Drug Development and Industrial Pharmacy, 33:373–380, 2007
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ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040600815178

informa
healthcare

Simultaneous Estradiol and Levonorgestrel Transdermal Delivery from a 7-day Patch: In Vitro and In Vivo Drug Deliveries of Three Formulations

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ABSTRACT A new drug-in-adhesive transdermal patch was developed to deliver both estradiol and levonorgestrel through the skin over a 7-day period, but at different rates. This report elucidates the in vitro and in vivo biopharmaceutical studies that were necessary during the development of this product. Three test patches had to be manufactured, all delivering estradiol at the same rate, but delivering levonorgestrel at three different rates so that a levonorgestrel dose response could be studied in the clinic. An in vitro hairless mouse skin model (HMS) using modified Franz diffusion cells was used to select the test products delivering levonorgestrel in the order of 1:2:3. HMS experiments also demonstrated that the presence of estradiol did not affect the flux of levonorgestrel. Two in vivo studies in postmenopausal women showed that at steady state (four weeks of once-weekly dosing) the three test products all delivered estradiol at comparable rates. Similarly, the levonorgestrel deliveries for the three test products were in the order expected. The target fluxes of both drugs were achieved in these three test products by varying the drug loads and patch size. That this approach was successful is evidence of the value of using the HMS penetration experiments in transdermal product development and should provide useful insights for other formulations having to develop complex systems. One of the test products is now marketed as Climara Pro™.

KEYWORDS Transdermal, Estradiol, Levoneogestrel, Biopharmaceutics

INTRODUCTION

The passive delivery of drug through the skin continues to be a challenge for the formulator, but much progress has been made in both the amounts of drug that can be passively delivered and the control over the rate and duration of the drug delivered (Thomas & Finnin, 2004). From the initial transdermal patches that delivered drug over a 24 h interval, patches are now available that

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are designed to passively deliver drug over 3.5 and 7 day intervals.

A more recent challenge of passive transdermal delivery is the desire to deliver two drugs simultaneously, but at different rates, from the same patch. This has been accomplished for the simultaneous delivery of estradiol and norethindrone acetate over 4 days; ethinyl estradiol and norelgestromin over 7 days; and estradiol and levonorgestrel over 7 days (Sicat, 2003; Shulman, 2003; Archer et al., 1999). These three patch systems are approved and commercially available in the USA.

Formulators faced several challenges in designing the drug-in-adhesive matrix patch Climara Pro™ (Berlex Laboratories, Wayne, NJ) to passively deliver estradiol and levonorgestrel through the skin. The product concept required investigation of the levonorgestrel dose response for a given estradiol dose, to select the lowest effective levonorgestrel dose that offered protection against endometrial hyperplasia to a woman with an intact uterus for the selected estradiol dose. Therefore, three test formulations had to be developed, all delivering the same amounts of estradiol, but differing amounts of levonorgestrel. A further complication was the solubility limit of levonorgestrel in the adhesive/excipient mix, which required the use of multiple patch sizes to achieve the target levonorgestrel deliveries.

The purpose of this publication is to present the in vitro hairless mouse skin (HMS) penetration experiments and in vivo bioequivalence studies that were performed during the development of the Climara Pro™ combined estradiol and levonorgestrel transdermal patch. This information is instructive in that it highlights how extensive are the biopharmaceutical studies needed to support clinical development including dose response/dose ranging trials and pivotal safety and efficacy phase III clinical studies.

MATERIALS AND METHODS

Products Tested

All estradiol/levonorgestrel patches tested in the HMS penetration experiments were made on a laboratory scale with prototype formulations. For the drug-drug interaction experiments, the concentration of one active component was fixed while the other varied. For the levonorgestrel flux experiments, the estradiol/levonorgestrel ratio was held constant at 2:1.

For the clinical studies, all patches used were from scaled up lots that represented optimized formulations. Three patch formulations labeled AM, BM, and CM were studied. These patches were manufactured on production-scale equipment (Northridge, CA). Patch formulation AM has been marketed as Climara Pro™.

Formulation Strategy

In order to develop a thin, semitransparent, conformable and cosmetically appealing transdermal patch, both drugs were combined into a single polyacrylate adhesive matrix patch. Furthermore, to reduce the size of these drug-in-adhesive patches, relatively high loadings of both estradiol and levonorgestrel in the adhesive were pursued. A limitation of the levonorgestrel loading was its limited solubility in the adhesive. To overcome this solubility barrier, a levonorgestrel crystallization inhibitor (copovidone), as described previously, was included in the formulation (Lipp, 1998).

