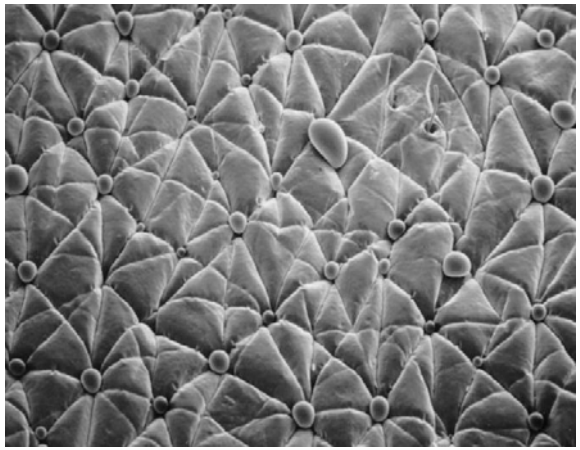
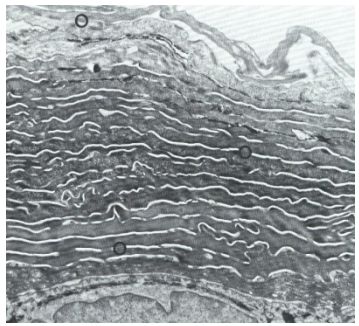
Formulation Strategies to overcome the skin's defence

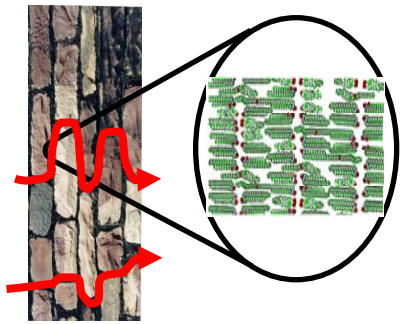
Skin – Target or Barrier?

SCI Meeting, London, 1st November 2007

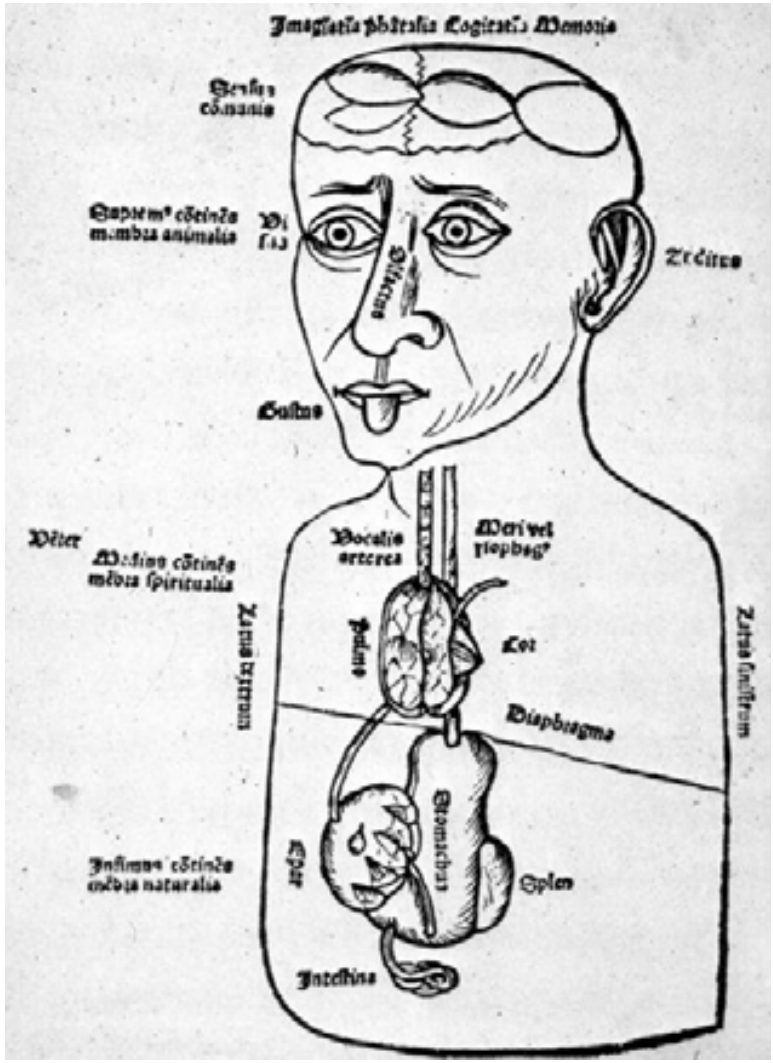
The Skin’s Defence Barrier

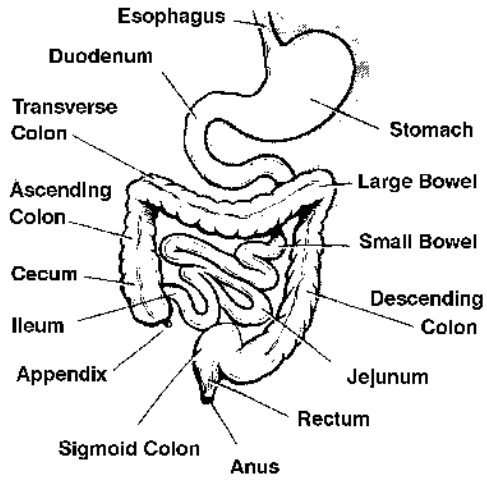




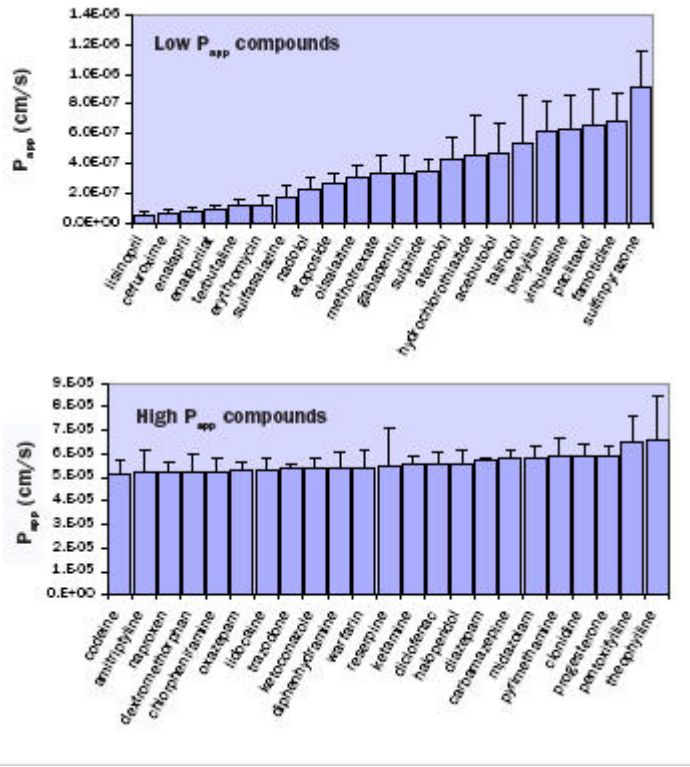


Barriers: GI tract versus Skin!





Drug permeability coefficient: Caco-2 versus human skin



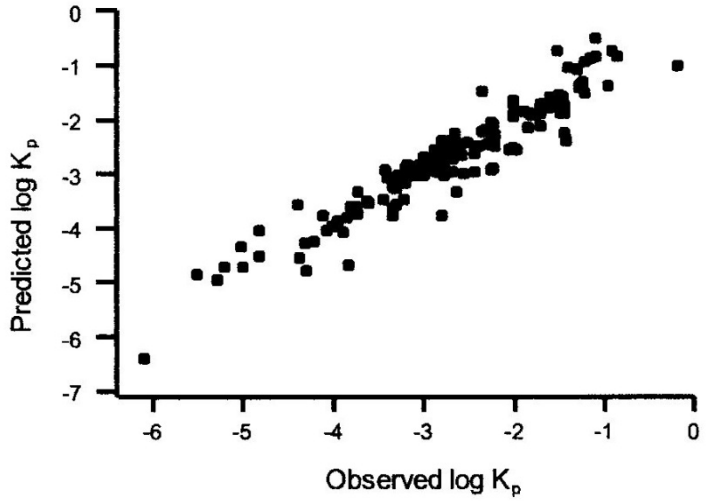


Fig. 1. Plot of observed log K_p values versus predicted log K_p values using Eq. (6).

