



# **Modelling of the Effect of Formulation Factors on Skin Penetration**

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# Absorption from Skin

- Release from the vehicle
- Penetration through the skin



# Release from the vehicle

- Formulation type (gel or emulsion)
- Viscosity
- Molecular size (Stokes-Einstein equation for diffusion of a particle)
- Solubility in vehicle and saturation

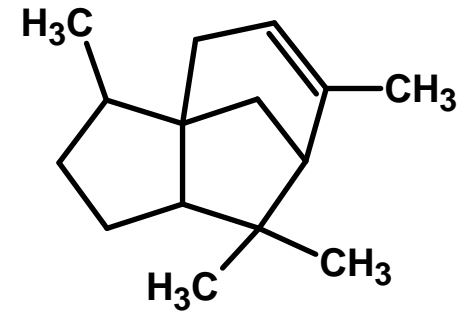
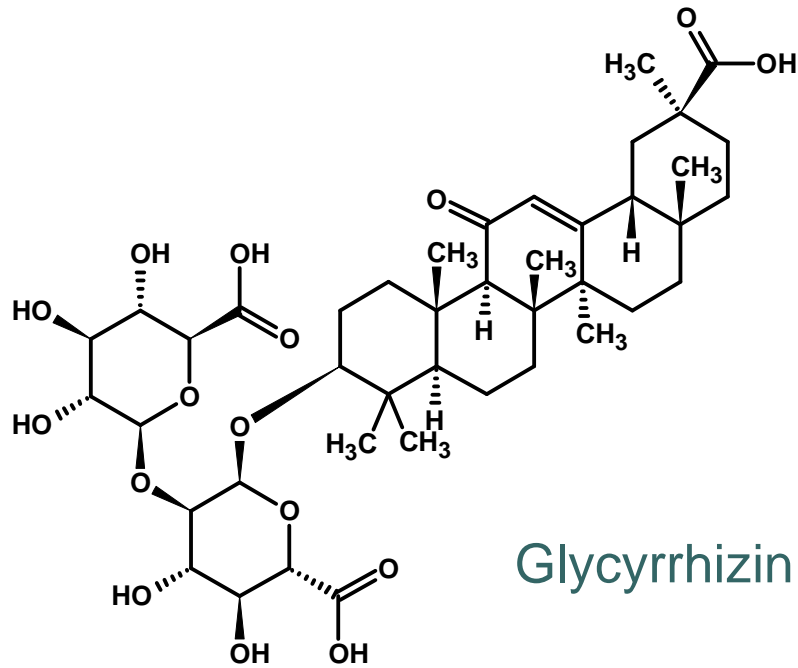
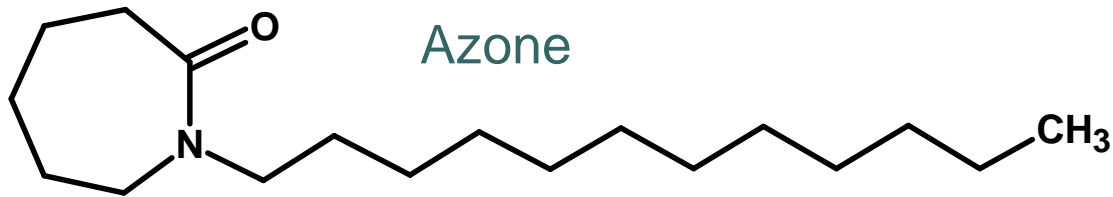


# Penetration through the skin

- Lipid content of the stratum corneum
- Lipid pathway vs. polar pathway of the stratum corneum
- Interaction with the proteins (keratin) and lipids



# Chemical penetration enhancement





# What is the mechanism?

- Increased drug release
- Increased partitioning of drug
- Increased fluidity of SC lipids
- Increased water content of the proteins in the barrier
- Specific interactions with drug

# Glycyrrhizin in diclofenac gels and emulsions

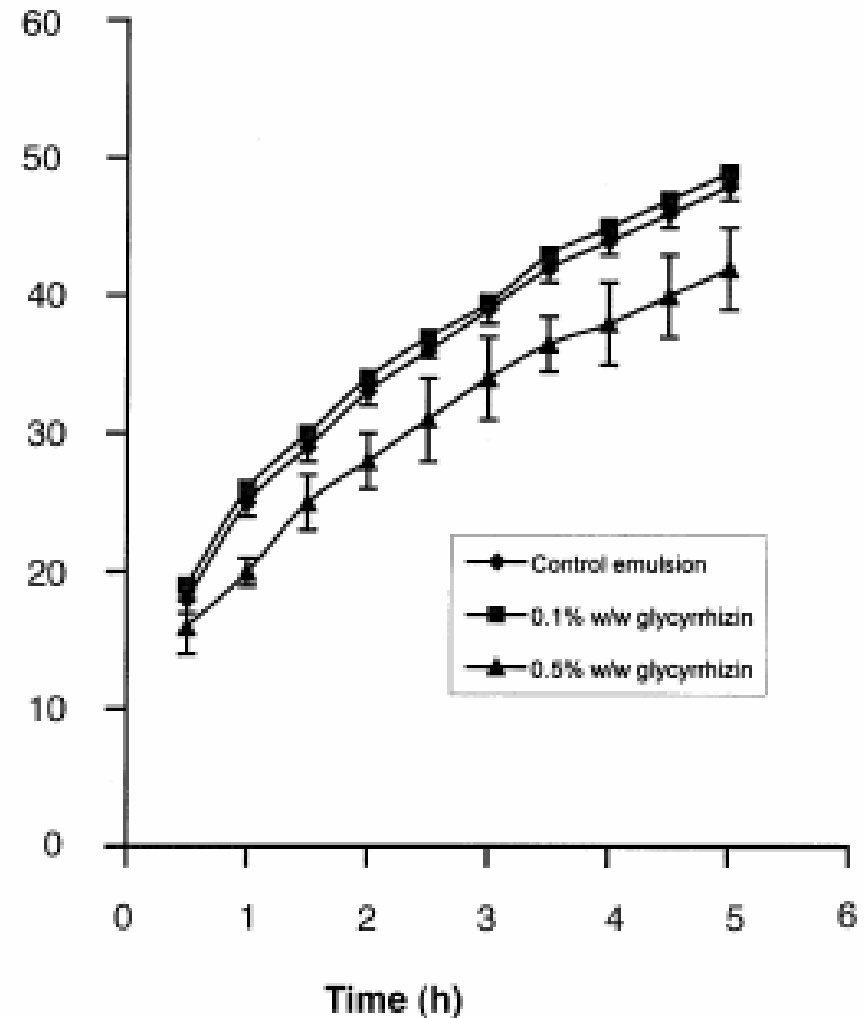
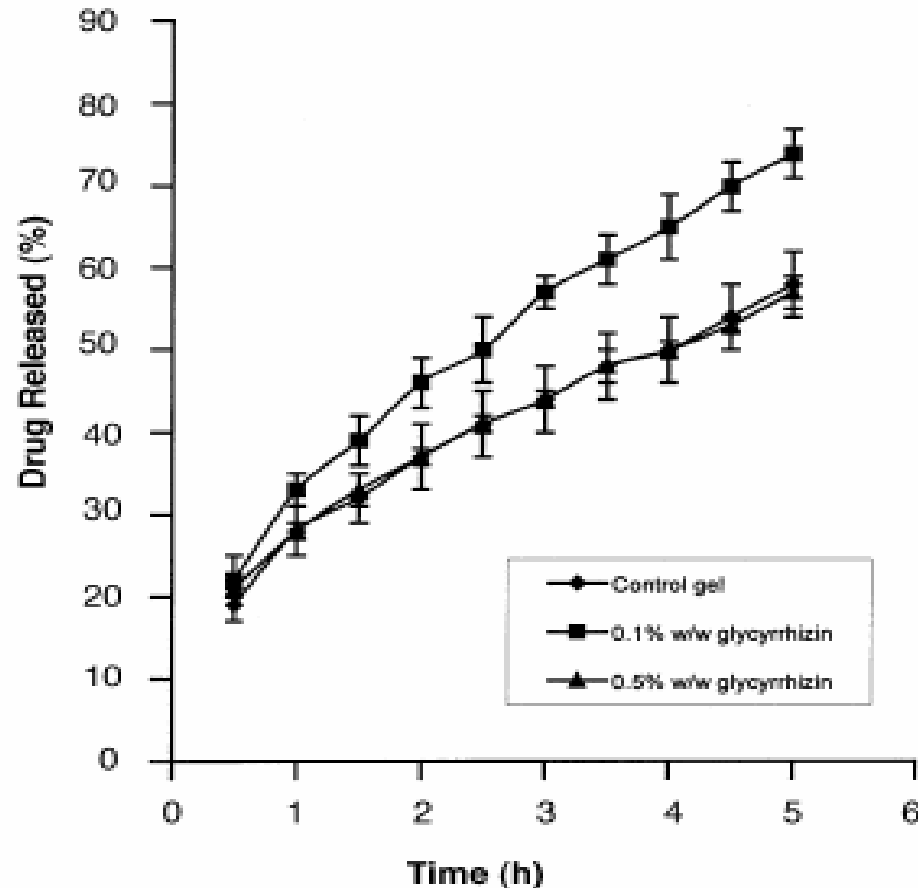