Based on previous experience, good release of steroids and progestins from the polyacrylate adhesive matrix for drug loads of up to 2% was expected (Harrison et al., 1996; Lipp et al., 1998). This allowed the selection of prototype formulations without any added excipients, besides the crystallization inhibitor.

HMS Experiments

Ventral and dorsal skins from 2-month-old male hairless mice (strain MF1, Harlan Olac, UK) were excised and the subcutaneous fat was carefully removed. Test patches were applied to the skins, which were then immediately mounted in modified Franz diffusion cells (Crown Glass, Somerville, NJ). The application area of the diffusion cell was 0.32 cm^2. The diffusion cell's receptor compartment was perfused at a flow rate of 1 mL/h with 50% (v/v) PEG 400 in water, supplemented with 1000 IU penicillin to prevent growth of microorganisms. Fractions of the effluent were collected at timed intervals. Skin temperature was maintained at 31°C throughout the experiment to maintain the temperature that would be experienced at an in vivo skin surface. Each test patch was applied to six skins from six different animals.

Clinical Studies

Two pharmacokinetic studies were performed. Each study had two objectives, i.e., to test for the bioequivalence of estradiol delivery, and to test for the proportional delivery of levonorgestrel. One study was a randomized two way crossover design that compared the AM and BM patches in 43 individuals (study 1), and one study was a parallel design that compared the BM and CM patches in groups of 20 subjects (study 2). Each study included healthy, nonsmoking postmenopausal (natural or surgical) women at least 45 years of age and was adequately powered to meet the study objectives. To qualify, serum estradiol levels had to be ≤ 20 pg/mL within 3 weeks prior to dosing. In study 1, subjects had to be less than 70 years with predose serum follicle-stimulating hormone levels ≥ 40 mIU/mL. In study 2, subjects had to be less than 65 years with predose serum follicule-stimulating hormone levels ≥ 50 mIU/mL. Additional inclusion and exclusion criteria were as previously published (Harrison & Harari, 2002). All subjects gave written informed consent, and both protocols were reviewed and approved by independent investigational review boards.

All subjects in each study received four consecutive 1-week applications of the test patch formulation in each treatment period. Application was to the abdomen as described previously (Harrison et al., 1996). The site of application was washed before dosing and rotated systematically to a different site each week. All subjects from both studies received their test patch on the lower abdomen (below the waistline) on the fourth week. Taping of patches was not permitted; however, patches that fell off could be replaced. A 4-week interval separated the two treatment periods in each study.

The common blood sampling procedure for both studies focused on characterizing the steady-state dosing interval of week 4. As such, timed serum samples were collected prior to each treatment, and predose on days 21 through 28 of each treatment period. Serum handling procedures were as described previously (Harrison & Harari, 2002). Additional blood samples were collected on week 1 of study 2; these data are not presented.

Bioanalyses

For the HMS experiments, levonorgestrel and estradiol were measured using radioimmunoassays. A commercial kit (Biermann, FRG-Bad Nauheim) was used for the estradiol radioimmunoassay, which had a detection limit of 10 pg/mL. Levonorgestrel was measured with a proprietary assay that had a lower limit of detection of ca. 100 pg/mL (Kuhnz et al., 1992). Each radioimmunoassay was validated for specificity, accuracy, precision, and storage stability. The between assay coefficients of variation for the low and medium concentration control samples were less than 15% and 30%, respectively, for both assays.

For the clinical studies, estradiol and estrone were measured using a validated gas chromatography/mass spectrometry assay with detection limits of 5 and 10 pg/mL, respectively, for the two compounds. Levonorgestrel was measured with the same proprietary assay that was used for the HMS experiments. Details of both methods have been published (Harrison & Harari, 2002; Kuhnz et al., 1992).

Data Analyses

HMS drug flux can be calculated from the amount of drug recovered in the receptor medium divided by contact area of the donor compartment and the time as follows:

$$J = \frac{Q}{A * t}$$

where J is the drug flux in ng/cm^2/h, Q is the ng amount of drug in the receptor medium, A is the area of the flow-through cell (0.32 cm^2), and t is the sampling time interval in hr.

For the flow-through diffusion experiments, the amount of drug in the receptor medium can be found from the concentration of drug in the receptor medium, the flow rate of the receptor medium, and the collection interval as follows:

$$Q = c_r * k * t$$

where c_r is the ng/mL concentration of drug in the receptor medium and k is the receptor medium flow rate in mL/hr.

