Solubility-Physicochemical-Thermodynamic Theory of Penetration Enhancer Mechanism of Action

Authors: Anika Haq[1,2,3] , Mark Chandler[4], Bozena Michniak-Kohn[1,2]

1- Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854.
2- Center for Dermal Research, Life Sciences Building, Rutgers, The State University of New Jersey, Piscataway, NJ 08854.
3- Current affiliation- ORISE Fellow, Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, U.S. FDA, Silver Spring, MD, 20993.
4- ACT Solutions Corp, 550 S, College Ave, Suite 110, Newark, DE 19713.

Purpose

To propose for the first time a Solubility-Physicochemical-Thermodynamic (SPT) theory to define the action of penetration enhancers in a given formulation with a specific drug.

Methods

The FFE (Formulating for Efficacy™) Software can derive the Hansen Solubility Parameters of actives and excipients; from there, solubility profiles, permeation and different physico-chemical properties including ingredient active gap (IAG), ingredient skin gap (ISG), solubility of active in the formulation (SolV) and the formulation solubility in the skin (SolS) of drug actives (thymoquinone) and excipient ingredients (Azone - laurocapram, Transcutol® P (Tc), oleic acid, ethanol, polysorbate 80 (Tween 80), and N-methyl-pyrrolidone (NMP)) are calculated automatically. Measured drug permeation data were compared with the calculated permeation data and solubility parameters of the drugs.

Results and Discussion

The rank order of each enhancer/ingredient for the enhancement of thymoquinone (TQ) skin permeation was as follows: Azone + Oleic acid>Transcutol® P>Control + Tween 80>Ethanol>NMP. From the solubility data it was found that TQ has highest solubility in ethanol. On the other hand, the permeation data showed that TQ flux was lower than the control formulation with 5% of ethanol. It confirmed that the flux is actually proportional to a gradient of thermodynamic activity rather than the concentration. The thermodynamic activity of TQ was reduced since ethanol has the highest IAG value and it is also very soluble in the skin. Transcutol® P has a lower IAG value but does not possess an optimum SolV : SolS ratio, thus did not provide better skin flux of TQ. It can be stated that, the more extreme the difference in solubility between the formulation and the skin the greater the driving force for partitioning of the active into the stratum corneum. These studies suggest that there is an inverse relationship between measured flux and IAG values given that there is an optimum ingredient skin gap, SolV and SolS ratio. The study demonstrated that maximum skin penetration and deposition can be achieved when the drug is at its highest thermodynamic activity.

Table 1. Hansen solubility parameters and molar volume of thymoquinone and different solvents/enhancers.

Solvent	δ_D	δ_P	δ_H	Mvol
Thymoquinone	18.3	9.2	5.1	159.9
Propylene Glycol	16.8	10.4	21.3	73.7
Tween 80	16.2	6.6	9.6	1265
N-Methyl Pyrrolidone	18.1	10.3	6.6	98.1
Azone	17	1.6	3.2	311.7
Oleic Acid	16.5	3.2	5.7	317.5
Ethanol	15.4	9.2	19.6	58.7
Transcutol® P	16.3	7.1	11.9	135.2

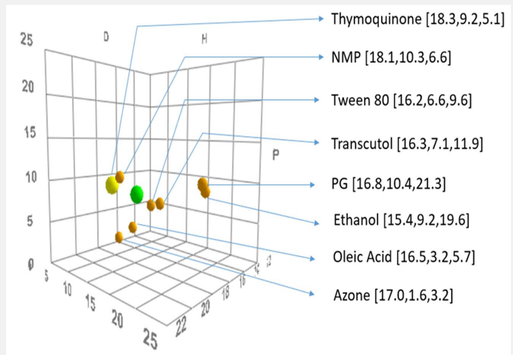

Figure 1. Position of the active Thymoquinone and penetration enhancers/ingredients in 3D Hansen Space.

Table 2. Physicochemical parameters of thymoquinone and different enhancers.

Penetration enhancers	ASG	IAG	ISG	SolV (%)	SolS (%)
Thymoquinone	4.08			73.4	100
Propylene Glycol		16.52	9.96	1.3	100
Tween 80		6.68	33.66	21.7	0.6
N-Methyl Pyrrolidone		1.9	3.41	81.6	100
Azone		8.25	24.94	22.4	0.2
Oleic Acid		7.02	17.19	35.3	0.2
Ethanol		15.62	7.1	4.9	100
Transcutol® P		8.16	5.73	67	100

Table 4. Penetration parameters of thymoquinone through human cadaver skin (N=5, mean ± SD) after 24 hours.