Patel, Cronin et al. 2002

Phenylcarbamic acid permeability coefficient: Caco-2 versus human skin

Compound #	C_n =	Pc Caco-2 $*10^{-6}$cm/sec	Pc human skin $*10^{-6}$cm/sec
V	$-C_2H_5$	28	0.01
V111	$-C_3H_7$	27	1.86
XI	$-C_4H_9$	26	2.19
XIV	$-C_5H_{11}$	17	2.14
XV11	$-C_6H_{13}$	3.3	2.14
XX	$-C_7H_{15}$	Not detected	1.42
XX111	$-C_8H_{17}$	Not detected	Not detected

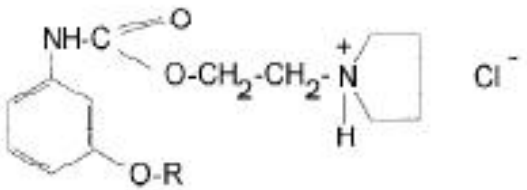
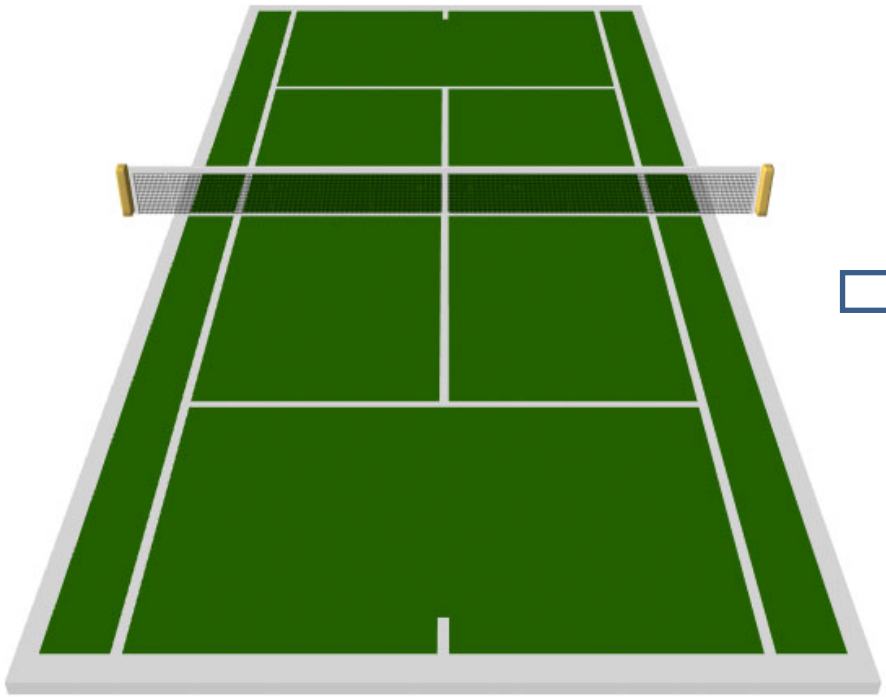


Fig. 1. Structure of the phenylcarbamic acid esters studied. R – $C_n H_{2n+1}$, when n – 1–10. In compound II the n – 1, and in V–XXIX the n – 2–10, respectively (see also Table I).

Gyurosliova e t al. Pharm. Res. 19(2); 162-168: 2002

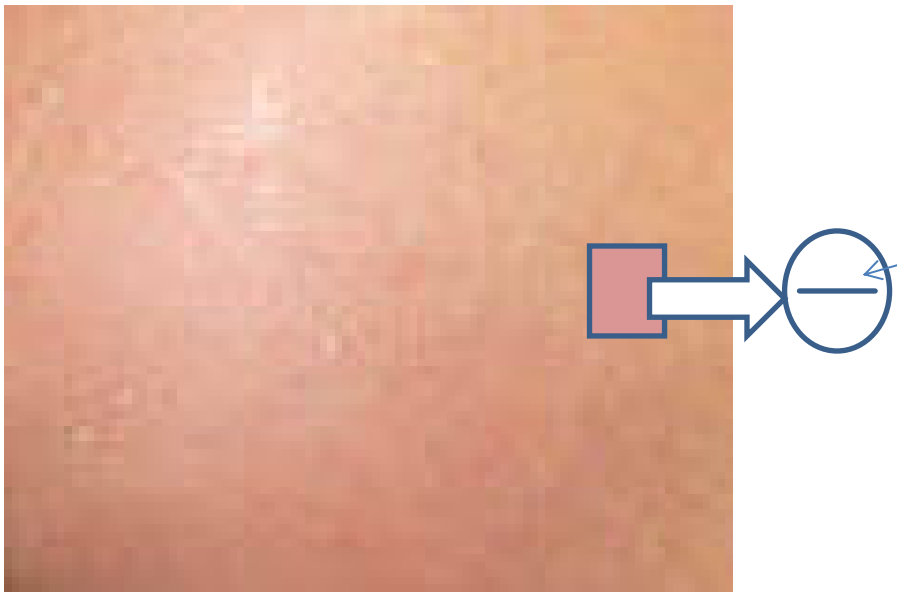
Pharmacokinetics: areas and volumes

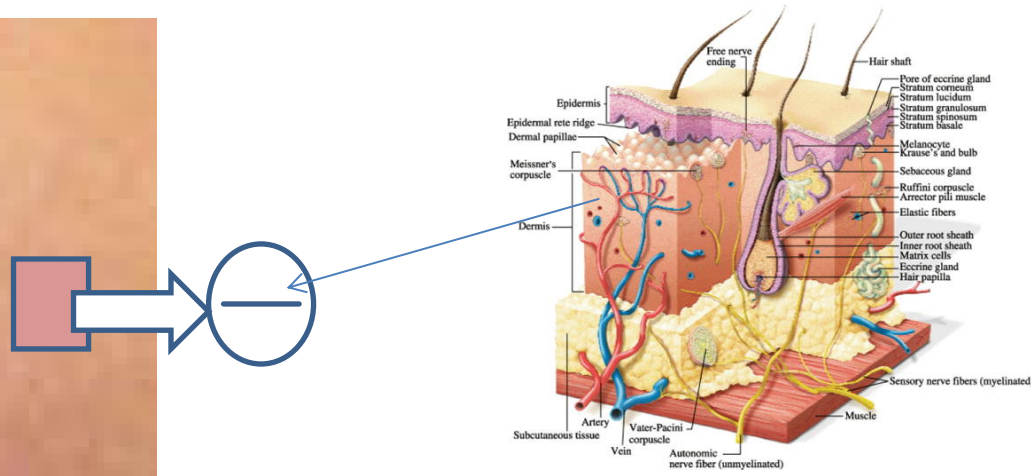
GI tract: 1cm2 area supplies 0.05cm3 volume