Substituting for Q in the flux equation above gives the following equation that was used to calculate the drug flux in the HMS experiments:

$$J = \frac{c_r * k}{A}$$

The steady-state flux was defined as the average flux over the 26–50 h sampling interval.

For simplicity, only the mean flux values for the six HMS replicates for each test patch were graphed. Standard deviations of the mean flux after 6 h were consistently less than 30% of the mean. More variability of the SD was seen for the initial determinations, approaching 50%. The largest SD observed was 98% of a mean value at 2 h.

For the pharmacokinetic studies, the procedures for calculating the maximum serum concentration (C_{max}), the area under the serum concentration versus time curve for a dosing interval (AUC) using the trapezoidal rule, and the bioequivalence analyses using 90% confidence intervals (two one sided tests) have been published (Harrison & Harari, 2002). One subject in study 2 had all her pharmacokinetic data rejected as a conservative measure because her C_{max} value was three standard deviations from the mean.

Only mean serum concentrations were graphed for clarity. Standard deviations were generally between 30–40% of the mean concentrations for estradiol, and between 30–50% for levonorgestrel. The largest SD observed was 85% of an estradiol mean concentration.

RESULTS

HMS Flux

Ideally, flux from a patch should vary in direct proportion to the drug load for a fixed surface area. This goal was tested in the HMS model for the levonorgestrel component of the patches. The results of these experiments are shown in Fig. 1. The steady-state flux (26–50 hr) through HMS averaged 50 ± 1, 125 ± 17, and 237 ± 20 ng/cm^2/hr (mean ± SD) over this interval for the 0.5, 1, and 2% levonorgestrel loads, respectively. The levonorgestrel flux thus appeared to be reasonably proportional over the range of drug loads contemplated for clinical trails.

A lag time was observed in the levonorgestrel flux that was sensitive to the drug load. The first measurable concentration in the receptor fluid occurred at 26 h with the 0.5% levonorgestrel load. By doubling the drug load to 1%, the same concentration in the receptor fluid was observed at 5 h. As the goal was to maintain the same estradiol flux for all formulations, dose proportionality was not investigated for different estradiol loads.

Drug-Drug Interaction

HMS penetration experiments were run to investigate potential percutaneous absorption interactions between the two drugs in the patch. Concentrations of the test drugs were chosen to be higher than those proposed for the final marketed product, to magnify any potential interactions. The levonorgestrel flux was not significantly affected by the presence of estradiol (Fig. 2). For levonorgestrel, steady-state flux values for the 26–50 h interval averaged 237 ± 20 and 240 ± 15 ng/cm^2/h (mean ± SD) for drug delivery in the presence and absence of estradiol. Dissolution data (not presented) using transdermal dissolution apparatus five from USP 23-NF18, fifth supplement, were similarly used to establish that levonorgestrel concentration did not affect estradiol dissolution.

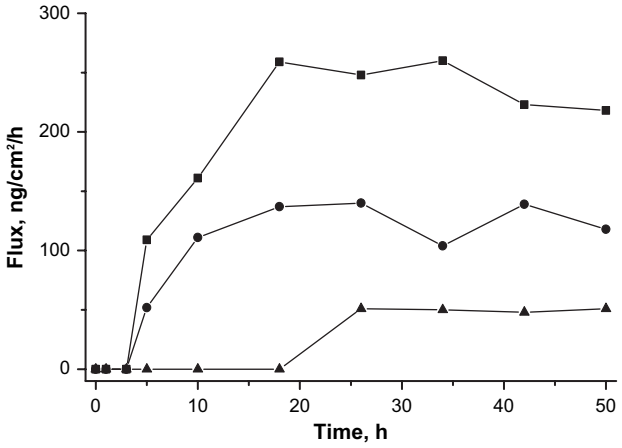

FIGURE 1 Levonorgestrel Flux Through HMS for Drug Loads of 0.5% (▲), 1% (●) and 2% (■).

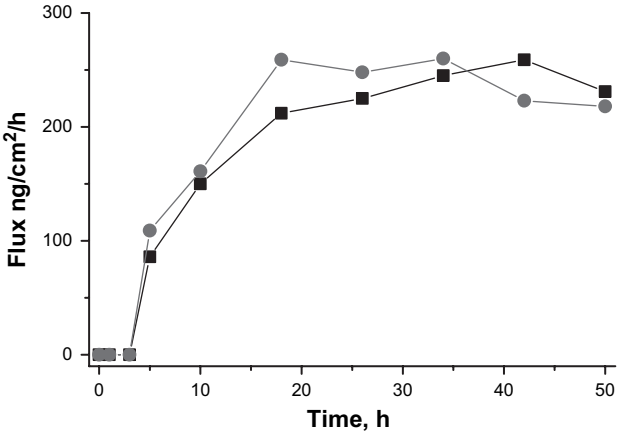

FIGURE 2 Flux of a 2% Concentration of Levonorgestrel in the Absence (■) and Presence (●) of 4% Estradiol by Weight.