Natural enhancer from licorice roots

Constituents	Gels			Emulsions (O/W)		
	Formulation code					
	F1	F2	F3	F4	F5	F6
Diclofenac sodium	1	1	1	1	1	1
NaCMC	3	3	3			
Propylene glycol	40	40	40			
Glycyrrhizin		0.1	0.5		0.1	0.5
Lanette O				13	13	13
Eutanol G				13.5	13.5	13.5
Arlacel 63				2	2	2
Tween 80				1	1	1
Water	66	65.9	65.5	69.5	69.4	69

# Glycyrrhizin in diclofenac gels and emulsions

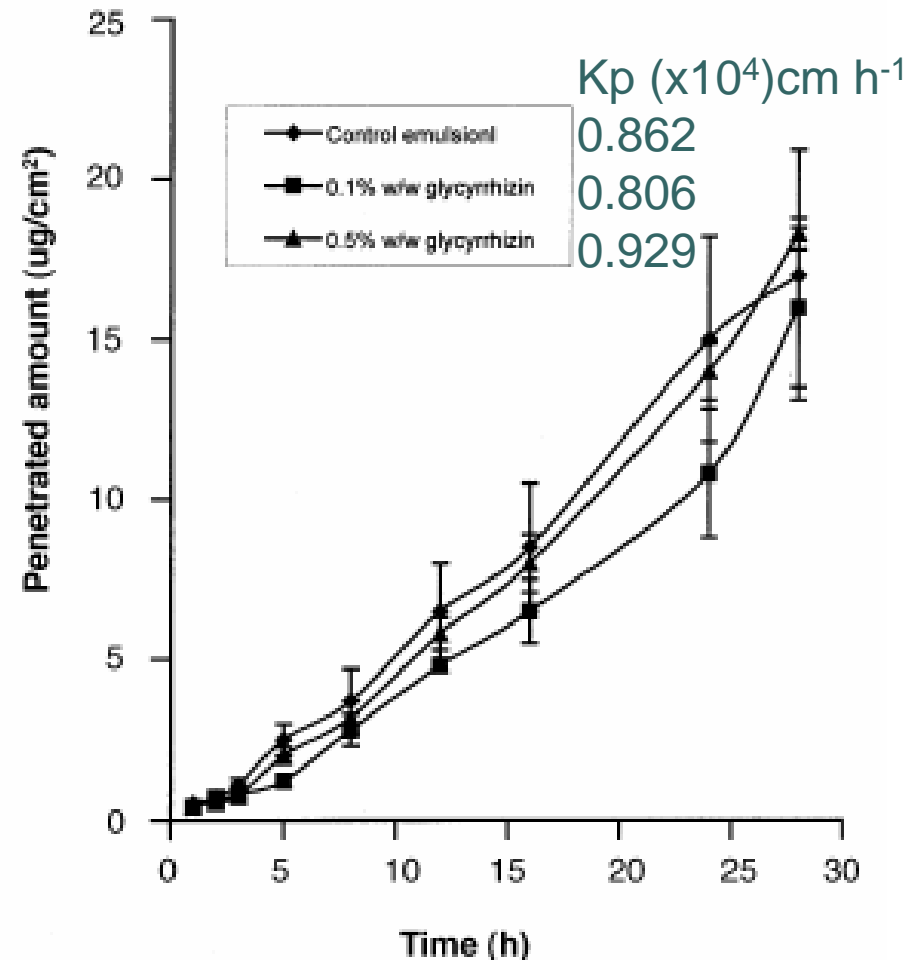
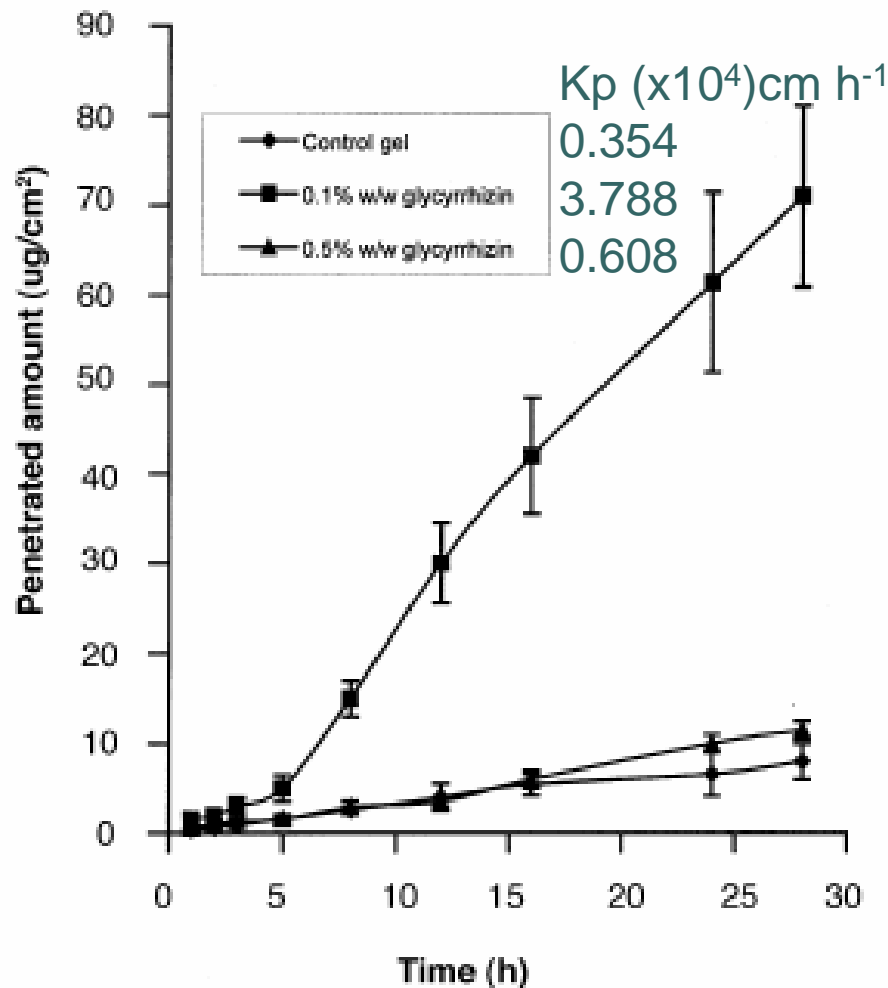
## Release kinetics





# Glycyrrhizin in diclofenac gels and emulsions

## ● ● ● | Permeation through rat skin





# Enhancement ratios of 0.1%w/w glycyrrhizin

Formulation	ER
Gel	10.7
Emulsion	0.94
Applied to skin before gel	7.72
Applied to skin before emulsion	1.20