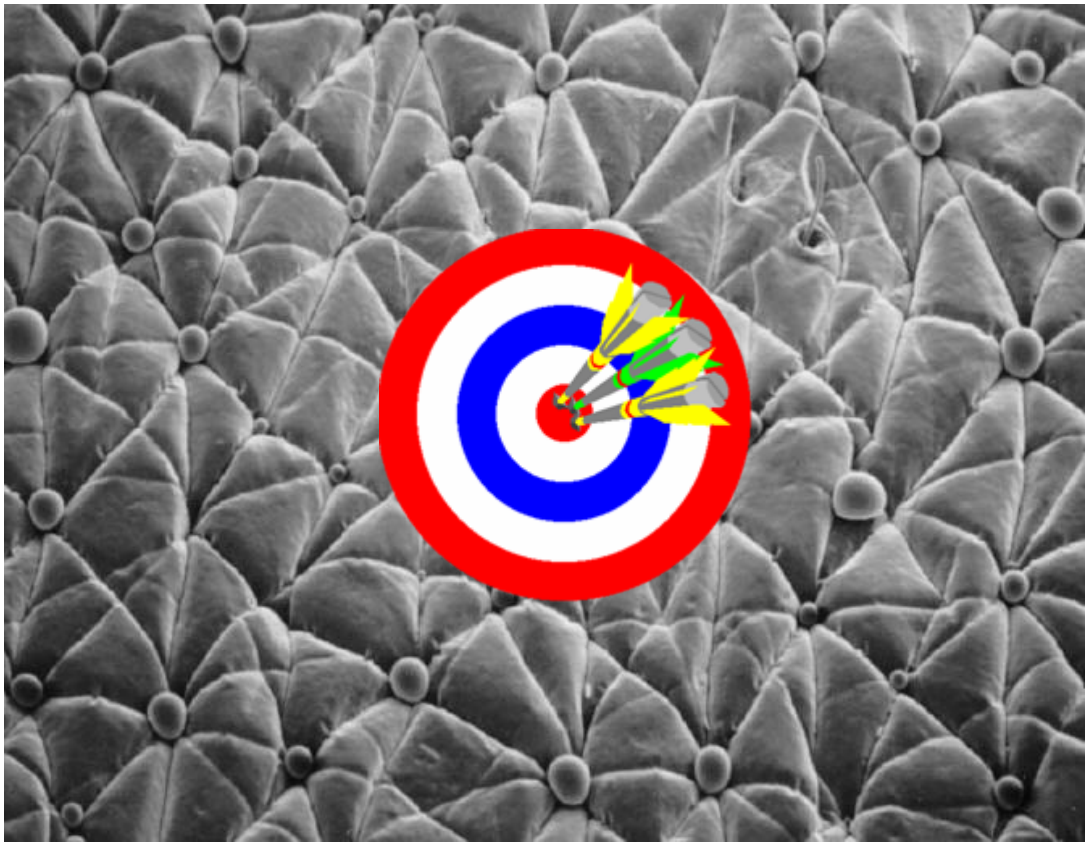
Pharmacokinetics: areas and volumes

Skin: 1cm2 area supplies 0.05cm3 volume



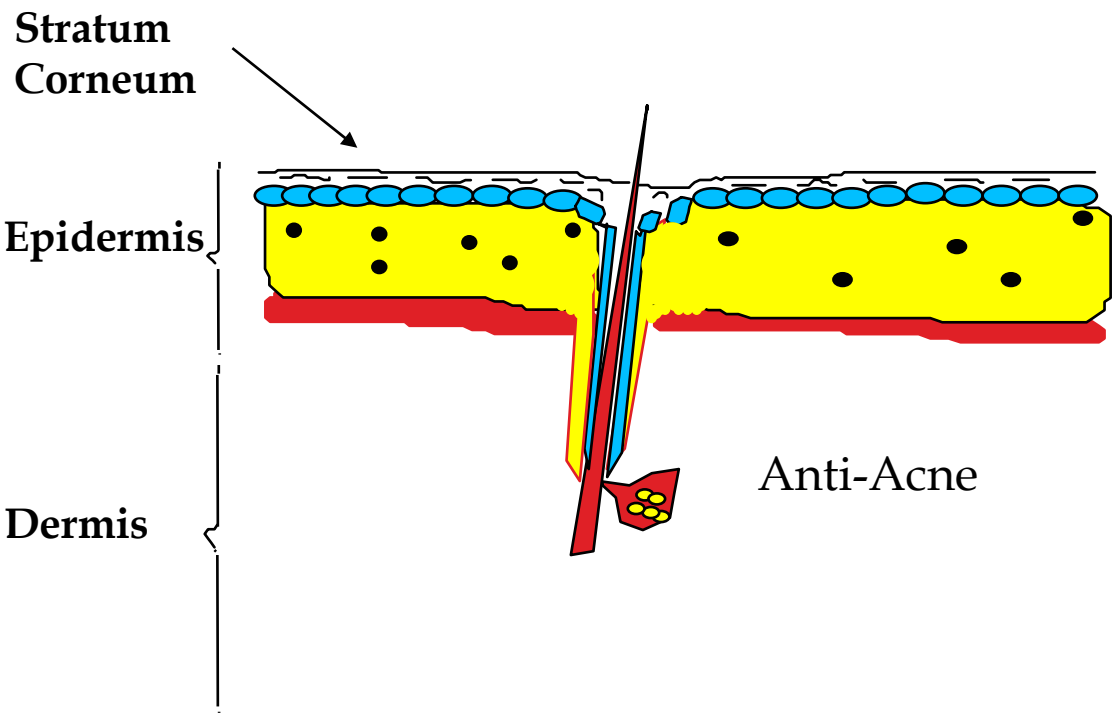


The Skin is a Viable Target not an impenetrable Barrier



Formulation Strategy 1:
Choose the right drug

Choose the right drug to get effective levels to the target site in the Skin

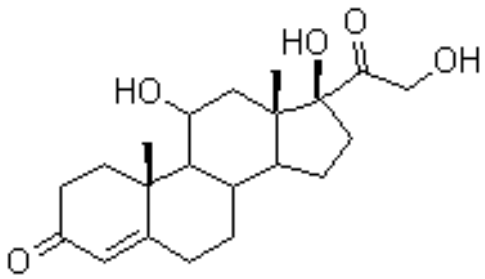


Keratolitics
Antifungals

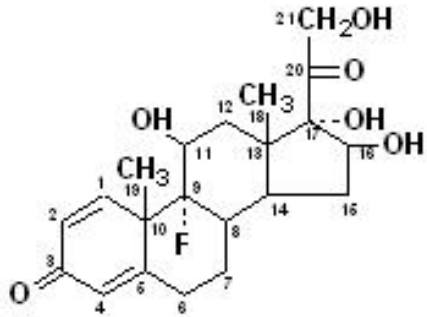
Antipsoriatics
Antiviral
Superficial itch and pain
Anti-inflammatory
- Eczema
- Dermatitis

- Muscle Pain

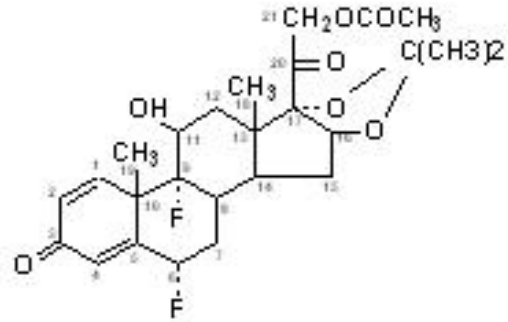
Drug Potency and Skin Penetration are equally important



Hydrocortisone



Triamcinolone



Fluocinonide

The ratio of Penetration / Potency allows Efficacy Ranking

Flux / Potency = Efficacy *{PK black box}

$J / C_{\text{plasma effective}} = EI * \{Cl/A\}$

Formulation Strategy 1:
Choose the right drug

NSAID	**Flux, J ug/cm2/hr**	**IC 50 (COX-2), uM**	**EI (COX-2)***
Diclofenac	**1.4**	**0.03**	**46.7**
Ketorolac	13	0.38	34.2
Ketoprofen	16	0.74	21.6
Indomethacin	0.7	0.16	4.4
Tenoxicam	0.7	55.26	0.01
Piroxicam	0.08	34.9	0.002

In vitro based index of topical anti-inflammatory activity to compare a series of NSAIDs. Cordero JA et al. European Journal of Pharmaceutics and Biopharmaceutics. 2001: 51(2): 135-142.

Penetration to Potency ratio may predict Topical Efficacy : NSAIDs

$$Flux/Potency = Efficacy * \{ black\ box \}$$

$$J/IC_{50} = Efficacy * \{ 2D_d / h_d \}$$

$$\mathbf{ITAA = J * / IC_{50} * h_d / 2D_d}$$

NSAID	J ug/cm2/hr	IC 50 (COX-2), uM	EI (COX-2)*	ITAA
Diclofenac	1.4	0.03	46.7	43.8
Ketorolac	13	0.38	34.2	37.2
Ketoprofen	16	0.74	21.6	23.6
Indomethacin	0.7	0.16	4.4	3.4
				1.00
Tenoxicam	0.7	55.26	0.01	0.01
Piroxicam	0.08	34.9	0.002	0.002

In vitro based index of topical anti-inflammatory activity to compare a series of NSAIDs. Cordero JA et al. European Journal of Pharmaceutics and Biopharmaceutics. 2001: 51(2): 135-142.