Selection of Clinical Formulations

To investigate the appropriate endometrium protective dose of levonorgestrel needed for a fixed estradiol dose, three levonorgestrel delivery rates were desired. The target levonorgestrel delivery rates were 0.015, 0.030, and 0.045 mg/day. Based on levonorgestrel solubility in the acrylate adhesive in the presence of a crystallization inhibitor, the smallest patch that would give an in vitro delivery of 0.030 mg/day levonorgestrel through human cadaver skin was a 22 cm^2 patch. The target 0.015 mg/day levonorgestrel delivery could be obtained by decreasing the levonorgestrel load in half while maintaining the same patch size. For the highest of levonorgestrel, however, the limited levonorgestrel solubility required a 30 cm^2 patch to approach 0.040 mg/day. Patches greater than 30 cm^2 were not pursued for commercial reasons.

The solubility of estradiol in the acrylate adhesive was sufficient to achieve a target estradiol delivery of 0.050 mg/day through HMS. As experiments showed that there was no delivery interaction between estradiol and levonorgestrel, the same estradiol load was used for the 0.015 and 0.030 mg/day levonorgestrel 22 cm^2 patches. Based on in vitro studies, the estradiol load in the 30 cm^2 patch was increased 2% to maintain the same rate of estradiol release from the larger patch size.

The levonorgestrel and estradiol loads in the resulting patch formulations that were taken into the clinical trials are given in Table 1. Patches AM and BM were 22 cm^2, and patch CM was 30 cm^2.

Bioequivalence of Estradiol Delivery In Vivo

The average age of the subjects in each study was 57 years. There were no differences in the study populations with respect to predose hormone levels, body weight, or medical history.

TABLE 1 **Composition of the Patches Tested in the Pharmacokinetic Studies**

	Levonorgestrel		Estradiol	
Patch	mg	%[a]	mg	%
AM[b]	1.39	0.63	4.4	2.0
BM	2.75	1.25	4.4	2.0
CM	3.75	1.25	4.5	1.5

[a]% in formulation (w/w).
[b]marketed as Climara Pro™.

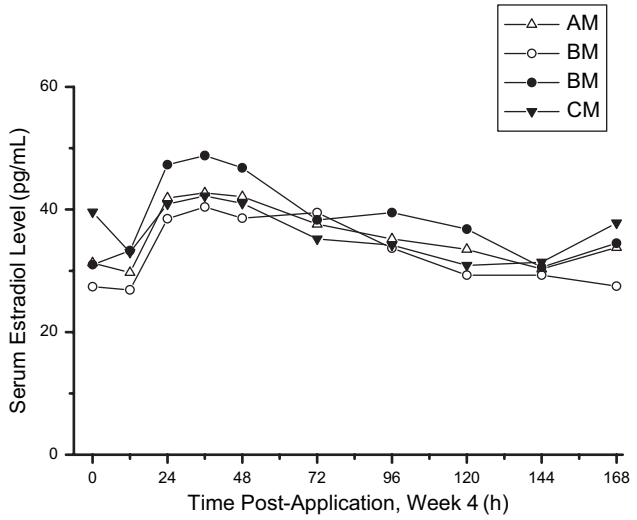

FIGURE 3 **Mean Steady-State Serum Estradiol Concentrations in Study 1 (Open Symbols) and Study 2 (Closed Symbols).**

The mean serum estradiol curves from the subjects in both studies are presented in Fig. 3. Good agreement was observed for the estradiol concentrations of the BM formulation that was common to both studies. In fact, similar estradiol profiles were observed for all formulations.

The bioequivalence analyses performed in study 1 indicated that AM and BM had bioequivalent estradiol delivery since both the estradiol C_{max} and AUC values met the 80–125 acceptance criteria for the 90% confidence interval (Table 2). Because study two utilized a parallel design, confidence intervals could not be calculated. A Student *t*-test comparison of the mean values for C_{max} and AUC indicated no significant differences in these estradiol parameters between BM and CM. Overall, these results indicate that comparable estradiol delivery can be expected from all three formulations.

