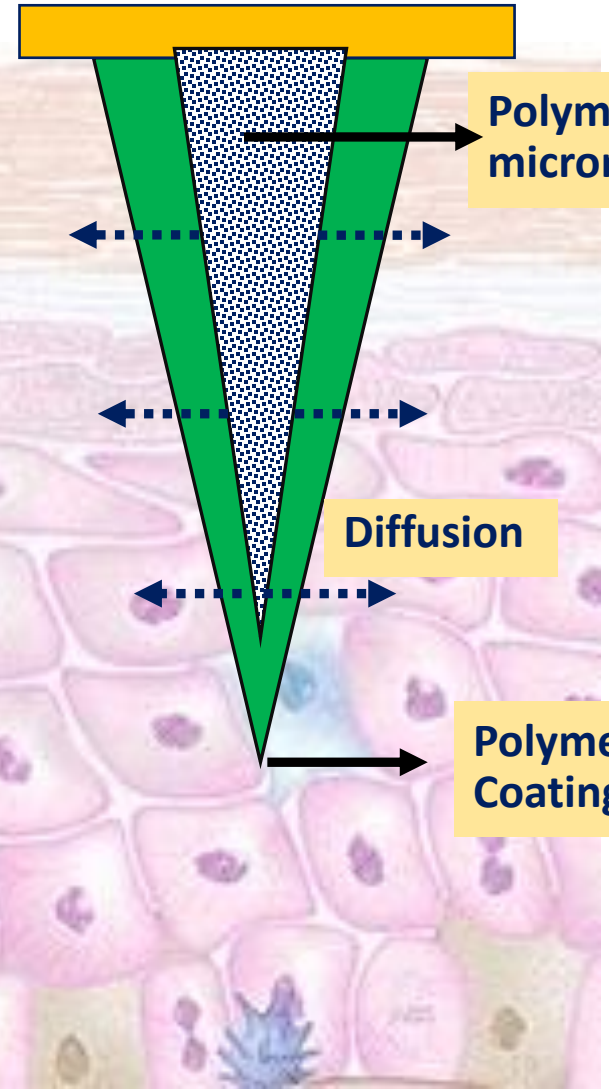


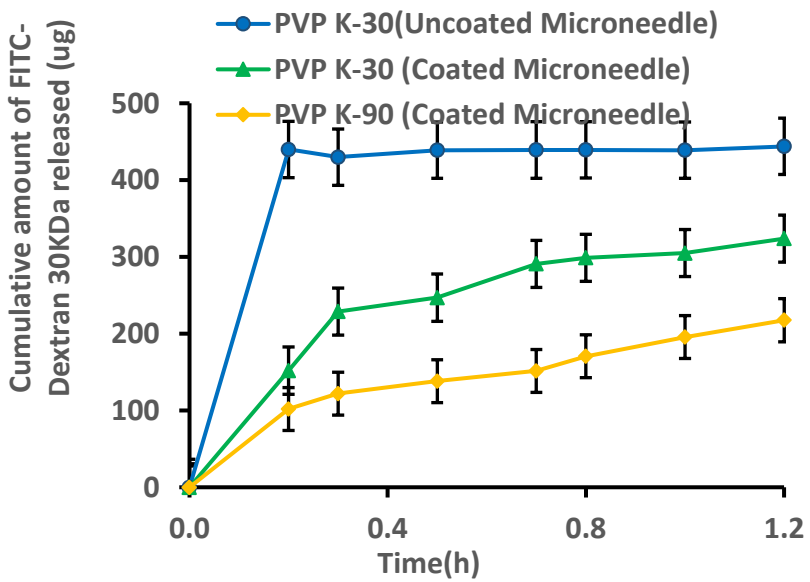
Drug in the Core only	Drug in the Core and Coat	Drug in the Core and Base

