

Abstract

This study evaluates the In-vitro to In-vivo correlation for the delivery of Scopolamine base in a drug-in-adhesive transdermal system over 3 days. Modified Franz diffusion cells were utilized to evaluate In-vitro delivery. The In-vivo study was conducted with 12 healthy volunteers. Based on the comparison of T_{max} , the Peak and Trough, Steady State Delivery, and the Total amount of Scopolamine Delivered between In-vitro and In-vivo studies, the results show the In-vitro delivery correlates to the In-vivo delivery.

Purpose

During the formulation development for transdermal delivery of a drug molecule, it is useful to have an In-vitro model that correlates the delivery to the delivery profile In-vivo. With the In-vitro models, the formulators can evaluate large numbers of formulas before selecting one for a clinical trial. To illustrate the In-vitro to In-vivo correlation for the transdermal delivery of Scopolamine base, this study compares the results of T_{max} , Peak and Trough, Steady State Delivery and Total amount of delivery of the two studies.

Methods

Transdermal Systems

The transdermal systems were fabricated with a backing layer, a drug-in-adhesive matrix layer, and a layer of protective release film. The drug-in-adhesive matrix layer was composed of a mixture of Scopolamine base, silicone adhesive, acrylic adhesive, oleyl alcohol, and dipropylene glycol. The systems had a delivery area of 2.5 sq.cm and contain 1.5 mg of Scopolamine base.

In-Vitro Study

Modified Franz flux cells were utilized for the In-Vitro model as shown in Figure 1. The permeation barrier was the stratum corneum of human cadaver skin. The flux cells have a defined receiving volume and delivery area. The receiving solution was normal saline with an anti-microbial agent. The receiving solution was stirred by magnetic bars to ensure a constant homogeneous solution. The flux cells were stored in an incubator at approximately 32 °C. Samples were taken from the receiving solution at 6, 12, 24, 36, 48, 60, and 72 hours from the setup time. The samples were analyzed by HPLC for the Scopolamine base concentration. Knowing the Scopolamine concentrations, the receiver volume, the delivery area, and the time, an Excel spread sheet was used to calculate the Total amount of Delivery, the average delivery rates, and to plot the delivery profile of n=5 cells.

In-Vivo Study

The clinical trail was conducted with 12 healthy volunteers, 6 males and 6 females age 18-45. The transdermal systems were applied behind the ears of the volunteers for 72 hrs. Venous blood samples were collected at 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours following application of the transdermal systems. After the removal of the systems, the used systems were assayed for residual Scopolamine base. The amounts of Scopolamine lost from the systems were calculated as the total amount of Scopolamine delivered. The plasma samples were processed from the blood samples and were assayed for scopolamine concentration. The average Scopolamine concentrations were plotted for the evaluation of the delivery profile.

Figure 1

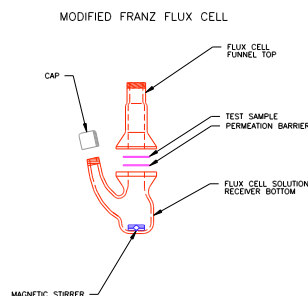


Figure 2

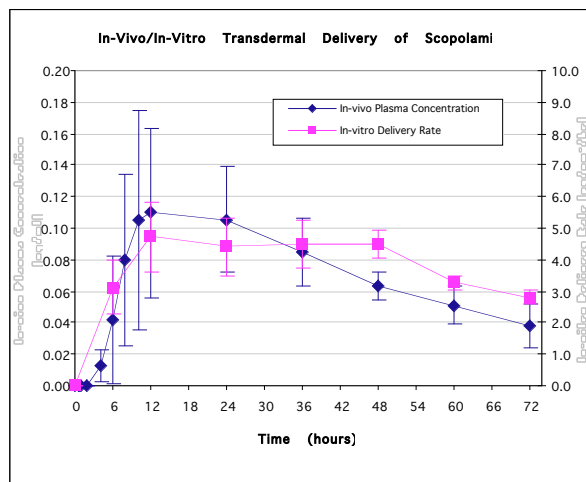


Table 1

	Total Amount of Scopolamine Base Delivered Over 72 Hours (mg)
In-vitro Study	0.7
In-vivo Study	1.0

Results

The average delivery rates of the In-vitro results and the average Scopolamine concentration in the plasma from the In-vivo results are plotted in Figure 2 for the In-vitro to In-vivo evaluation.

T_{max} Comparison

T_{max} is the time for the drug to reach its highest concentration in the blood stream following the application of a dose. The plot shows that the T_{max} of the plasma concentration In-vivo study is at 12 hours, and the T_{max} of the delivery rate In-vitro study is also at 12 hours.

Peak and Trough Comparison

In-vitro study shows that the delivery rate peaks at 4.7 µg/cm²/hr and then drops to 2.8 µg/cm²/hr at the end. The difference between the peak and the trough of the delivery rate is 1.9 µg/cm²/hr, which is 40% drop in the delivery rate. For the In-vivo study, the plasma concentration peaks at 0.11 ng/ml and then drops to 0.04 ng/ml at the end. The plasma concentration drops 64% from the peak to the trough. The percentage difference between In-vivo study and In-vitro study is 24%.

Steady State Comparison

The plot shows the In-vitro study had steady delivery rate from 12 hour to 48 hour and then gradually declined. In-vivo study shows the plasma concentration was steady from 12 hour to 24 hour and then declined. The difference in the steady state delivery between In-vitro and In-vivo studies is 24 hours.

Total Delivery Comparison

The total amount of Scopolamine delivered In-vitro was calculated to be 0.7 mg over the three days as shown in Table 1. For the In-vivo study, the total amounts of Scopolamine lost from the systems after dosing was 1.0mg. In-vivo study shows 30% higher delivery than In-vitro. However, some of the Scopolamine lost from the systems was in the adhesive residue which is left on the skin after the removal of the systems.

Conclusion

The comparison between In-vitro and In-vivo results show that the T_{max} has an exact match, the Peak and Trough has a 24% difference, the Steady State Delivery has 24 hours difference, and the Total Amount of Delivered has a 30% difference. The In-vitro delivery profiles and the In-vivo plasma concentration profiles are similar. The results show that the In-vitro delivery very well predicts the In-vivo delivery. Therefore, it is concluded that the In-vitro delivery is well correlated with the In-vivo delivery.