Proportional Delivery of Levonorgestrel In Vivo

The mean serum levonorgestrel curves for the subjects in studies 1 and 2 are presented in Fig. 4. It is unclear why the mean levonorgestrel levels from the BM formulation that was common to both studies differed by approximately 25% between studies. C_{max} and AUC increased in each study in a manner that supported the proportionality relationship based on the HMS projections (Table 3). In each study, the hypothesis of the expected proportionality could not be rejected.

TABLE 2 **Bioequivalence Analyses of Estradiol Delivery**

Parameter	Test	BM	Test/BM	90% CI or *p* value
Study 1[a]				
C_{max} (pg/mL)	46.3	42	1.10	(101, 121)
AUC (pg/h/mL)	5720	5320	1.08	(101, 115)
Study 2[b]				
C_{max} (pg/mL)	53.0 ± 11.5	59.7 ± 16.3	0.89	$p = 0.144$
AUC (pg/h/mL)	6100 ± 1300	6430 ± 1430	0.95	$p = 0.456$

[a]geometric mean.
[b]mean ± SD.

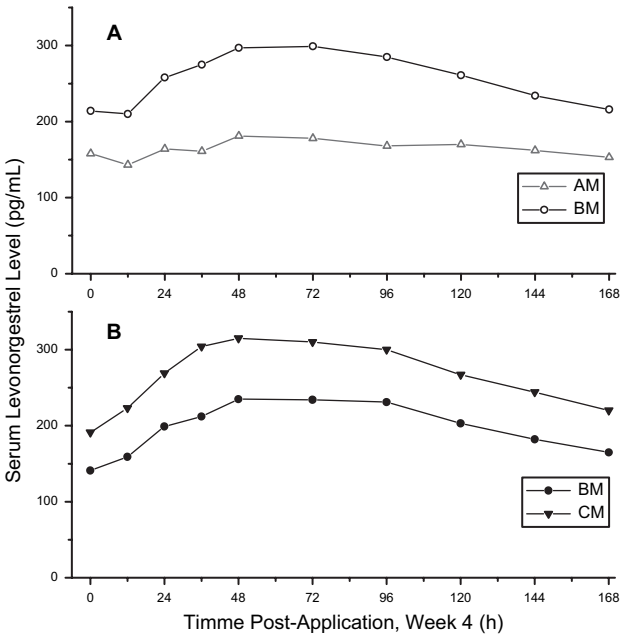

FIGURE 4 **Mean Steady-State Serum Levonorgestrel Concentrations in (A) Study 1 and (B) Study 2.**

Performance of Patches in Studies1 and 2

The patches were well tolerated by the subjects in both studies. Over 95% of the adverse events reported were mild. The majority of adverse events that were probably related to drug study were changes in menstrual bleeding patterns with breast and nipple tenderness, vasodilation, headache, and diarrhoea. There were sporadic changes from screening values for various laboratory parameters although none was clinically significant. There were no changes in vital signs or physical examinations. No subject withdrew from either study or was discontinued.

All three patch formulations adhered as designed. No patches fell off or required replacement. A few application site reactions were reported. All were mild, the majority consisting of itching or rash at the application site.

DISCUSSION

Only one formulation of estradiol/levonorgestrel was intended to be marketed, but this formulation could not be selected until the results of the pivotal phase three safety and efficacy trials were completed and analyzed. As a pharmaceutical company is under intense competitive pressure to accelerate drug development, all possible formulations had to be ready to commercialize at that time. Thus, three formulations had to be developed and manufactured. The bioequivalence studies were necessary to establish that all three tested formulations delivered the same dose of estradiol, but varied as desired in levonorgestrel delivery.

TABLE 3 **Dose Proportionality of Levonorgestrel Pharmacokinetics**

Parameter	Test	BM	Test/BM	HMS ratio
Study 1				
C_{max} (pg/mL)	194 ± 111	314 ± 140	0.62	0.5
AUC (pg/h/mL)	27900 ± 16400	44000 ± 19100	0.63	0.5
Study 2				
C_{max} (pg/mL)	339 ± 114	257 ± 84	1.32	1.33
AUC (pg/h/mL)	45900 ± 15500	34100 ± 11200	1.35	1.33

It is recognized that the clinical bioequivalence program was not ideal, being a mix of crossover and parallel group designs. The appeal of the parallel group design was the ability to complete the clinical portion in half the time of the more established crossover study, and with potentially fewer discontinuations. The choice of the common reference in both studies was formulation BM (containing the middle levonorgestrel dose) as it was unknown which formulation would be selected when these pharmacokinetic studies began. Overall, each study was appropriately powered to meet its objectives and provided the needed pharmacokinetic information on each formulation in a timely manner.