**Glycyrrhizin penetrates the skin and changes the barrier function of the skin**

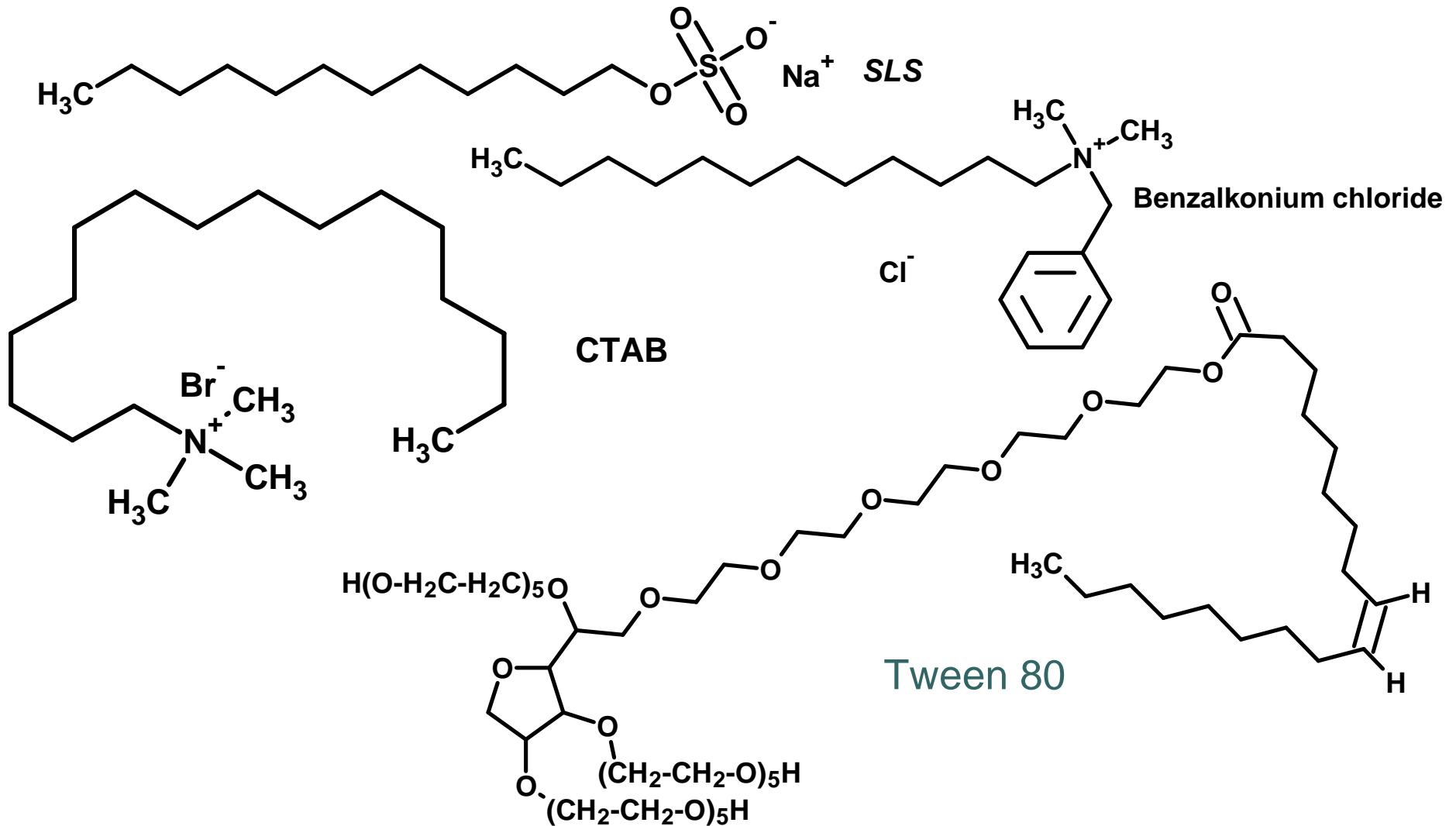


# Effect of enhancer Concentration

- Are they acting as surfactants?
- Micelle formation at higher concentrations
- CMC of glycyrrhizin in water is 0.025%w/v but it is increased due to propylene glycol vehicle by a factor of 10



# Effect of concentrations of surfactants



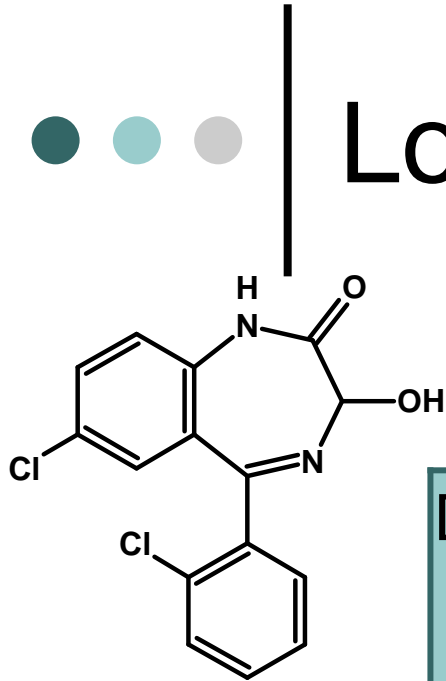


# Application of surfactants

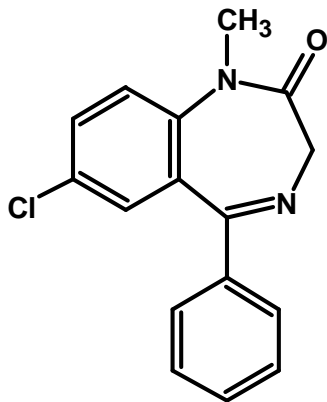
- Emulsifiers in emulsions
- Solubilising agents in gels
- Foaming agent
- Detergent
- Wetting agent