Penetration and Potency may predict Topical Efficacy : TIMS

Compounds	MW	Potency (nM)	Flux (in AD) (ng/cm2 /hr)	Efficacy Index	Systemic Safety Index
Cyclosporin A	1203	14	< 1.25	**< 0.04**	**96**
Tacrolimus	804	0.17	1.25	**5.5**	**252**
Pimecrolimus	810	0.23	~ 0.65	**~ 2.1**	**~ 960**

Topical Pharmacokinetics for a Rational and Effective Topical Drug Development Process. Trottet L. PhD thesis, July 2004.

Formulation Strategy 2:
Get an idea of the drug dose
(because design is drug and dose specific)

Calculation of topical dose from flux

Flux/Potency = Efficacy * { black box}

$$C_{free} = J * h_d / 2D_d$$

$$C_{free} / C^{\#} = J * h_d / C_{\#} * 2D_d$$

$$J\# = \frac{2C^{\#} D_d}{h_d} \qquad \textit{Equ. 1}$$

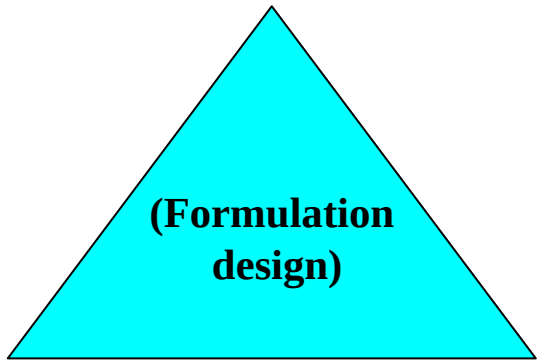
Prediction of minimum dose

Drug potency: ng/cm3 (5000 range) C#	Flux, J#, for efficacy in dermis: ng/cm2/hr	Dose/cm2/ 10hr: ng	% in product @2mg/cm2 (A) (/20,000)	Drug %age in typical products (B)	Estimate of bioavailability % (A) / (B) *100	Drug example with this potency
0.05	0.1	1	0.00005%	0.005-0.05%	1.0-0.1%	Fluticasone propionate (Cutivate)
0.1	0.2	2	0.0001%	0.025-0.1%	0.4 - 0.1%	Retinoic acid (Retin-A)
				0.005%	2.0%	Calcipotriol (Dovenex)
0.25	0.5	5	0.00025%	1.0%	0.025%	Diclofenac (Volterol)
0.5	1.0	10	0.0005%	0.03 – 0.1%	1.67 – 0.5%	Tacrolimus (Elidel)
				1.0	0.05%	Pimecrolimus (Protopic)
5	10	100	0.005%	0.5-1.0%	1.0 – 0.5%	Hydrocortisone (Generic)
				1%	0.5%	Terbinafine (Lamisil)
250	500	5,000	0.25%	5%	5%	Ibuprofen (Generic)

Formulation Strategy 3:
Design for the drug and its dose: residual phase solubility / saturation

Formulation Design

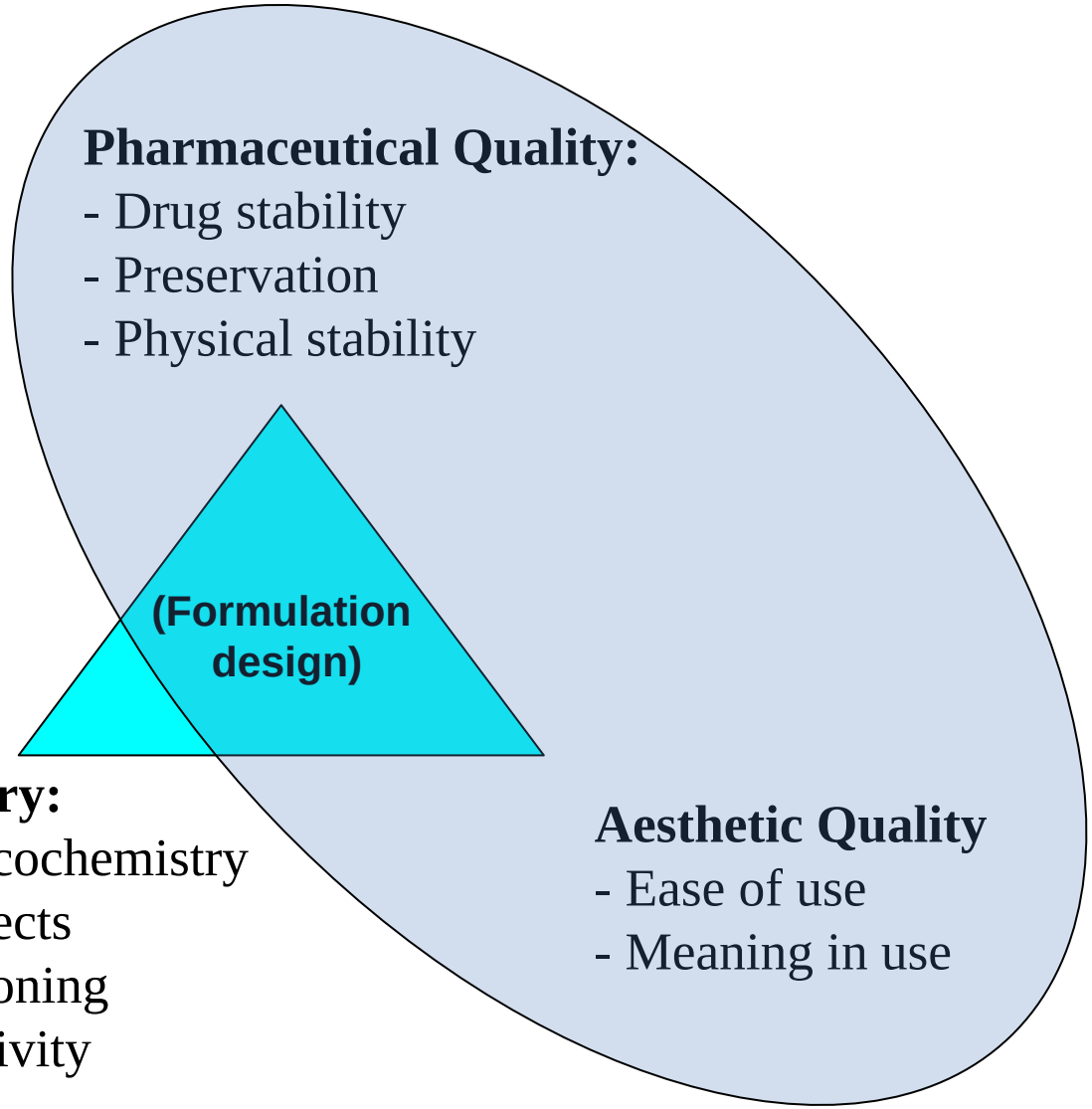
Pharmaceutical Quality:
- Drug stability
- Preservation
- Physical stability



Drug Delivery:
- Drug physicochemistry
- Vehicle effects
    - -Partitioning
    - -Diffusivity
- Dose