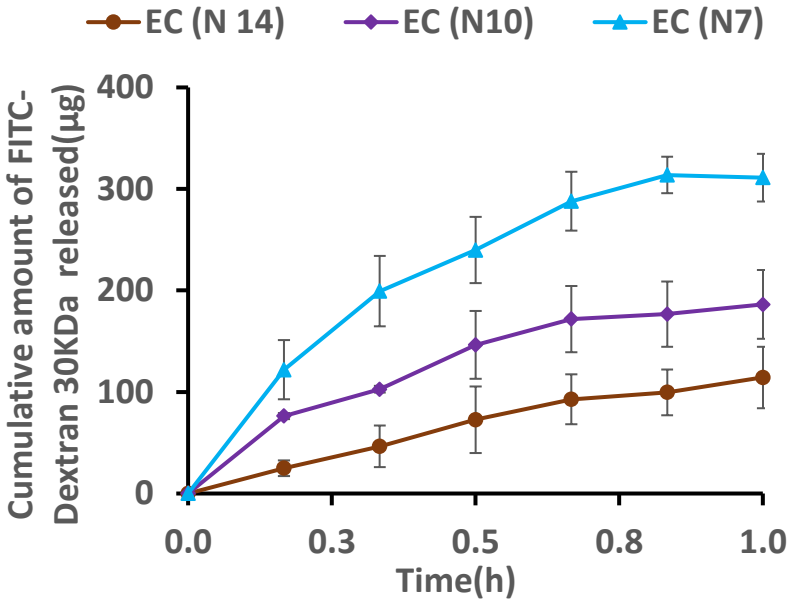


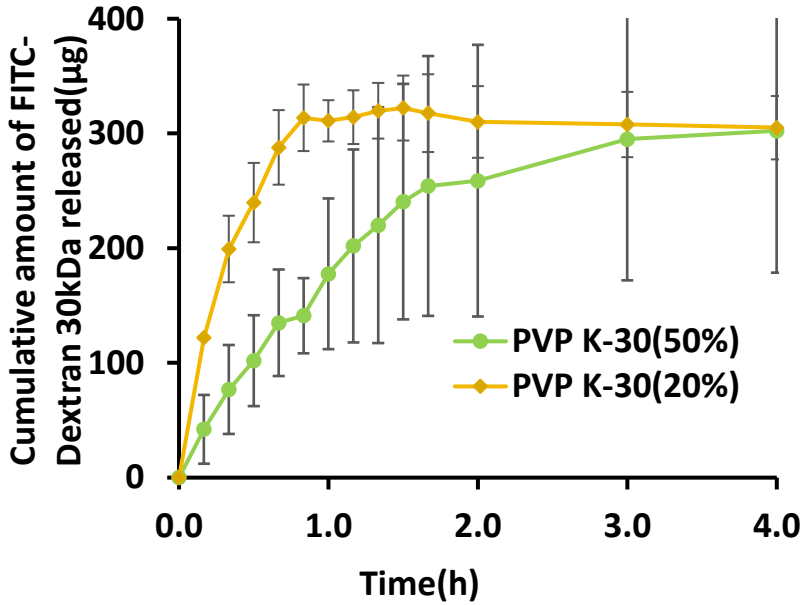
Type 1	Type 2	Type 3

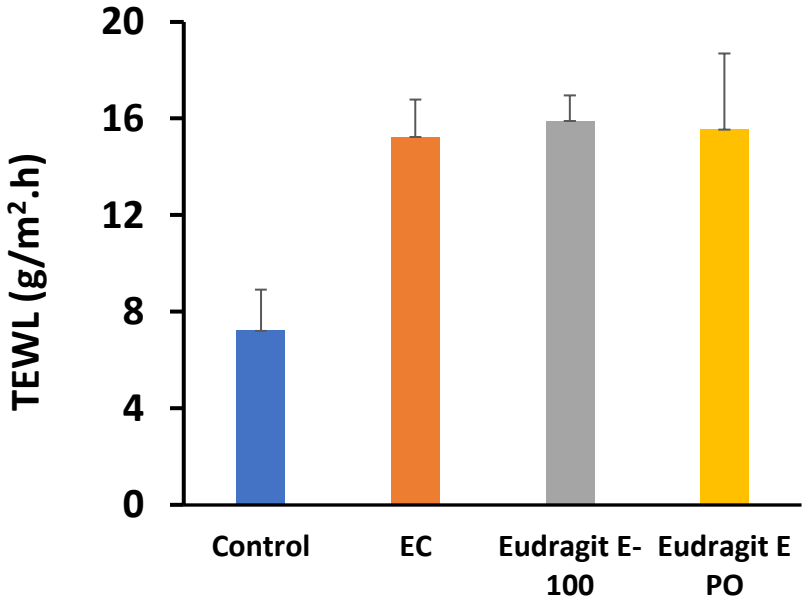
Polymer Coated Polymeric Microneedles



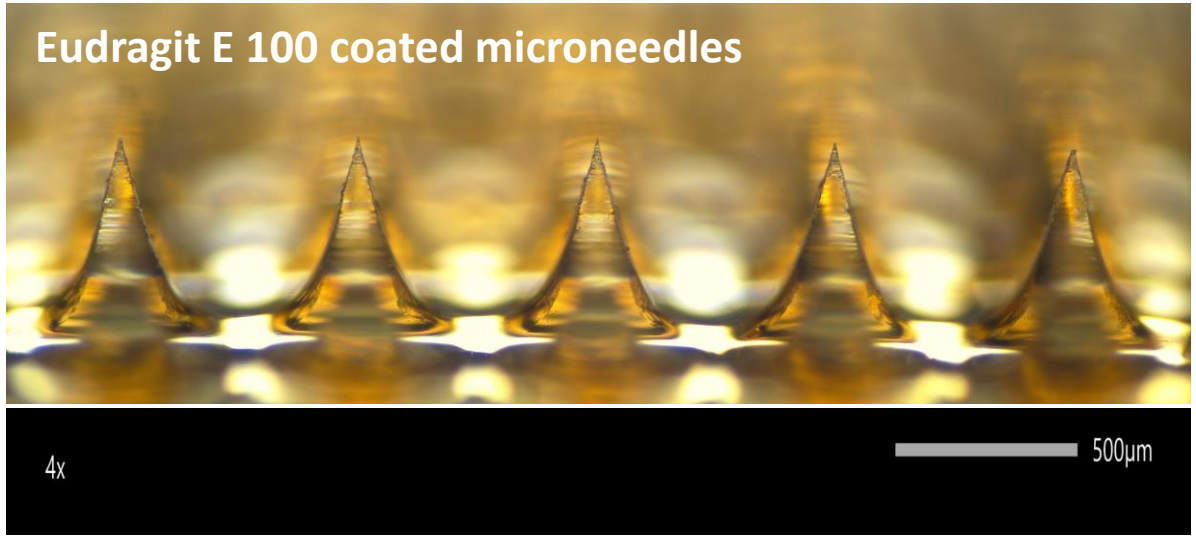


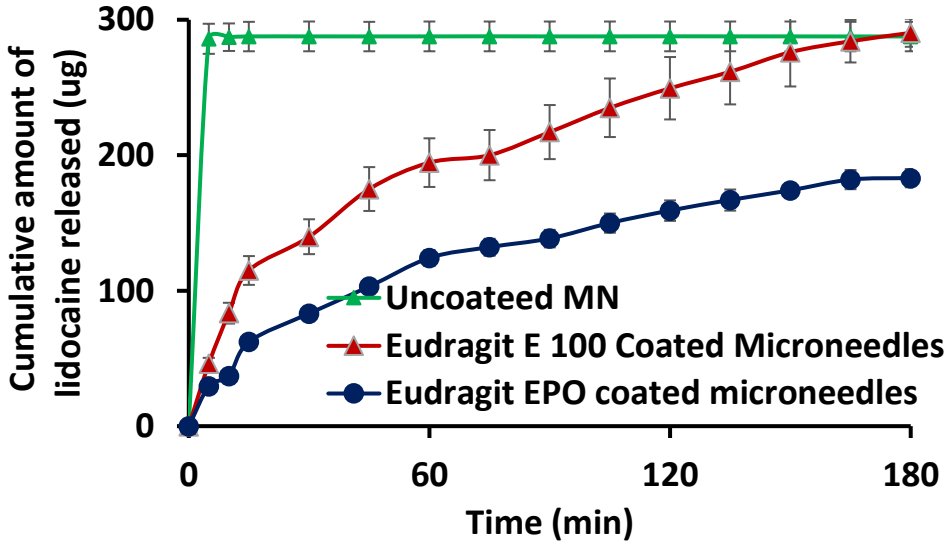




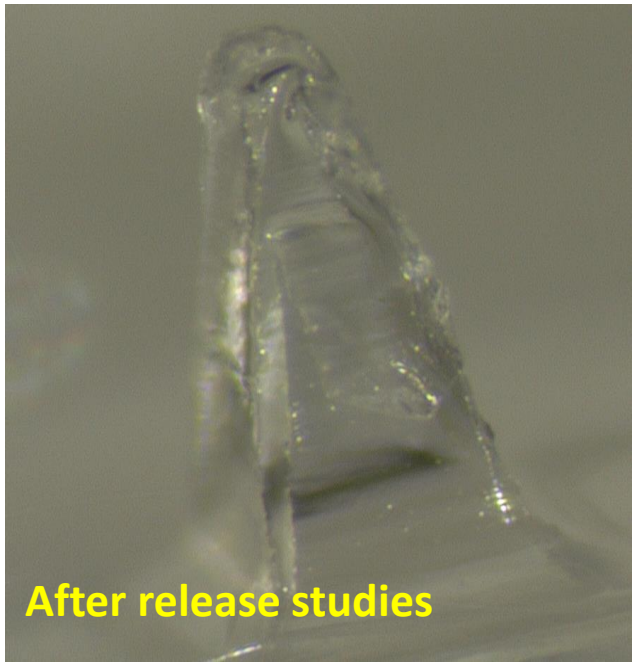