Surfactants are found in most skin products

# Lorazepam and Diazepam



**Lorazepam**

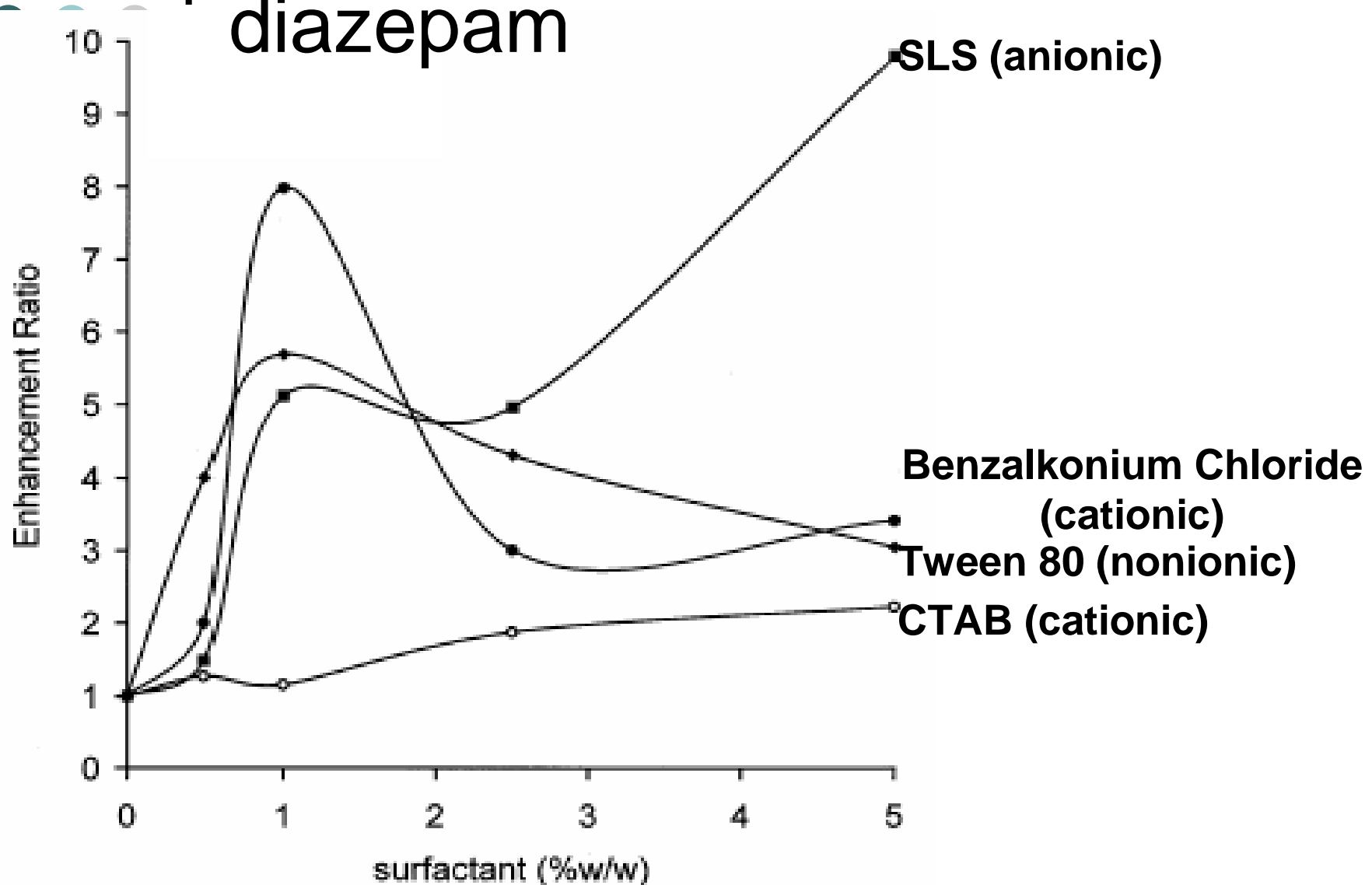


**Diazepam**

Drug	log P	solubility in water:propylene glycol 50:50 (mg/ml)	kp ×10 <sup>3</sup> (cm h <sup>-1</sup> )
Lorazepam	2.47	2.48	0.051
Diazepam	2.96	1.53	0.184

Donor phase: saturated solution of the drugs in water: propylene glycol (50:50% v/v) with or without surfactant

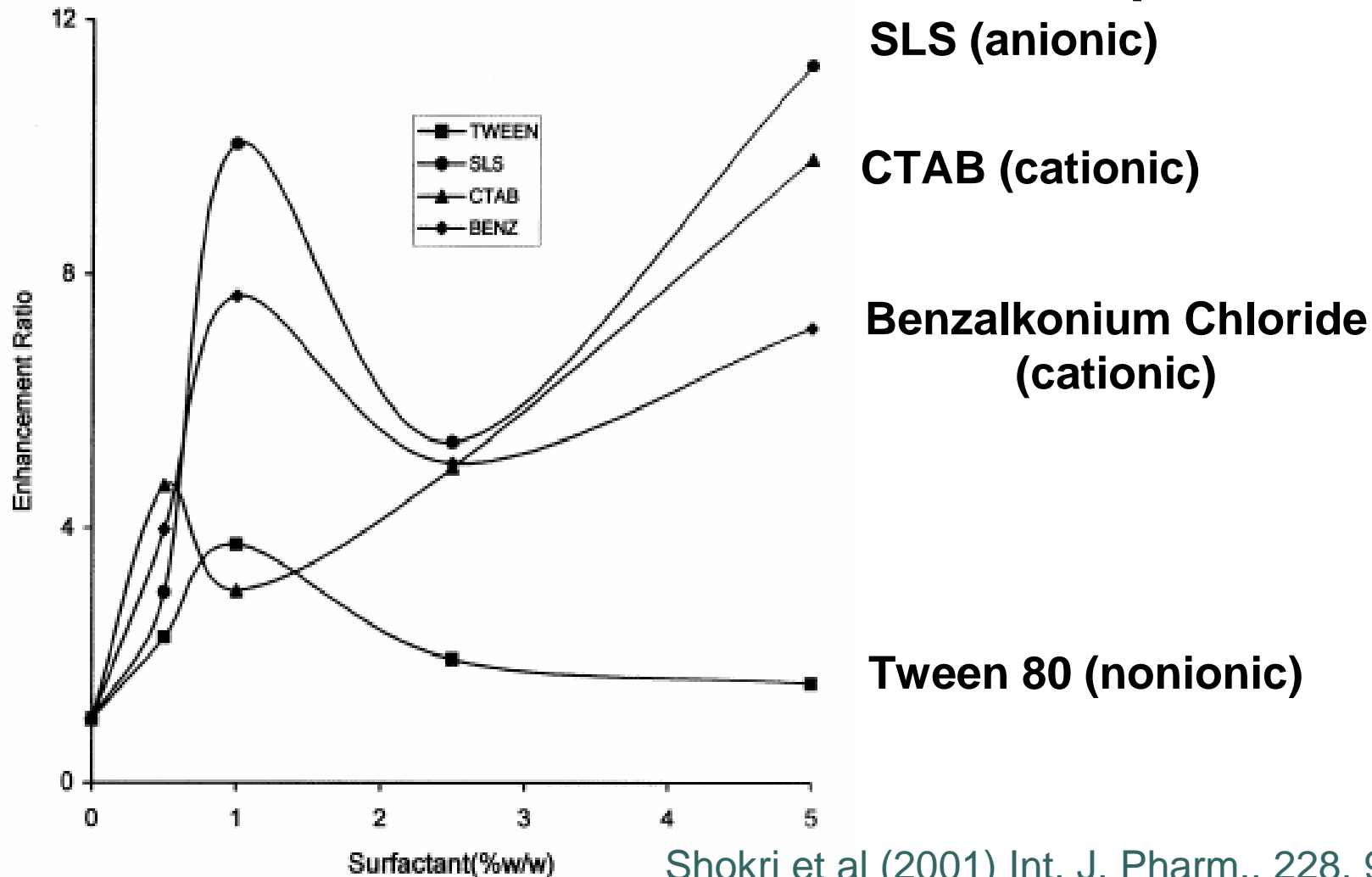
# Effect on the skin penetration of diazepam



Shokri et al (2001) Int. J. Pharm., 228, 99-107

Nokhodchi et al (2003) Int. J. Pharm., 250 359-369

# Effect on the skin penetration of lorazepam



Shokri et al (2001) Int. J. Pharm., 228, 99-107  
Nokhodchi et al (2003) Int. J. Pharm., 250 359-369