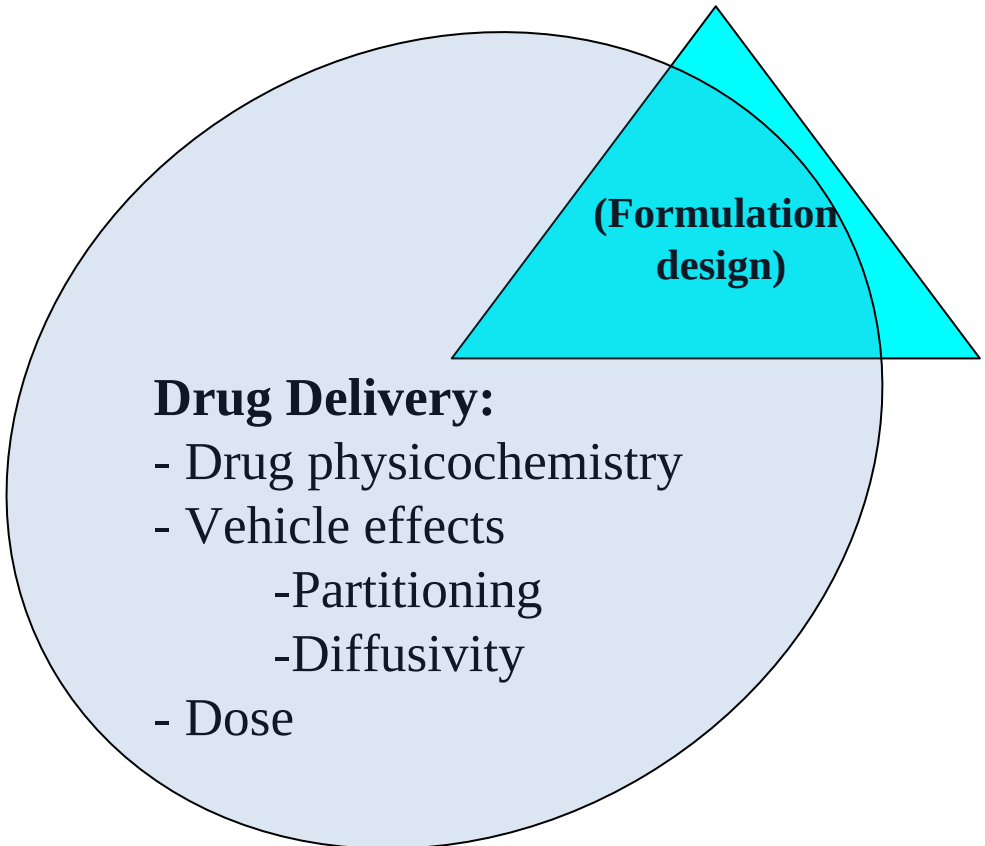
Aesthetic Quality
- Ease of use
- Meaning in use

Formulation Design: Whole vehicle effects



Formulation Design: Residual Phase effects

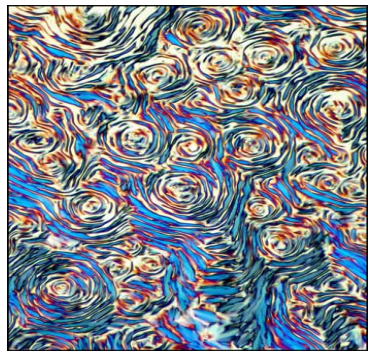
Pharmaceutical Quality:
- Drug stability
- Preservation
- Physical stability



Drug Delivery:
- Drug physicochemistry
- Vehicle effects
  - -Partitioning
  - -Diffusivity
- Dose

Aesthetic Quality
- Ease of use
- Meaning in use

Residual phase as formulation basis



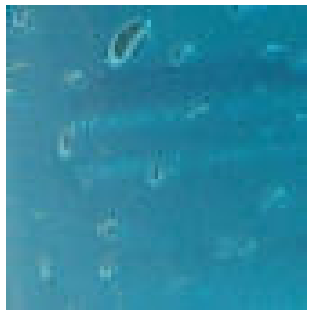
- drug in solution (saturation or >)
- non volatile solvent phase

+ water, surfactants, waxes

+ volatile solvent, polymer

+ patch (Alza, Cygnus)

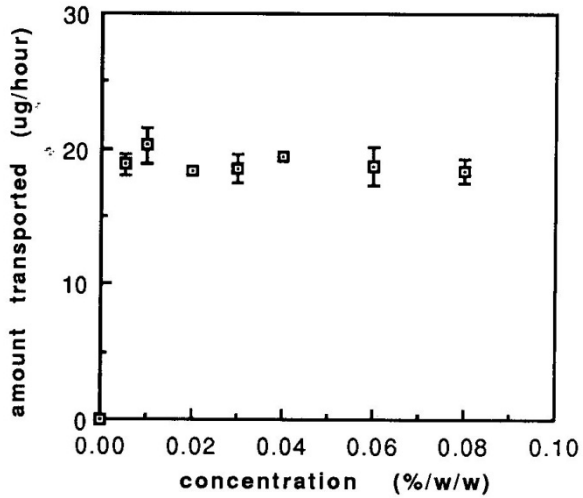
Cream

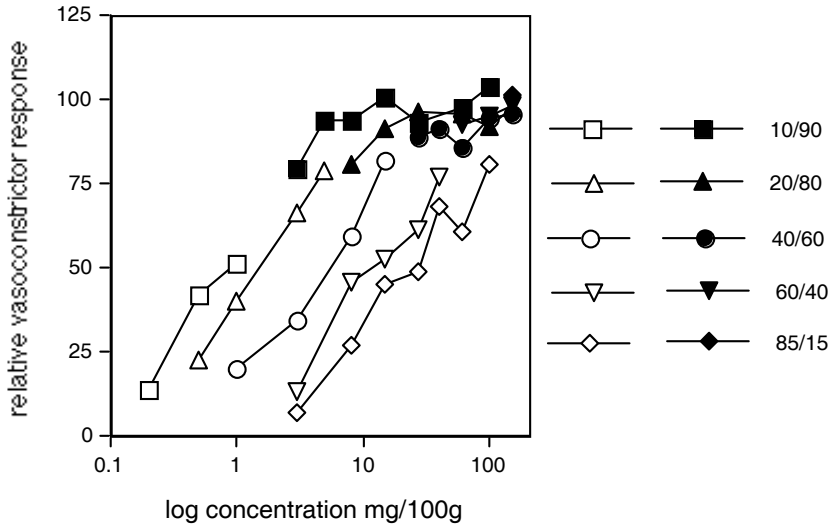


Spray / Gel

Patch

Degree of saturation, not concentration, drives penetration



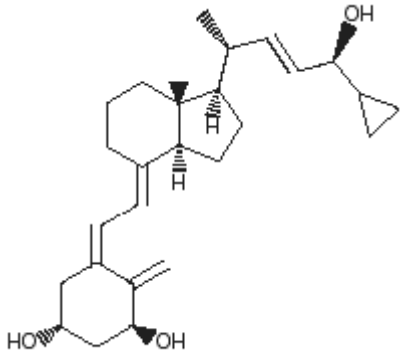


Relative vasoconstrictor response from subsaturated solutions (open symbols) and saturated solution and suspension (filled symbols) formulations of betamethasone benzoate in mineral oil/myglyol.

VITAMIN D3 ANALOG
Dovonex
(calcipotriene) 0.005%

Full U.S. Prescribing Information
- Dovonex Ointment
- Dovonex Cream
- Dovonex Scalp Solution

Lotion 0.005%



- Calcipotriene 50 ug/g
- isopropanol (51% v/v)
- propylene glycol and water
- menthol
- hydroxypropyl cellulose
- sodium citrate

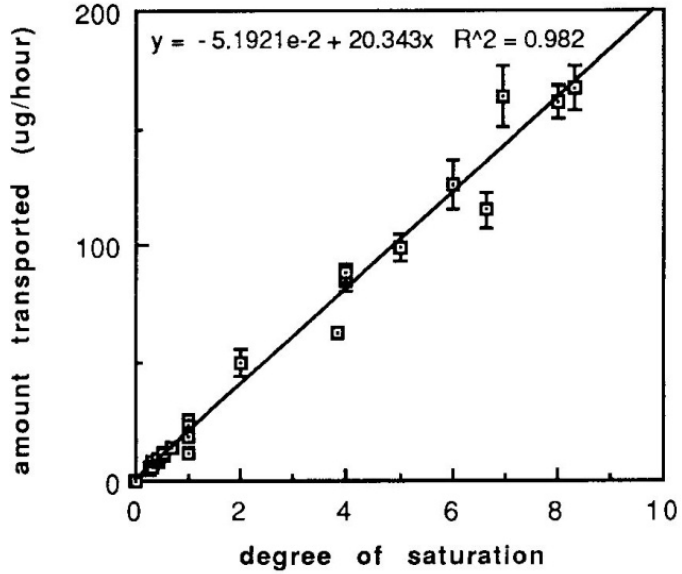
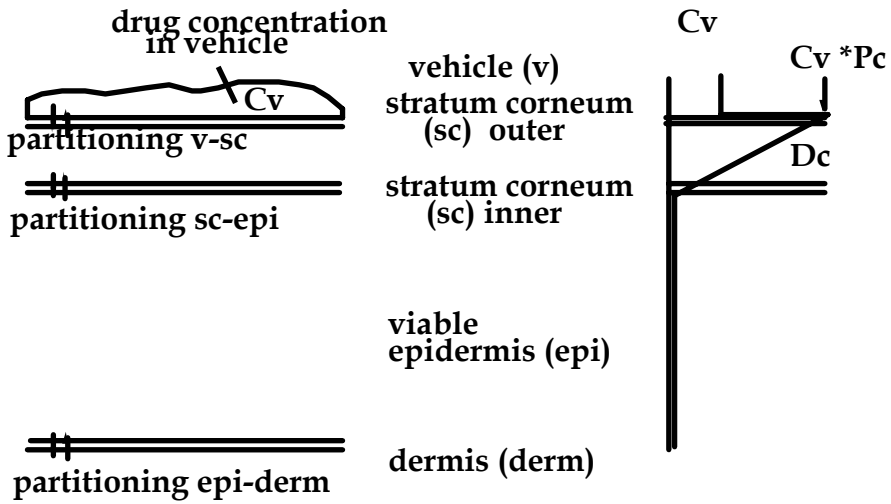


