

## **Influence of Piperine and Cosmoperine® as Transdermal Drug Delivery Promoters.**

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### **Focal Points.**

- Literature review suggested that Piperine enhances the oral bioavailability of several pharmaceutical compounds.
- *In-vitro* transdermal diffusion studies were undertaken to determine the influence of Piperine and Cosmoperine® as transdermal drug delivery promoters.
- Lidocaine was used as the model drug.
- Amphiphilogels were assessed for their suitability as drug delivery systems.
- Solid Phase Extraction (SPE) technique was employed to aid in the preparation of biological samples (rat skin with the retained drug) for subsequent HPLC analysis.

### **Introduction.**

In spite of the several advantages offered by the non-invasive transdermal route the stratum corneum layer of the skin acts as a formidable barrier to drug delivery. The use of chemical penetration enhancers is one of the many techniques used to surmount this barrier.

Literature review suggested the ability of Piperine to act as an oral bioavailability enhancer. The ultimate aim of this study was to determine whether this bioavailability augmentation role of Piperine could be extended to the transdermal route. As a derivative of Piperine, Tetrahydropiperine (Cosmoperine® supplied by Sabinsa Corp., U.S.A.) was also evaluated.

Bearing in mind the lipophilic character of the model drug Lidocaine, amphiphilogels superlatively served the purpose of a delivery medium, due to their superior tendency to dissolve poorly water soluble drugs<sup>1</sup>. Use of water (enhancer) was avoided. The rationale behind *in-vitro* permeation investigation was not only to establish the rate and extent of absorption of the active component through the skin, but also evaluating the degree of compound retention within the skin<sup>2</sup>. To satisfy this supplementary intention, it was decided to specifically employ the SPE technique. This technique also helped to prepare the sample for subsequent HPLC analysis.

### **Method.**

The establishment of HPLC analysis method for the model drug Lidocaine was followed by the preparation and characterization of amphiphilogels. The conventional liquid-liquid extraction

method was considered as a benchmark for the evaluation of the developed SPE protocol. Franz diffusion cells were used to conduct drug diffusion studies through excised rat skin.

The four amphiphilic gels considered as formulations included a control formulation (5.0% w/w Lidocaine with no enhancer), with subsequent formulations incorporating the potential enhancer. 1.5% w/w Piperine along with 1.5% w/w and 3.0% w/w Cosmoperine® were independently considered as enhancers. The cumulative drug release per square centimeter was determined as a function of time for all the four formulations. Four repetitions were performed for each formulation.

## Results.

The results are summarized in table: 1.

**Table: 1, Mathematical treatment of permeation data.**

Formulation considered.	Mean L in hr (and ±STDev)	Mean J (and ±STDev)	Mean $k_p$ (and ±STDev).	Mean Ph (and ±STDev).	Mean $D/h^2$ (and ±STDev)
Control	1.85 0.11	11.640 2.444	0.0002328 0.0000489	0.002618 0.0006966	0.0903 0.0053
Piperine 1.5% w/w	1.64 0.15	17.130 1.533	0.0003426 0.0000307	0.003364 0.0004436	0.1029 0.0104
Cosmo.® 1.5% w/w	1.72 0.41	19.644 1.786	0.0003929 0.0000357	0.003987 0.0007375	0.1032 0.0258
Cosmo.® 3.0% w/w	1.79 0.13	23.735 1.406	0.0004747 0.0000281	0.005109 0.0006422	0.0937 0.0066

L: Lag time; J: *pseudo-steady-state*-flux;  $k_p$ : permeability coefficient; Ph: indicative partition coefficient;  $D/h^2$ : indicative diffusion coefficient. The indicative values were considered because the value of h (thickness) was unknown.

In order to reach explicit conclusions, further statistical analysis of the data was undertaken, while comparing the different formulations.

### **Discussion.**

With extremely limited reservations it can be concluded that (compared to the control) Piperine at a concentration of 1.5% w/w augments the drug diffusion of the model drug Lidocaine across rat skin. The influence of Cosmoperine® at a concentration of 1.5% w/w is similar to that of Piperine at the same concentration. Whereas, such an influence of Cosmoperine® at a concentration of 3.0% w/w is more than that exerted at a concentration of 1.5% w/w. This influence of Piperine and Cosmoperine® does not seem to be due the alteration in the diffusion coefficient, but most likely (with statistical reservations) due to alterations in the partitioning effect.

### **Future work.**

In order to enhance further statistical recognition of the results, repetition of the diffusion studies would be beneficial. Precaution should be taken to ensure measurement of the skin thickness; as such measurement is essential to proceed with the mathematical treatment of the data. Alternative ways of treating the data statistically should be explored.

It would be highly constructive to determine the reasons (mechanism of action) for the rise in the drug diffusion as a result of the incorporation of Piperine and Cosmoperine®. A more important step would be the attempt to classify these chemical entities as ‘chemical permeation enhancers’.

### **References.**

1. Jibry, N., Heenan, R. and Murdan, S. 2004, *Amphiphilic gels for Drug Delivery: Formulation and Characterization*. Pharmaceutical Research. Vol. 21(10), p. 1852-1861.
2. Witt, K. and Bucks, D. 2003, *Studying In Vitro: Skin Penetration and Drug Release to Optimize Dermatological Formulations*. Pharmaceutical Technology-North America. June. (Online). <http://www.dowpharm.com/publications/PharmTech.pdf> Accessed: 5<sup>th</sup> May 2005.