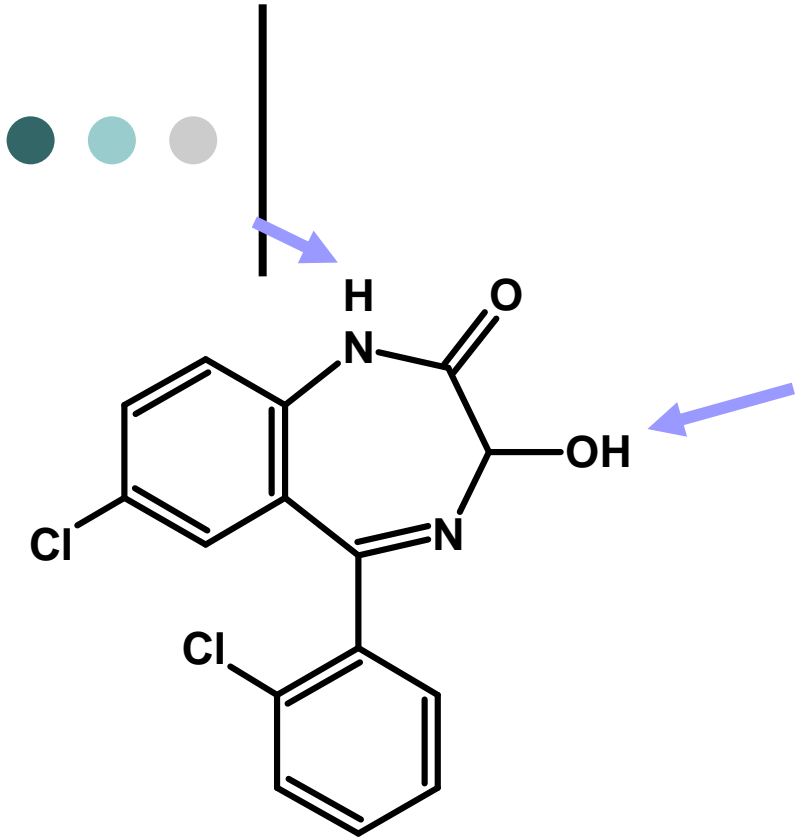




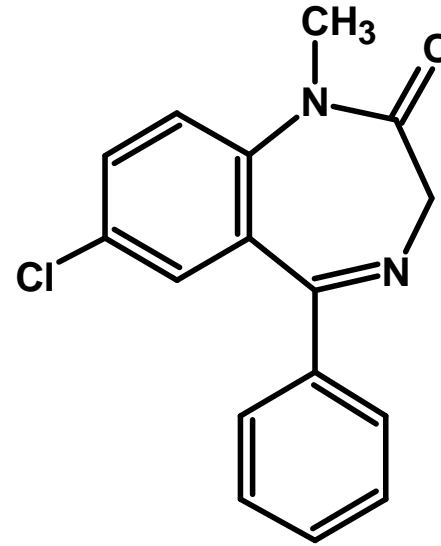
# Enhancement ratios (at concentrations below CMC)

Drug	SLS	CTAB	Benzalkonium	Tween 80	Control
Lorazepam	10.05 (0.50)	4.67 (0.23)	7.66 (0.38)	3.75 (0.19)	(0.051)
Diazepam	5.12 (0.94)	1.27 (0.23)	7.98 (1.47)	5.68 (1.05)	(0.184)

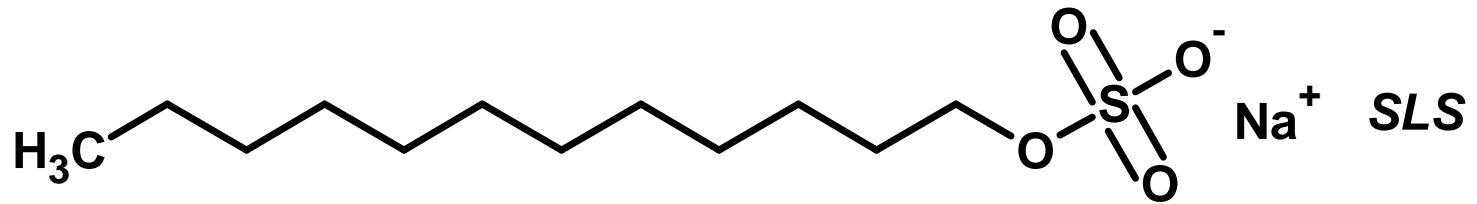
(Values in brackets are  $k_p \times 10^3$  in  $\text{cm h}^{-1}$ )



**Lorazepam**



**Diazepam**



**SLS**

● ● ● | Terpenes

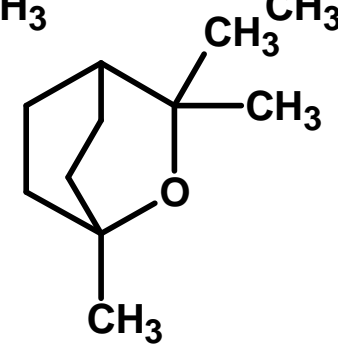
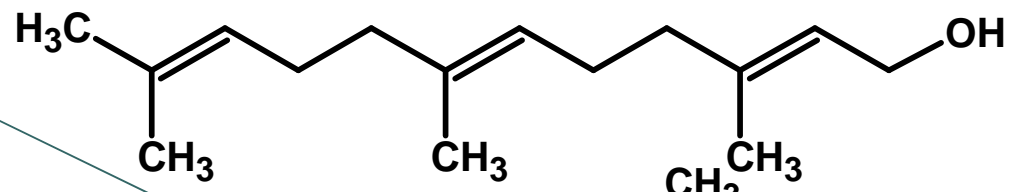
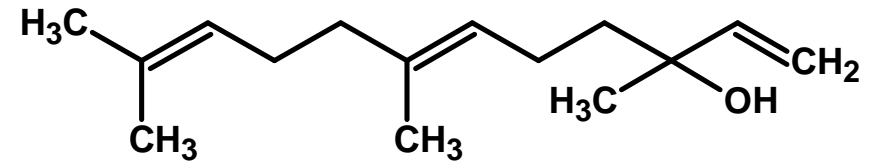
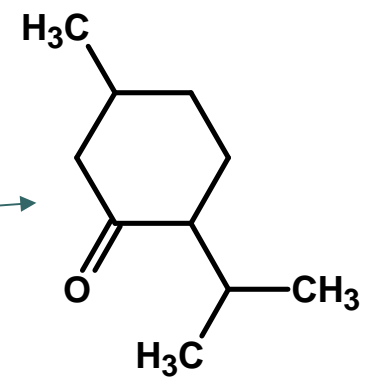
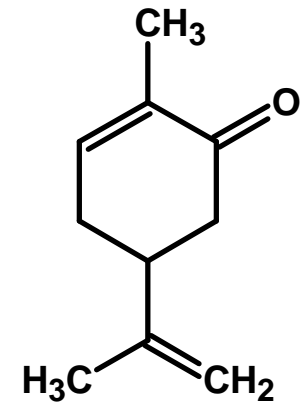
○ Carvone