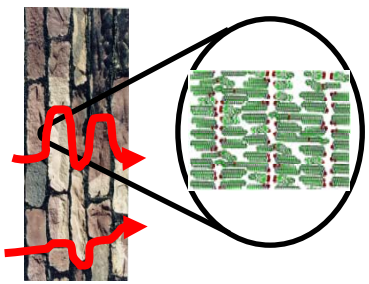
Fig. 7. Linear relationship between transport of hydrocortisone acetate and degree of saturation over the range of subsaturated to supersaturated systems. Combined data from Figs. 4–6. Mean ($n = 3$ or 6) ± S.E.

Formulation Strategy 4:
Choose the right enhancer system:
if you need one!

The Higuchi Physical Model (1960): In vitro Transport

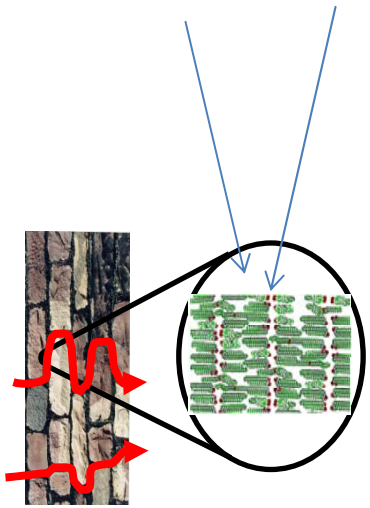


$$F = Cv * Pc / Dc * h$$

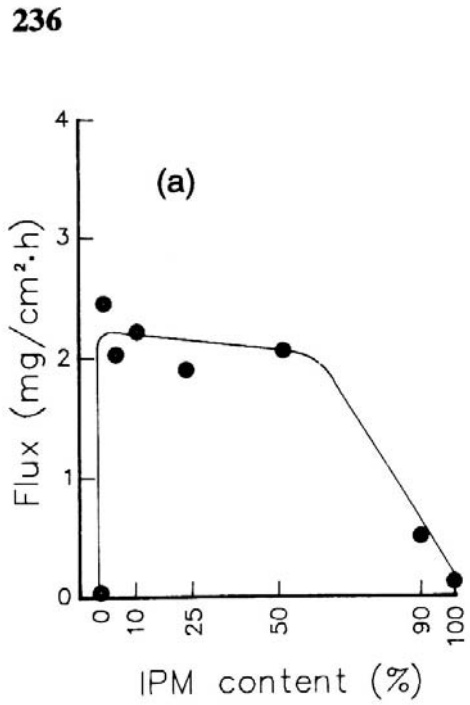


Alcohol/Glycol–Fatty acid derivative co-enhancers

$$F = Cv * Pc / Dc * h$$



Isopropyl myristate-propylene glycol: Nicorandil



Sato K et al. International Journal Pharmaceutics. 1988; 43: 31-40

Propylene glycol-Oleic acid co-enhancer

- 11. Larrucea, E., Arellano, A., Santoyo, S. & Ygartua, P. - Combined effect of oleic acid and propylene glycol on the percutaneous penetration of tenoxicam and its retention in the skin. - *Eur J Pharm Biopharm. 2001 Sep;52(2):113-9.*

- 12. Murakami, T. *et al.* - Topical delivery of keloid therapeutic drug, tranilast, by combined use of oleic acid and propylene glycol as a penetration enhancer: evaluation by skin microdialysis in rats. - *J Pharm Pharmacol. 1998 Jan;50(1):49-54.*

- 13. Ammar, H. O., Salama, H. A., Ghorab, M., El-Nahhas, S. A. & Elmotasem, H. - A transdermal delivery system for glipizide. - *Curr Drug Deliv. 2006 Jul;3(3):333-41.*

- 14. Wang, M. Y., Yang, Y. Y. & Heng, P. W. - Skin permeation of physostigmine from fatty acids-based formulations: evaluating the choice of solvent. - *Int J Pharm. 2005 Feb 16;290(1-2):25-36. Epub 2005 Jan 1.*

Propylene glycol-Oleyl alcohol co-enhancer

- 15. Cho, Y. A. & Gwak, H. S. - Transdermal delivery of ketorolac tromethamine: effects of vehicles and penetration enhancers. - Drug Dev Ind Pharm. 2004 Jul;30(6):557-64.

- 16. Gwak, H. S., Oh, I. S. & Chun, I. K. - Transdermal delivery of ondansetron hydrochloride: effects of vehicles and penetration enhancers. - Drug Dev Ind Pharm. 2004 Feb;30(2):187-94.

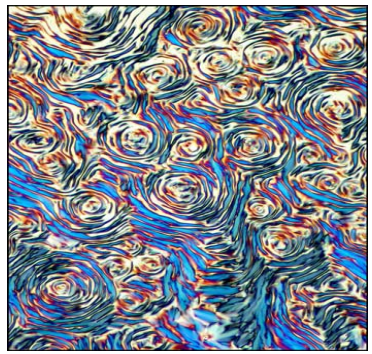
- 17. Gwak, H. S. & Chun, I. K. - Effect of vehicles and penetration enhancers on the in vitro percutaneous absorption of tenoxicam through hairless mouse skin. - Int J Pharm. 2002 Apr 2;236(1-2):57-64.

Transcutol-Oleic acid co-enhancer

- 18. Gungor, S. & Bergisadi, N. - Effect of penetration enhancers on in vitro percutaneous penetration of nimesulide through rat skin. - Pharmazie. 2004 Jan;59(1):39-41.

- 19. Escribano, E., Calpena, A. C., Queralt, J., Obach, R. & Domenech, J. - Assessment of diclofenac permeation with different formulations: anti-inflammatory study of a selected formula. - Eur J Pharm Sci. 2003 Jul;19(4):203-10.

Basic co-enhancer residual phase



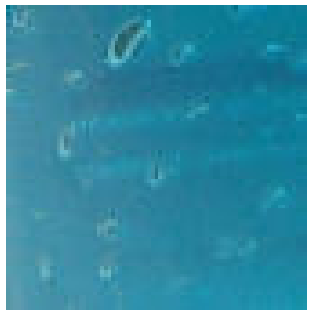
- drug in solution (saturation or >)
- polar solvent (propylene glycol) **Pc**
- polar lipid (glycol monolaurate) **Dc**

+ water, surfactants, waxes

+ volatile solvent, polymer

+ patch (Alza, Cygnus)