It was by design that the AM, BM, and CM formulations all met the stated objectives for in vivo deliveries of both drugs without the need for reformulation. This success can be attributed to extensive proprietary experience with the HMS model (Lipp, 1998; Lipp et al., 1998; Funke et al., 2002). In particular, the HMS levonorgestrel proportionality experiments provided the needed answers to questions on how to formulate levonorgestrel for clinical requirements. These experiments showed that levonorgestrel flux rates could be manipulated by varying the drug load and keeping the surface area constant, such as with formulations AM and BM.

Levonorgestrel solubility limitations in the adhesive required a change in the surface area as well as the drug load to achieve the target levonorgestrel flux for formulation CM. The calculations of this high levonorgestrel load and patch surface area were successfully accomplished by assuming that the HMS flux data could be extrapolated. However, it is unlikely that stable transdermal matrix formulations with levonorgestrel could have been developed without previous experience of the use of crystallization inhibitors for levonorgestrel (Lipp, 1998).

An equally challenging task was to keep the estradiol flux constant for the different formulations despite the changes in patch size and levonorestrel load. Dissolution experience with the estradiol release from different patch sizes of Climara™ (Berlex Labatories, Wayne, NJ) 7-day estradiol transdermal system helped to justify the calculation of the estradiol loads for the two different patch sizes (Harrison et al., 1997). The in vitro experiments were useful in showing the lack of effect of levonorgestrel on estradiol release, which simplified development of a combined product. The in vivo bioequivalence results for formulations AM and BM, which differed only in levonorgestrel load, confirm the in vitro findings that levonorgestrel does not affect the delivery of estradiol from the patches. The in vitro experiments also correctly predicted that only a 2% increase in estradiol load was needed to maintain the target estradiol delivery from the 30 cm^2 patch; it would have been difficult to arrive at this conclusion without these results. That this accomplishment was not trivial can be seen by the failure of another estradiol/progestin transdermal program to achieve bioequivalent estradiol delivery among three formulations (Pentikis et al., 1998).

One might suggest that the human cadaver skin would be a more relevant skin model, giving drug flux values that are more similar to those observed in clinical studies than with HMS. Indeed, human cadaver skin has been used successfully to model estradiol/levonorgestrel transdermal delivery (Chien et al., 1989). The goal of the Climara Pro™ development program was to use a reproducible skin model that could discriminate and provide a relative ranking of formulations. Proprietary experiences with various skin models indicated that both reliability and relative ranking could be accomplished with the HMS model for these drugs. Furthermore, it is highly desirable to have a skin model that is viable for greater than 24 h for testing transdermal systems designed for 168-h delivery, and proprietary experience with the HMS indicates that barrier function is not compromised over a 50-h experimental period. It is hoped that this information will help others to use the HMS model for transdermal formulation development.

The in vivo bioequivalence assessment was simplified by using a multiple dose design rather than a single dose. With this design, AUC values could be accurately calculated without the need to extrapolate any area. Extrapolation was of concern considering the difficulties of calculating both the long half-life of levonorgestrel and the short half-life of estradiol in a single study (Fotherby, 1995; Schulman et al., 2002). In addition, the HMS experiments suggested that in vivo, levonorgestrel transdermal absorption might show a lag time. A steady-state study had the added advantage of demonstrating what significance, if any, such a postulated levonorgestrel lag time would have during chronic use of the product.

Lastly, one can comment on the pharmacokinetic profile of the marketed formulation Climara Pro™ (AM).

This formulation maintained consistent estradiol serum concentrations of about 45 pg/mL over a 7-day interval. Levonorgestrel serum concentrations averaged approximately 150 pg/mL and were equally consistent. No evidence of any lag time in levonorgestrel transdermal absorption was observed. This pharmacokinetic profile was shown to be efficacious for the treatment of vasomotor symptoms and for the prevention of estrogen induced endometrial hyperplasia in postmenopausal women with intact uteri in two randomized, well-controlled phase III trials (Schulman et al., 2002).

ACKNOWLEDGMENT

The authors thank members of the research and medical staffs of Schering AG, Berlex Laboratories, 3M Drug Delivery, Bio-Kinetic Clinical Applications (Springfield MO), and Covance Clinical Research Unit (Madison, WI) for technical assistance.

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