

## IN-VITRO/IN-VIVO CORRELATION (IVIVC) OF TRANSDERMAL ESTRADIOL SYSTEMS

Mantelle, J.

Noven Pharmaceuticals, Inc., Miami, Florida

October 30-31, 2000

© 2000

### ABSTRACT:

Methodology used in establishment of in-vitro to in-vivo correlation (IVIVC) parameters has long been a subject of discussion with regards to transdermal drug delivery products. Many attempts have been made in the last twenty years at utilizing dissolution as well as permeation through artificial membranes and different animal models with very limited; if any, success. The data generated in the development of Noven's Vivelles-Dot™ product, using human cadaver skin, has enabled just such an IVIVC. Utilizing this human cadaver model, a ratio of skin permeation of 2.9 to 1.0 was established over five studies for Vivelles-Dot™ vs. Vivelles®. This ratio of skin permeation / estradiol delivery was subsequently confirmed, in-vivo, on human volunteers in a pharmacokinetic study involving 12 patients wherein bioequivalence was demonstrated.

### I. PURPOSE

Establishment of an in-vitro predictive tool which the formulator of transdermal drug delivery systems can utilize to predict the in-vivo pharmacokinetic behavior of formulations. By utilizing human cadaver skin and repeatedly assessing the permeation profile of the new Vivelles-Dot™ product vs. the well established properties of Noven's Vivelles® product, minor changes in the formulation and their impact on the new product's pharmacokinetics can be evaluated and adjusted, as needed, prior to embarking on more extensive pharmacokinetic trials. Two different polymeric ratios were evaluated for effect on the permeation / delivery profile and consequently the pharmacokinetic performance.

### II. METHODS

- A. *Formulations* – Two potential formulations for Vivelles-Dot™ were prepared in which the only difference was the ratio of silicone to acrylic pressure sensitive adhesives (PSA's). Oleyl alcohol, DPG, estradiol and PVP concentrations were kept constant, the formulations coated at equal thickness and dried under identical conditions. In Formulation #1, the ratio of silicone to acrylic was 2.85 to 1.0 whereas for Formulation #2, the ratio was set at 14.4 to 1.0. In both formulations the total PSA content (i.e., acrylic plus silicone) was held constant.
- B. *In-Vitro Permeation Studies* – The permeation rate of the drug was determined through a disc of cadaver skin. Epidermal sections from the same donor and site were used in order to factor out inter-subject variability in the evaluation of the skin permeation rate.

The receiving solution is an isotonic saline solution with a sodium azide preservative (0.9% NaCl and 0.01% NaN<sub>3</sub>) at a pH of 6.7. The flux cells are maintained at a constant temperature of 32°C while being stirred continuously at ~300 rpm. The number of replicate cells utilized per study ranged between 3 and 5 per skin donor. The entire 7.5 ml of receiver solution is removed and replaced with fresh solution at each time pull in order to allow for the characterization of the delivery profile and prevent saturation of the receiver solution. The estradiol concentration in the receiver at each time pull is determined via HPLC. The above procedure was repeated five times utilizing different skin donors so as to establish between-donor variability and its potential significance on the permeation properties of estradiol.

- C. *In-Vivo Pharmacokinetic Studies* – The two formulations above were dosed on twelve volunteers in crossover fashion vs. a commercial lot of the Vivelles® estradiol transdermal delivery system. Pharmacokinetic parameters of the two potential formulations were then evaluated and bioequivalence to Vivelles® assessed.

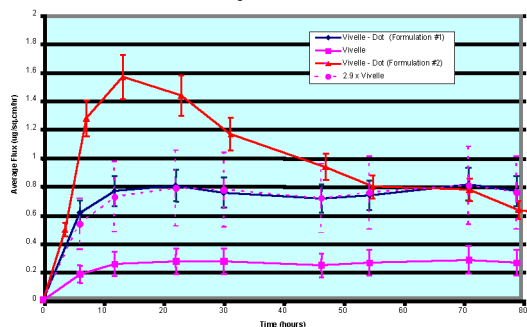
### III. RESULTS

- A. *In-Vitro* – Figure #1 illustrates the in-vitro flux curves for the three formulations averaged over five different skin donors. Formulation #1, with the 2.85 to 1 ratio of silicone to acrylic, closely mimics the behavior of the Vivelles® product from both a rate and extent standpoint (see the dashed line simulation of 2.9X Vivelles®).

The highest flux values ("Cmax"), lag time, duration and pseudo-zero-order delivery profile are all within ± 10% of the 2.9x Vivelles® values.

Figure #1

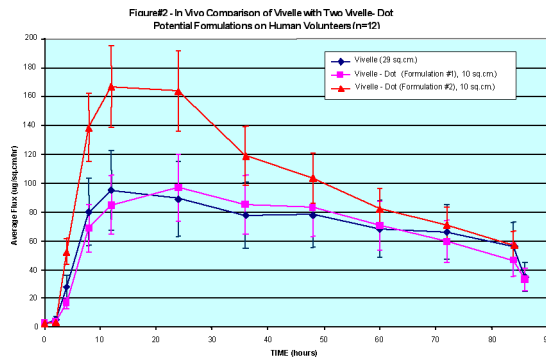
Figure #1 - In Vitro Human Cadaver Skin Permeation Study Summary. Averages For Five Different Skin Donors.



Formulation #2, conversely, exhibited a significant first order peak-and-drop behavior which is characteristic of the higher silicone to acrylic ratio in the adhesive composition. At the highest deliver point (“Cmax”), the value for Formulation #2 was approximately 1.9 time that of the 2.9x Vivelle® simulation curve. The total amount of estradiol delivery through the skin by this formulation over the eighty-hour period was approximately 1.5x that delivered by Formulation #1 and the 2.9X Vivelle® comparator.

B. *In-vivo* – Based on the in-vitro results detailed above, a decision was made to go to in-vivo pharmacokinetic studies with 10 cm<sup>2</sup> patch sizes for Formulations #'s 1 and 2 and use a 29 cm<sup>2</sup> Vivelle® as a comparator. The intent of this study was to; a) duplicate the results seen in-vitro, and b) deliver 100 ug/day of estradiol for a 3.5 day period from each of the formulations. Analysis of the data for Formulation #1 vs. Vivelle® has shown that all pharmacokinetic parameters of interest met the bioequivalence criteria set forth by the FDA. As can be seen in Figure #2, rate and extent, Cmax and delivery duration for the 84 hour period are all within the ± 20% criteria.

Figure #2



Formulation #2, as was predicted by the in-vitro work, exhibited a significant first order peak-and-drop behavior. Upon comparison to Vivelle®, it was determined that the AUC and Cmax values for Formulation #2 were 1.5 and 1.75 times higher, respectively than those for Vivelle®. Bioequivalence criteria were not met by Formulation #2.

#### IV. CONCLUSION

Human cadaver skin, when used as a qualitative tool over a series of permeation studies with multiple donors and multiple cells per donor, can be used as an effective tool to predict IVIVC for Noven’s estradiol drug-in-adhesive transdermal drug delivery systems. Hence, formulation changes as well as process changes and their subsequent effect on pharmacokinetics can be appropriately monitored with the use of a control formulation over three to five in-vitro studies with different skin donors. Although this study focused on estradiol as the permeant molecule it is believed that this model can be used effectively with all other permeant molecules and the Noven proprietary drug-in-adhesive system. Further applicability in transdermals, although likely, needs to be assessed.