Cream

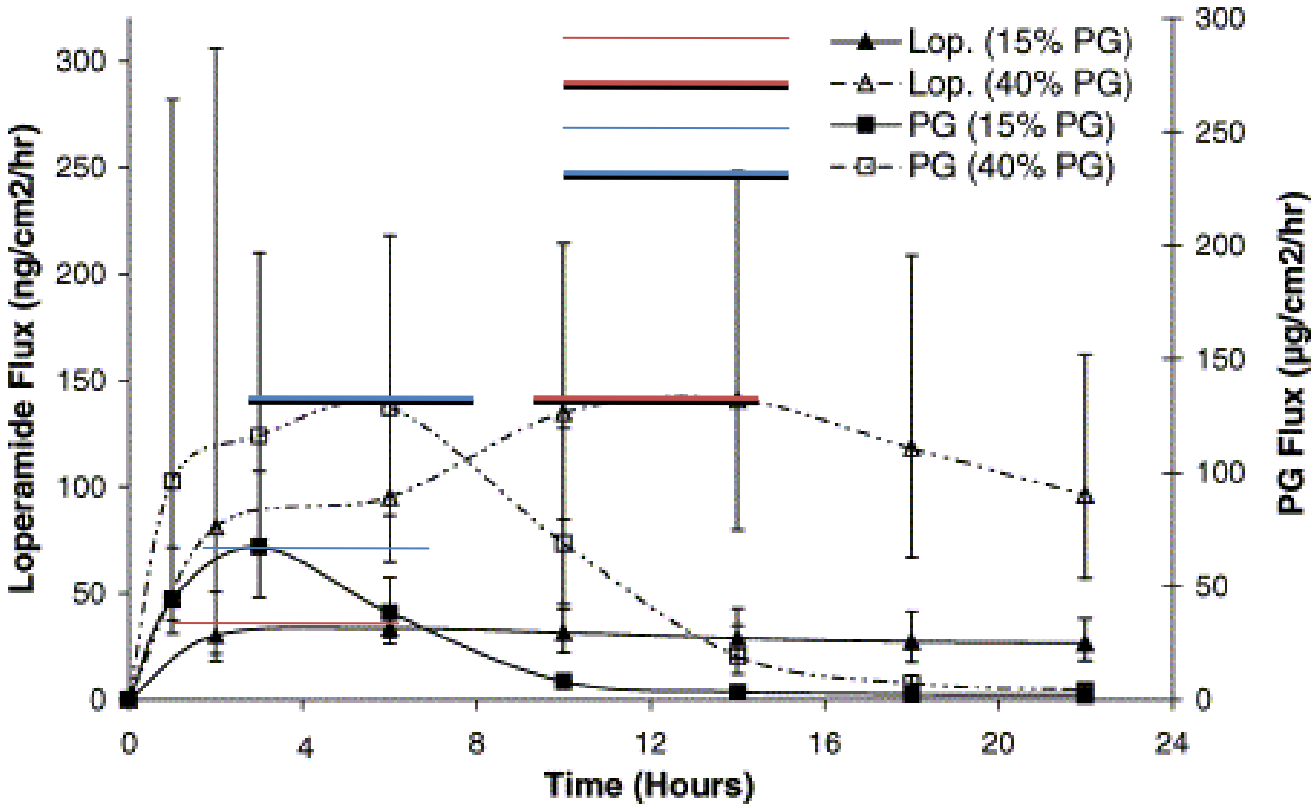


Spray / Gel

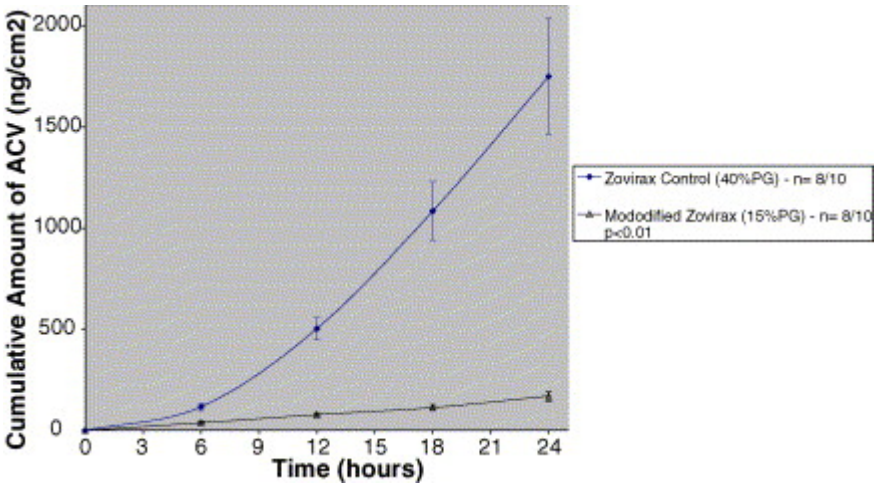
Patch

Formulation Strategy 5:
Get an idea of the dose of the polar solvent enhancer:

Loperamide penetration is propylene glycol dose dependent



Aciclovir penetration is propylene glycol dose dependent



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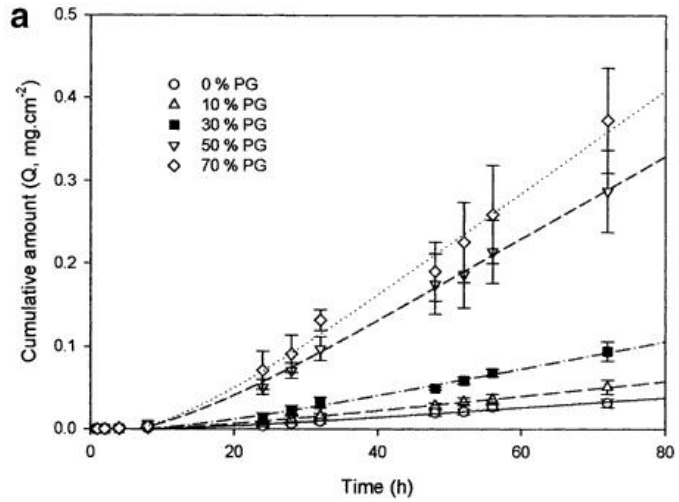
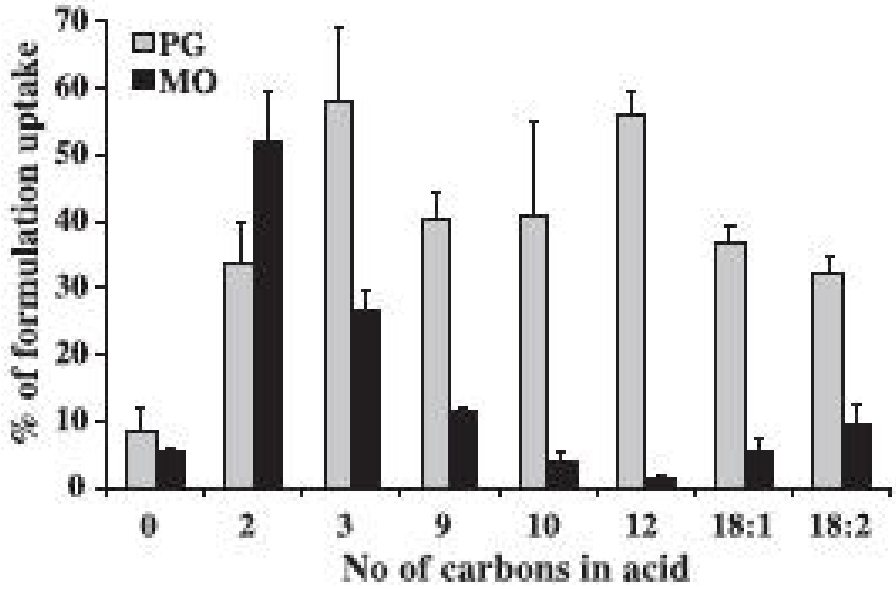


Diez-Sales O et al.
Journal Pharmaceutical Sci.
2005; 94(5): 1039-47

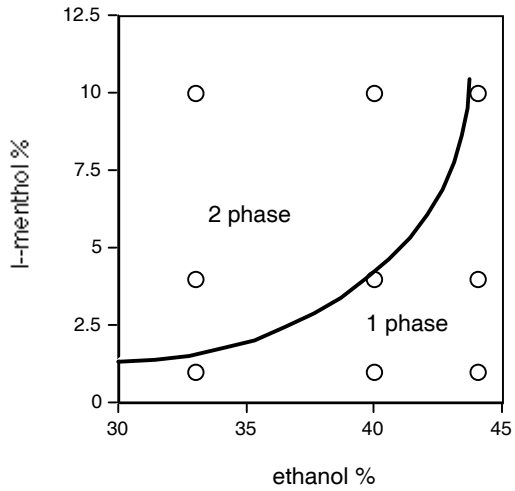
Formulation Strategy 6: Design the formulation to deliver the polar lipid co-enhancer