Formulation	TQ Flux (µg/cm²/h)	TQ Q $_{24}$ (µg/cm²)	ER
Control	11.02±1.2	208±23	
Tween 80	11.09±1.5	208±16	1
N-Methyl Pyrrolidone	9±1.5[b]	167±38	0.81
Azone	49.3±5.6[a]	854±93	4.47
Oleic Acid	46.3±4.5[a]	865±113	4.2
Ethanol	10.59±1	180±55	0.96
Transcutol® P	14.23±1.4[a]	247±26	1.29

Table 3. Summary of the solubility study results showing the effect of 5% penetration enhancers on the solubility of TQ using propylene glycol. The values represent the mean concentration of TQ ± SD (N=3) in mg/mL at 48 hours.

Enhancers	Solubility (mg/mL) ± SD
Propylene Glycol	8.6 ± 0.3
Tween 80	9.4 ± 1.1
N-Methyl Pyrrolidone	8.5 ± 0.2
Azone	15.0 ± 1.4
Oleic Acid	13.6 ± 2.1
Ethanol	15.7 ± 0.5
Transcutol® P	11.1 ± 0.7

ER= Enhancement Ratio
a, significant increase in TQ flux ($p<0.05$)
b, significant reduction in TQ flux ($p<0.05$

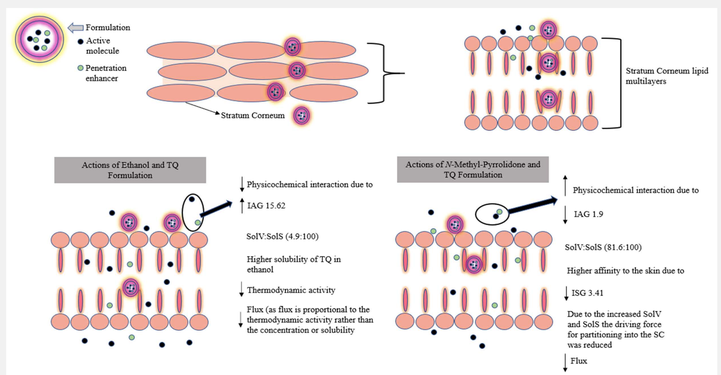

Figure 2. A representation of the active-enhancer and stratum corneum interactions promoting partitioning into the stratum corneum.

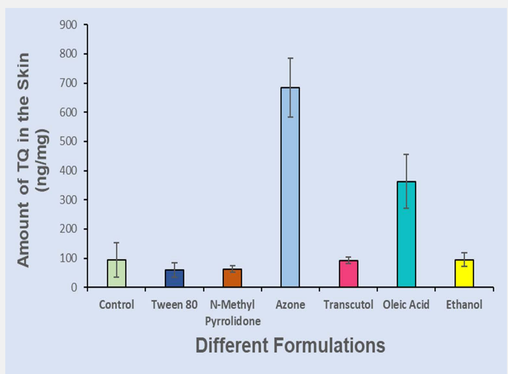

Figure 4. Amount of Thymoquinone detected at 24 hours in human cadaver skin (N=5, mean ± SD).

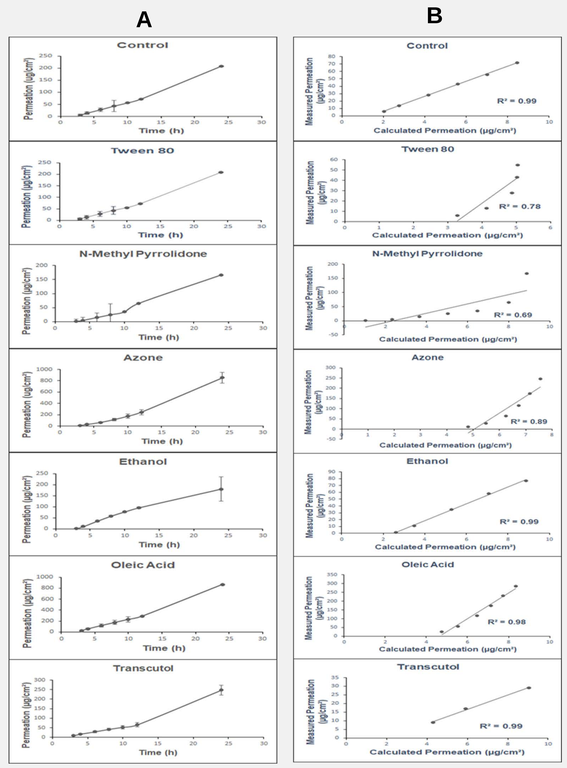

Figure 3. Thymoquinone permeation profiles of transdermal formulations (A) with the Franz diffusion cell method using human cadaver skin (N=5, mean ± SD), (B) the correlations between the calculated and measured permeation of Thymoquinone.

Conclusion

Better understanding of the physicochemical properties and solubility parameters of the active and enhancers, as well as the interaction of enhancers with the drug and skin will aid to address the mechanism of enhancement.