○ Menthone

○ Nerolidol

○ Farnesol

○ Limonenoxide



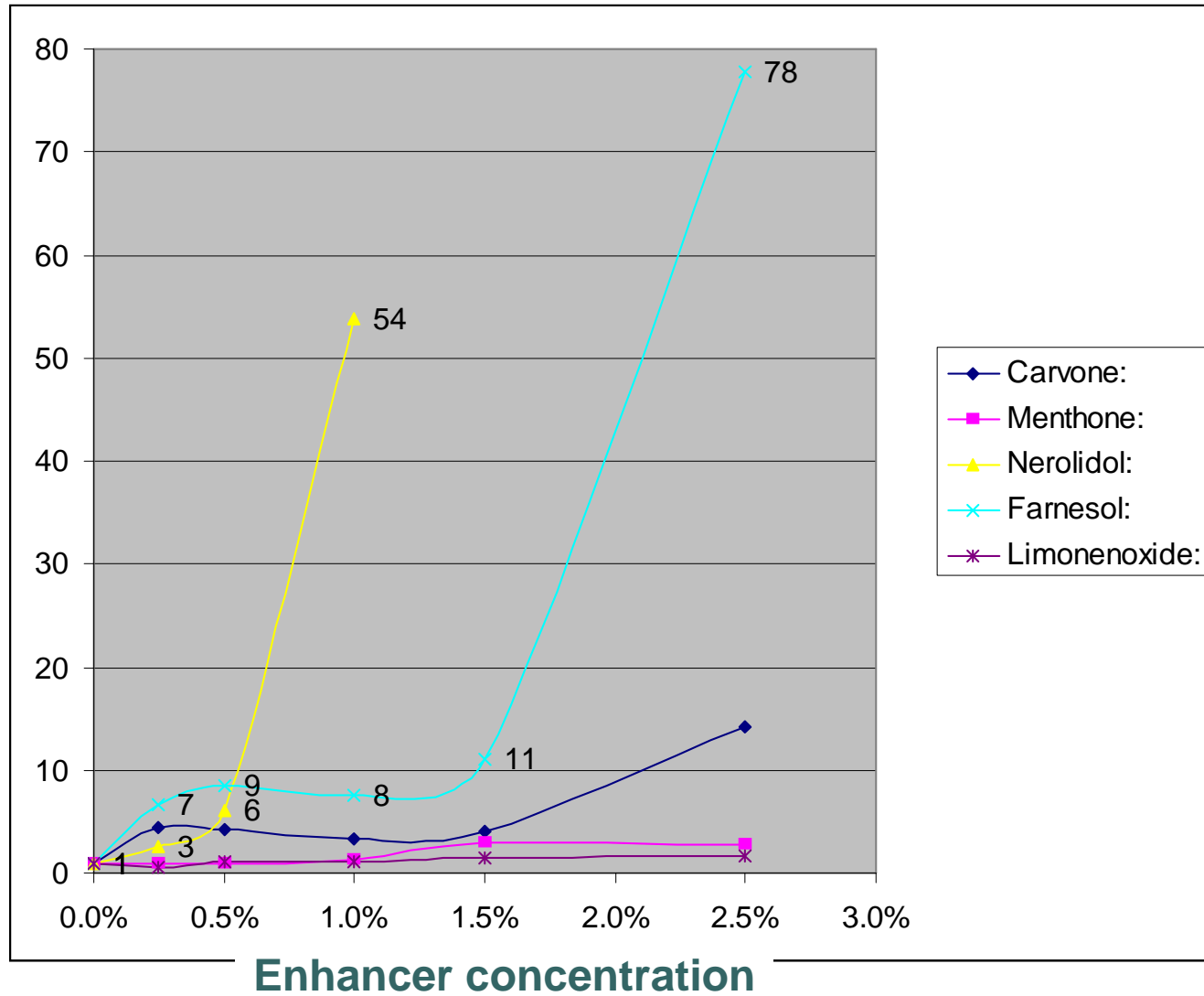


# Effect of concentration of terpenes

- Penetration of diclofenac sodium through rat skin
- Donor phase: saturated solutions of diclofenac in solvent mixture of ethanol: glycerin: phosphate buffer (60:10:30 ratio) with or without terpene concentrations



ER





# Estimation problems

- Large datasets are required
- The effect of enhancers are different on different penetrants
- Several possible mechanisms



# Estimation by QSAR

- Quantitative Structure – Activity Relationship
- For a dataset with known skin effect (increase/ reduction of penetration of other chemicals through skin):

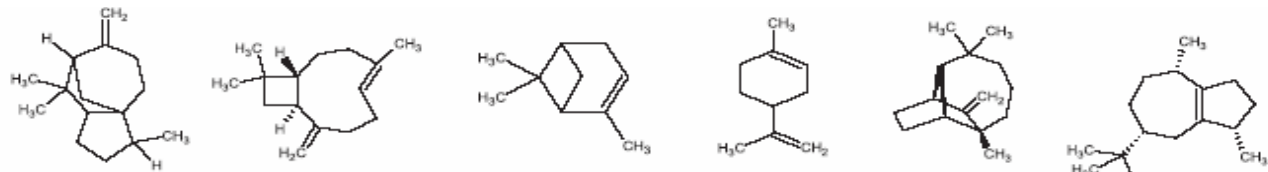
$$\textit{Skin effect} = f(\textit{structural properties})$$



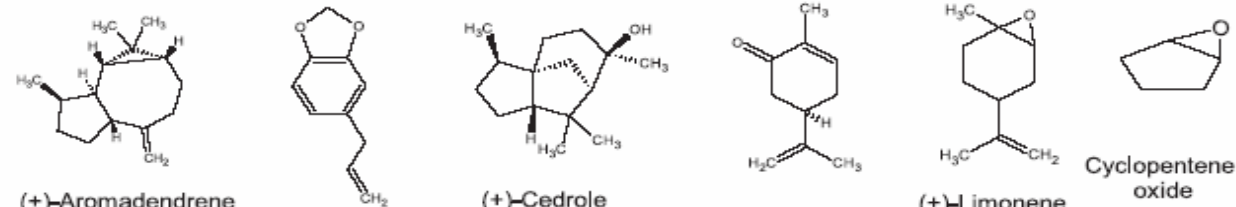
# Estimation of the effect of enhancers: Datasets

- Terpene enhancement effects on 4 penetrants
  - 5FU
  - Hydrocortisone
  - Diclofenac sodium
  - Estradiol
- Enhancement activities of pyrrolidinone derivatives towards hydrocortisone

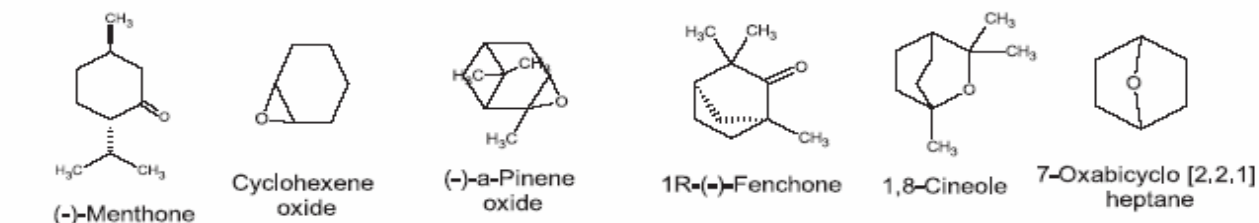




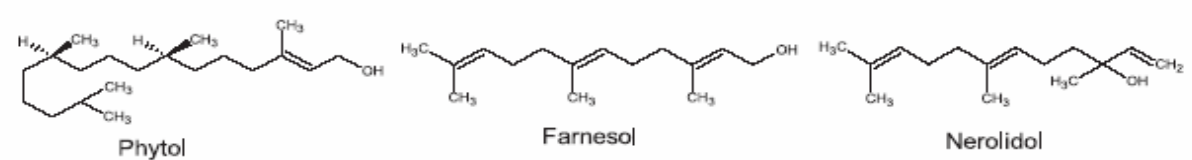
(+)-β-Cedrene (-)-trans-Caryophyllene 1R-(+)-α-Pinene (+)-Limonene (+)-Longifolene (-)-Guaaiol



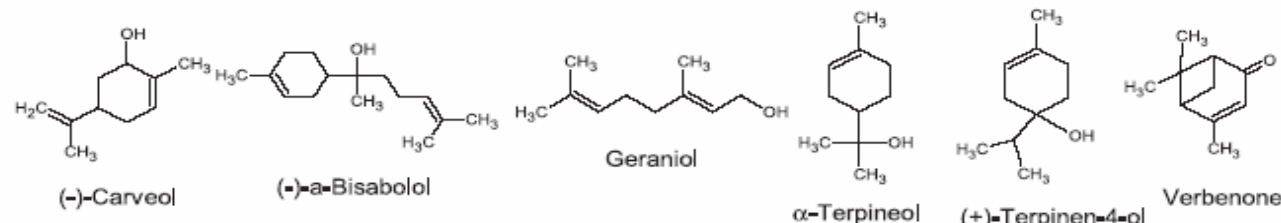
(+)-Aromadendrene Safrole (+)-Cedrole R-(-)-Carvone (+)-Limonene oxide Cyclopentene oxide



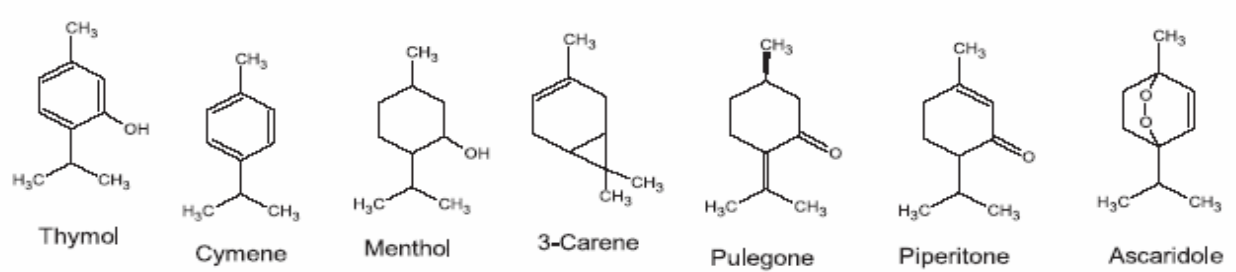
(-)-Menthone Cyclohexene oxide (-)-α-Pinene oxide 1R-(+)-Fenchone 1,8-Cineole 7-Oxabicyclo [2.2.1] heptane