Polymer Coated Polymeric Microneedles





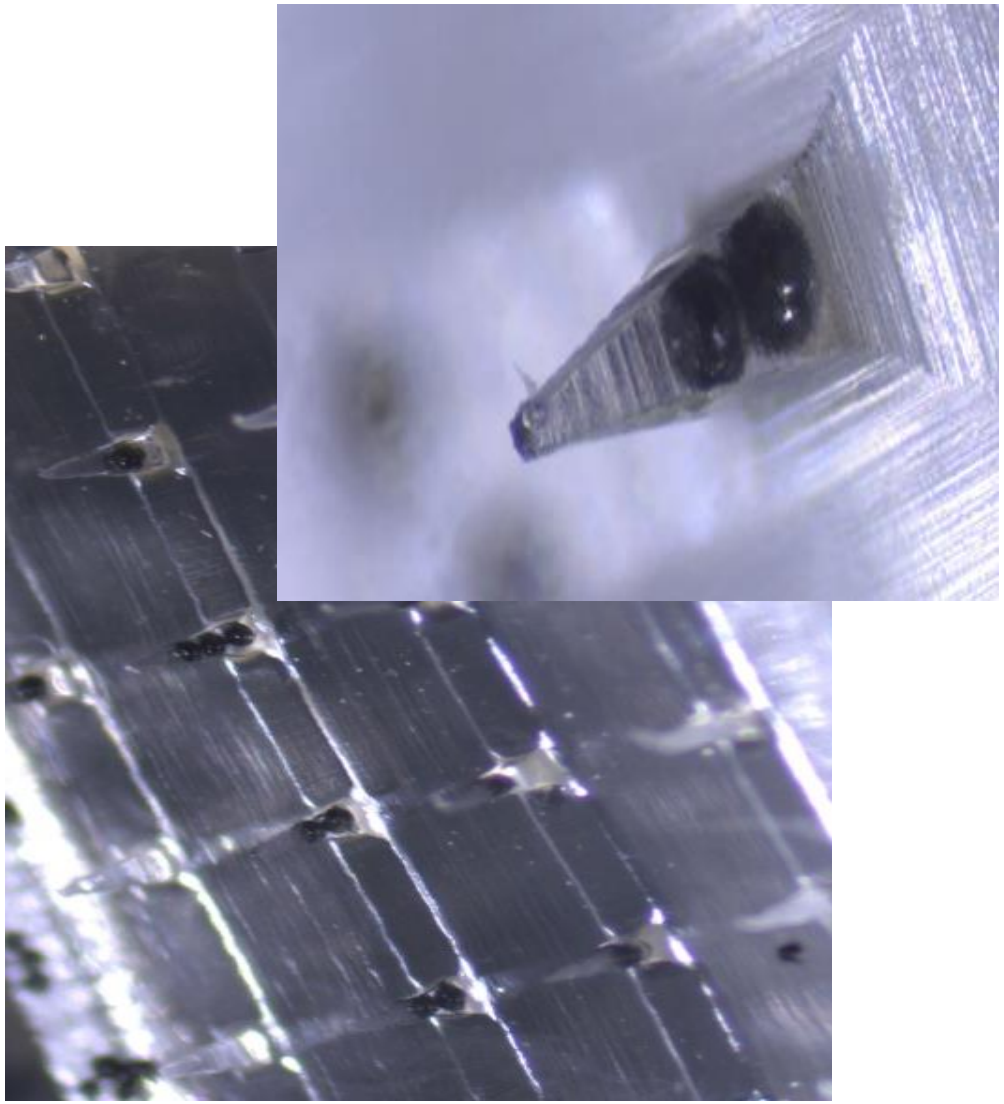
Source of Eudragit®: Evonik, USA

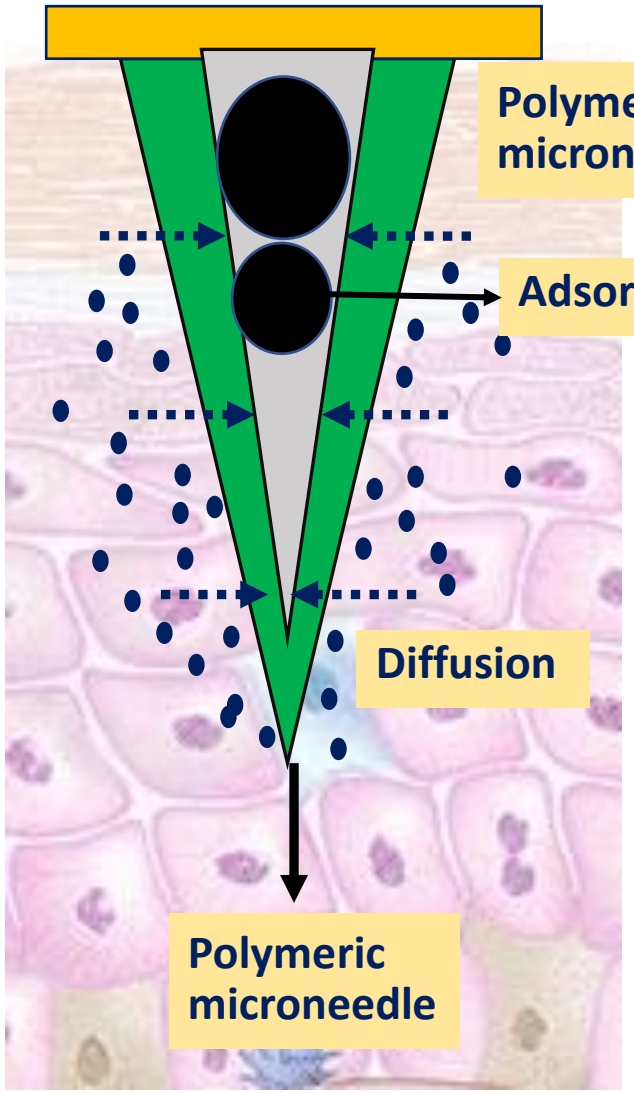


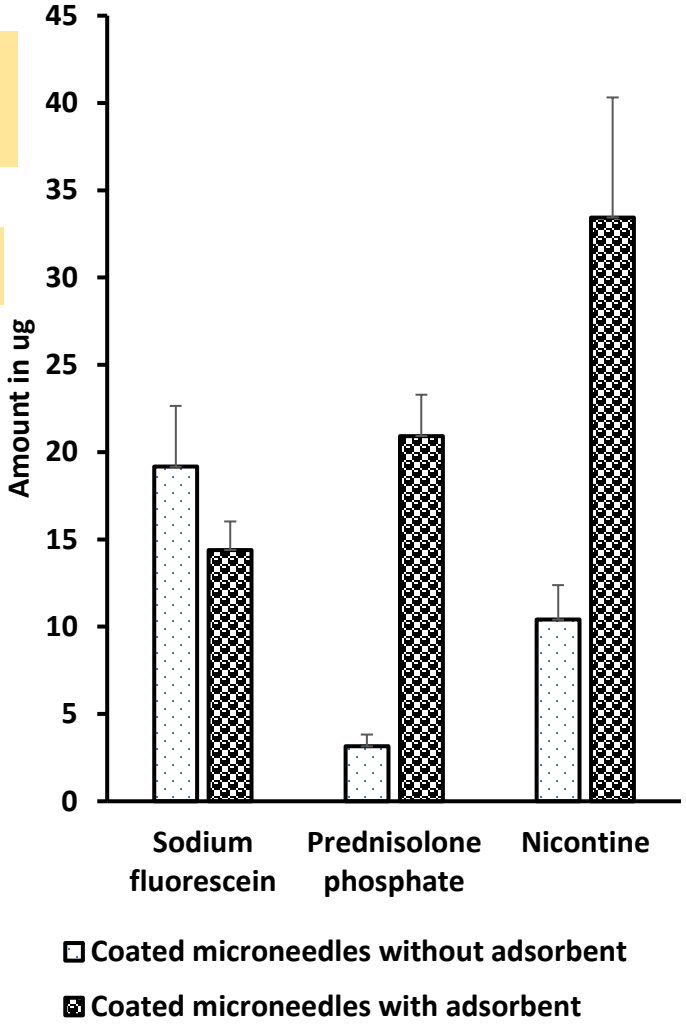
Potential applications being explored

- Delivery of drugs that are metabolized by enzyme sin the skin tissue. Ex: anandamide, testosterone.
- Delivery of drugs by diffusion without dumping polymer and other excipients into the back of the eye.

Adsorbent loaded Polymer Coated Microneedles







Conclusions

- Combination of enhancers could be a potential way to address some of the dermal drug delivery issues.
- Emollients, lipid excipients and polymers could influence the dermal absorption of drug as well.
- Complexation of drugs to render them soluble in aqueous phase of the cream could facilitate dermal absorption.
- Continuous manufacturing process of formulating complex semisolids products would help overcoming the limitations of conventional method of processing.
- Polymer coated polymeric microneedle is a novel mode of gradual administration of drugs into skin and other tissues without dumping the API and excipients.
- The Eudragit E 100, Eudragit E PO and Ethyl cellulose are excellent coating excipients for development of polymer coated polymeric microneedles.