Effect of vehicle on partitioning of fatty acid co-enhancers into skin

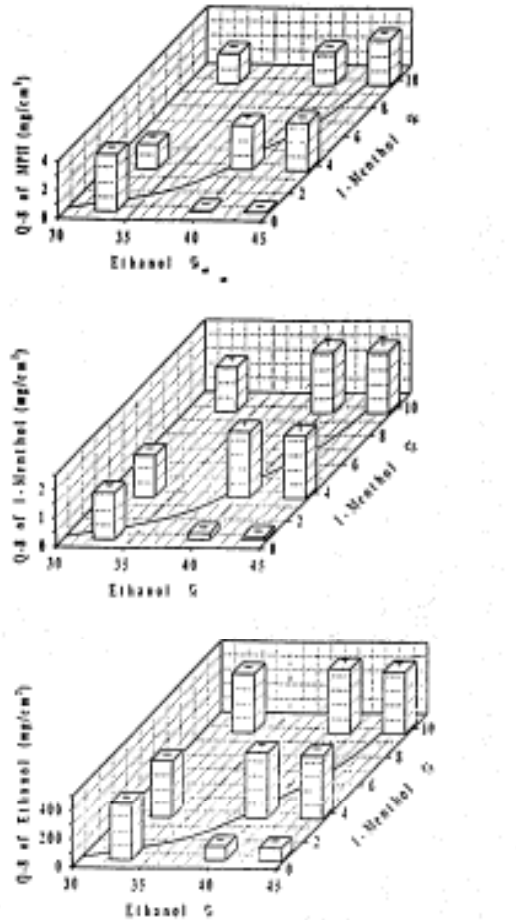


Wang MY et al. Journal Controlled Release. 2004; 94: 207-216

Penetration of morphine depends upon that of menthol and ethanol and their partitioning



Phase diagram for ethanol-menthol-water.
Data from Wada 1994.



Effect of the Phase Condition on the Skin Permeations of MPH, *l*-Menthol and Ethanol
Q-8: cumulative amount of MPH permeated through the excised abdominal skin over 8 h.

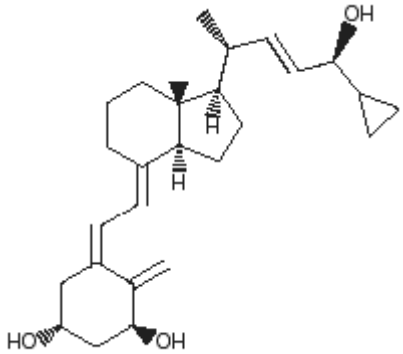
Wada Y et al.
Biol. Pharm. Bull. 1993; 16(6): 600-3

Formulation Strategy 7:
Design the formulation to deliver the drug, also.

VITAMIN D3 ANALOG
Dovonex
(calcipotriene) 0.005%

Full U.S. Prescribing Information
- Dovonex Ointment
- Dovonex Cream
- Dovonex Scalp Solution

Lotion 0.005%



- Calcipotriene 50 ug/g
- isopropanol (51% v/v)
- propylene glycol and water
- menthol
- hydroxypropyl cellulose
- sodium citrate

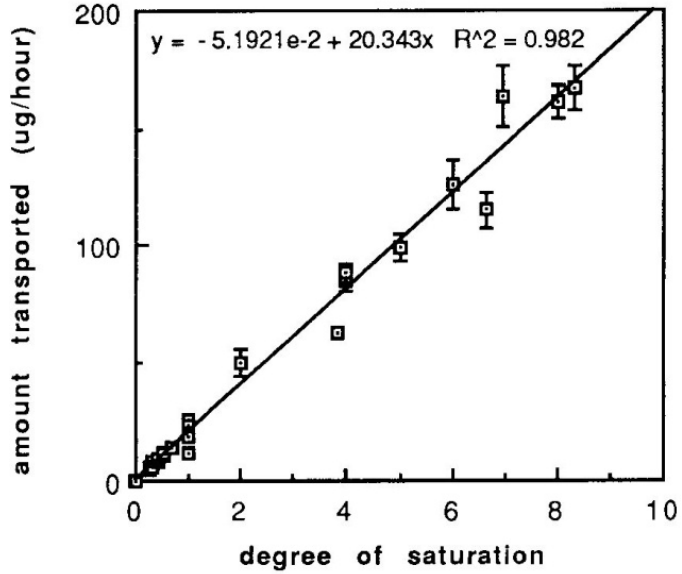
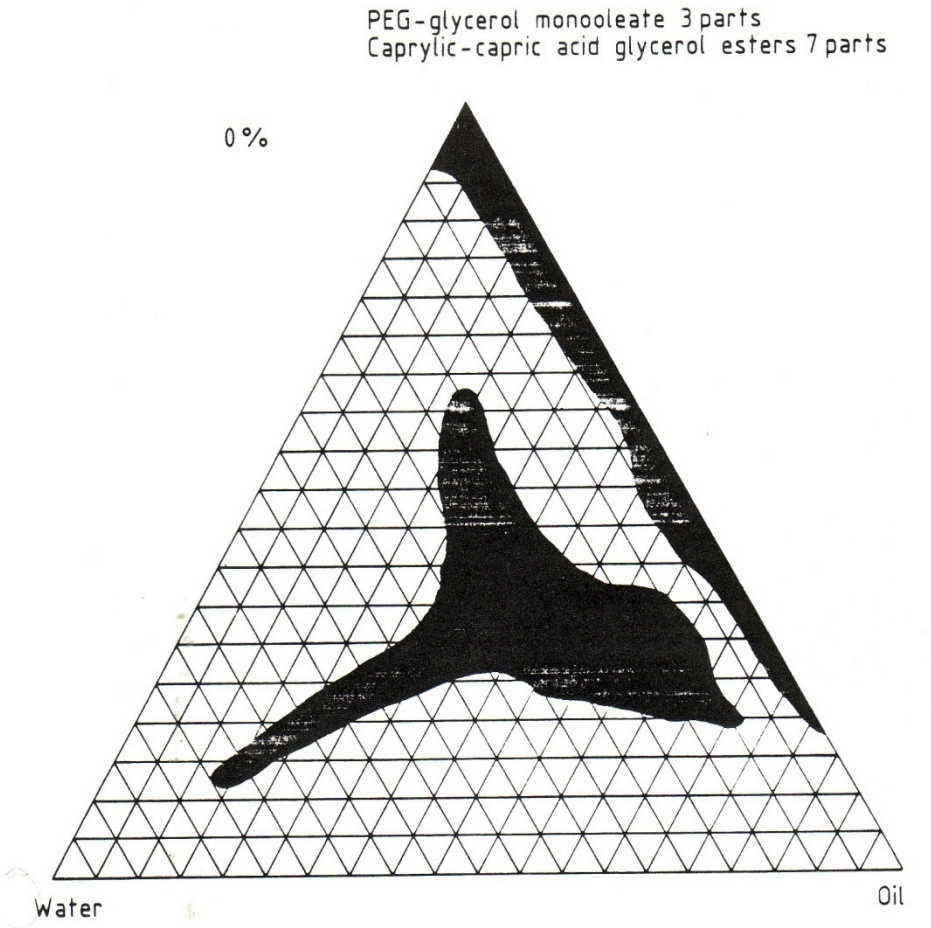


Fig. 7. Linear relationship between transport of hydrocortisone acetate and degree of saturation over the range of subsaturated to supersaturated systems. Combined data from Figs. 4–6. Mean ($n = 3$ or 6) ± S.E.

Liquid Crystal Residual Phase with drug supersaturation



Muller BW. US Patent 4,719239

Formulation strategy

DRUG AND DOSE SELECTION
- Choose best drug (and form) based on penetration / potency
- Get an idea of the drug dose

RESIDUAL PHASE and SATURATION
- Design solution system around residual phase
- Drug at saturation or higher

ENHANCEMENT
- Consider co-enhancer system
    - Consider dose of polar (Pc) enhancer
    - Consider saturation-partitioning of lipid co-enhancer in residual
    - Consider saturation-partitioning of the drug in residual

FORMATING
- Disguise the residual phase as appropriate for indication

Strategies to overcome barriers