Phytol Farnesol Nerolidol

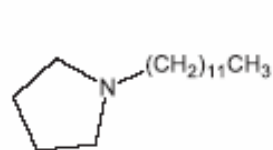


(-)-Carveol (+)-α-Bisabolol Geraniol α-Terpineol (+)-Terpinen-4-ol Verbenone

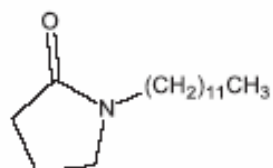


Thymol Cymene Menthol 3-Carene Pulegone Piperitone Ascaridole

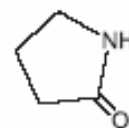
# Pyrrolidinone derivatives



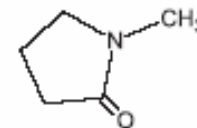
N-dodecyl-pyrrolidine



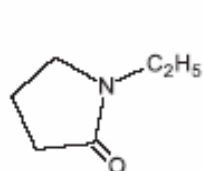
N-dodecyl-2-pyrrolidinone



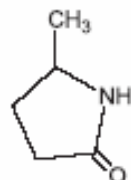
2-pyrrolidinone



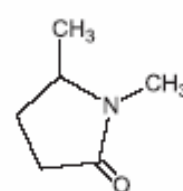
1-methyl-2-pyrrolidinone



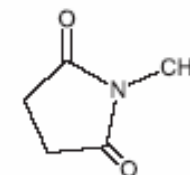
1-ethyl-2-pyrrolidinone



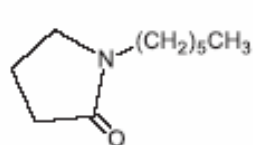
5-methyl-2-pyrrolidinone



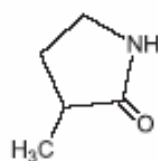
1,5-dimethyl-2-pyrrolidinone



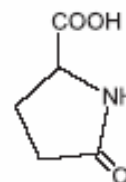
1-methylsuccinimide



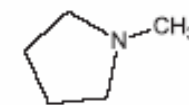
1-hexyl-2-pyrrolidinone



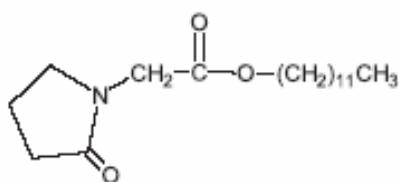
3-methyl-2-pyrrolidinone



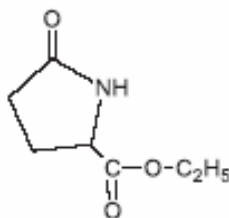
2-pyrrolidinone-5-carboxylic acid



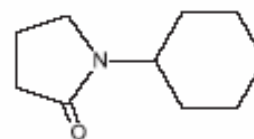
1-methylpyrrolidine



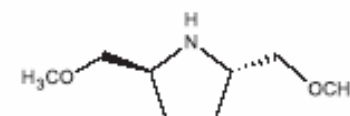
2-pyrrolidinone-1-acetic acid  
dodecyl ester



ethyl-2-pyrrolidinone-  
5-carboxylate



1-cyclohexyl-2-pyrrolidinone

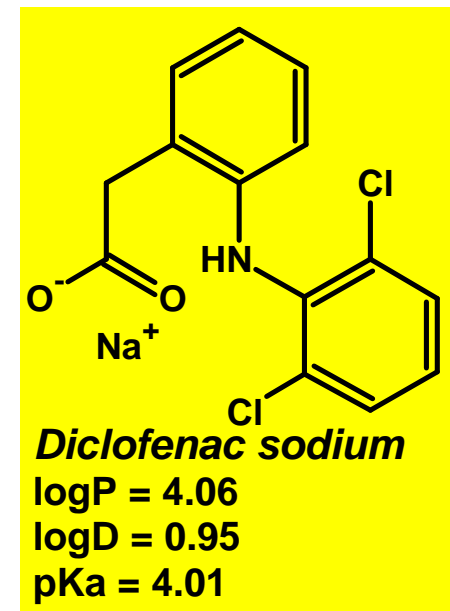


2,5-bis(methoxymethyl)  
pyrrolidine

# Enhancement of diclofenac sodium penetration

$$\log ER = 0.297 + 0.017ESP^+$$
$$n = 8 \quad s = 0.298 \quad r^2 = 0.554 \quad F = 7.4$$

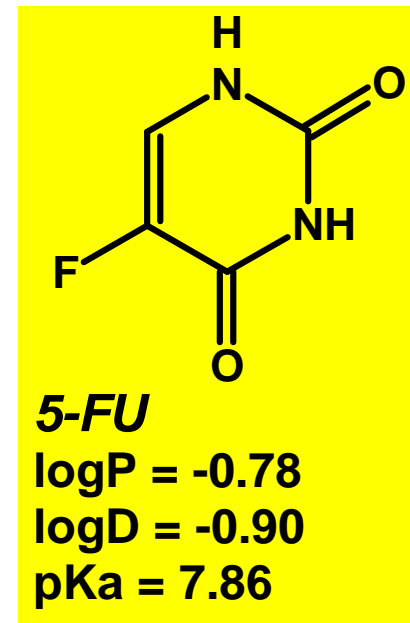
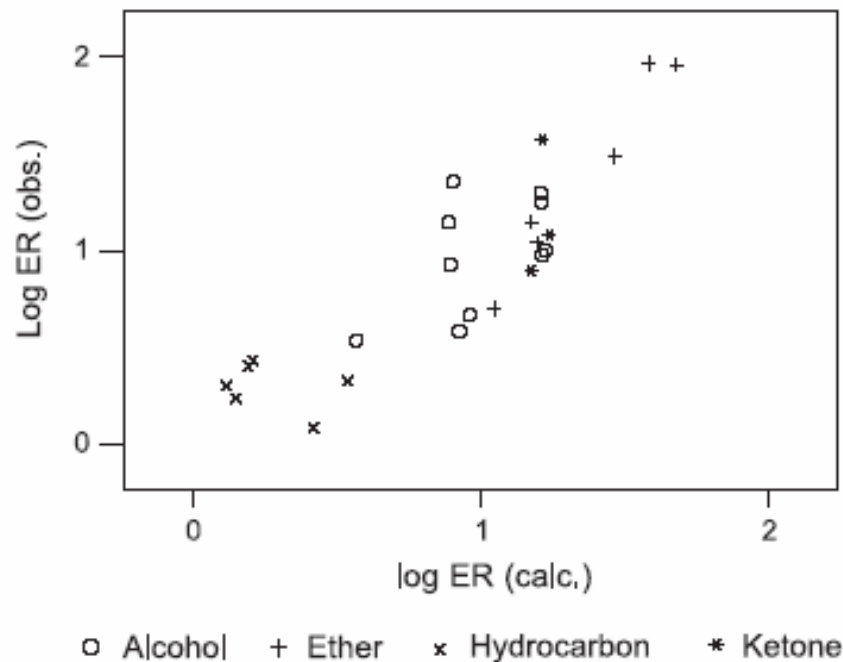
- Gels containing propylene glycol and 1% (w/w) terpene
- Penetration through rat skin



# Enhancement effect of terpenes towards 5FU

Cyclic ethers and alcohols possess the lowest and the highest EV

$$\log ER = 0.138 - 5.79q^- - 0.46E_v$$
$$n = 26 \quad r^2 = 0.627 \quad s = 0.329 \quad F = 19$$



# Enhancement of Hydrocortisone penetration

## Terpenes

$$\log ER = 0.719 + 0.153 \log P$$

$$n = 12 \quad r^2 = 0.76 \quad s = 0.089 \quad F = 32$$

Gels with 2% terpene  
Hairless mouse skin

## Pyrrolidinone derivatives

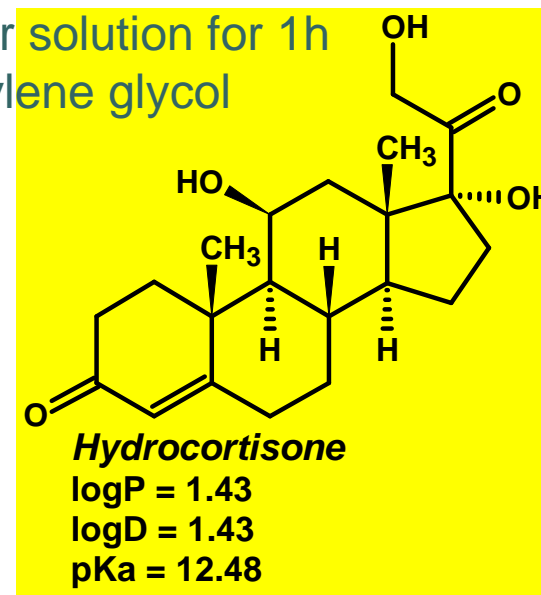
$$\log ER(Q_{24}) = 0.083 + 0.84SA^2$$

$$n = 16 \quad r^2 = 0.809 \quad s = 0.18 \quad F = 59$$

$$\log ER = 0.114 + 0.172 \log P$$

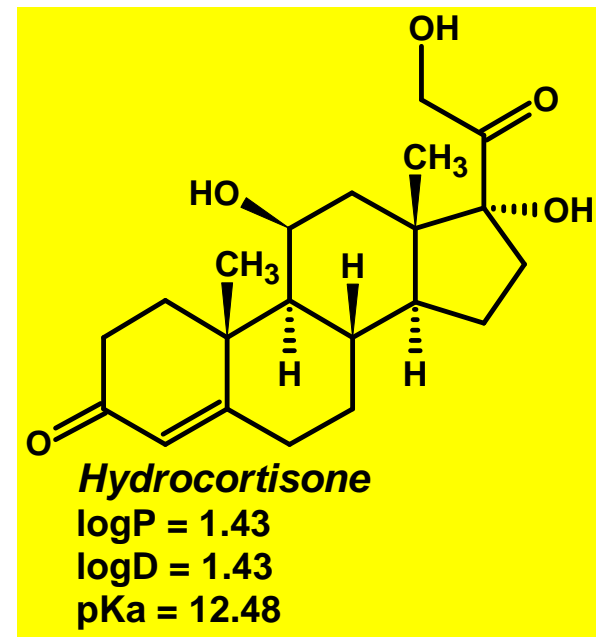
$$n = 16 \quad r^2 = 0.621 \quad s = 0.38 \quad F = 23$$

- Treated with enhancer solution for 1h
- Drug solution in propylene glycol
- Hairless rat skin



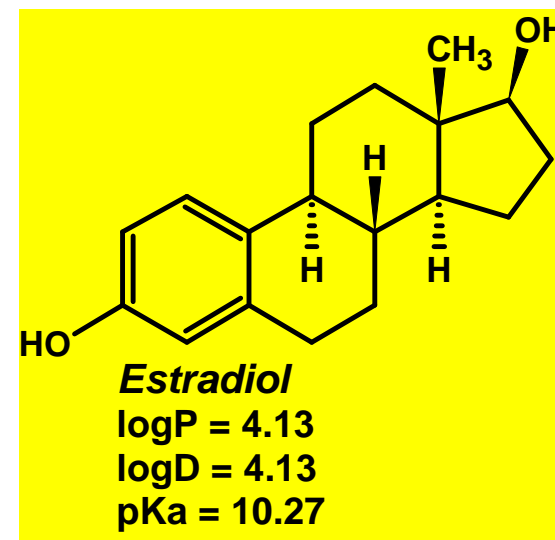
# Enhancement of Hydrocortisone penetration

According to Pugh et al (2005):  
Hydrogen bonding has a negative effect  
Number of chain carbon atoms has a positive effect



# Enhancement of estradiol penetration

$$\log ER = 0.743 - 0.206S(I) - 2.91q^-$$
$$n = 12 \quad s = 0.232 \quad r^2 = 0.853 \quad F = 26$$





# Effect of solvents

- Partitioning of penetrant between solvent and SC

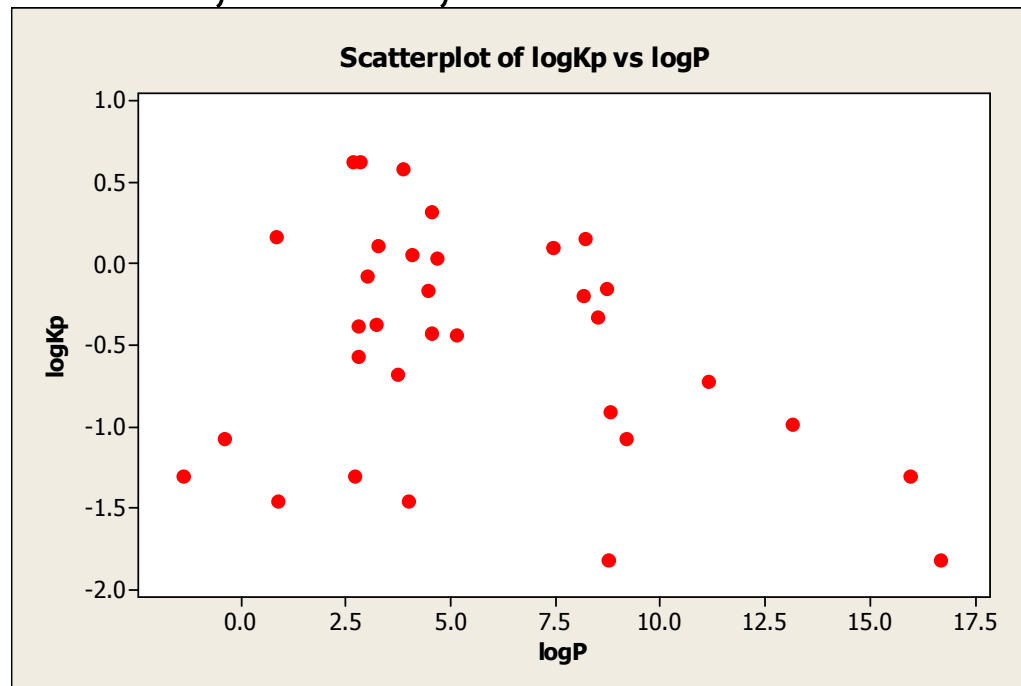
$$P_{SC/Vehicle} = \frac{P_{SC/Water}}{P_{Vehicle/Water}}$$

- Diffusion of penetrant in the vehicle and the SC
  - Viscosity of vehicle
  - Penetration of vehicle into the skin
  - Effect of vehicle on the skin



# Formoterol in 32 different solvents

- Terpenes, Ethyl Linoleate, Butyl myristate, n-Octanol, water, Formamide



- Rat skin, same concentration of drug in the solvents containing small fraction of ethanol

# Penetration of formoterol from solvents

$$\log Q_{24} = -0.937atoms - 2.51^9 \chi_p^v - 1.72aromatics - 0.177E_{LUMO} + 1.58$$

$N = 32 \quad S = 0.401 \quad R^2 = 0.611$

$$\log kp = -2.87 - 9.96^9 \chi_p + 0.0191MW + 0.0515lipole$$

$n = 32 \quad s = 0.430 \quad R^2 = 0.654 \quad F = 18$

