

Abstract

To evaluate the feasibility of transdermal delivery of Fludrocortisone Acetate, this study performed an in-vitro delivery of a Fludrocortisone Acetate drug-in-adhesive transdermal system. The results demonstrate that Fludrocortisone Acetate can be delivered at the rate of 0.1mg per day for three days from a 9cm² transdermal system.

Purpose

Fludrocortisone Acetate has been used for the treatment of salt-losing adrenogenital syndrome. The oral dose of the Fludrocortisone Acetate is 0.1mg daily, and the plasma half-life of this compound is about 3.5 hours. Transdermal delivery has the advantages of providing steady state delivery for a long period of time and also having hepatic by-pass. This study aims to evaluate the feasibility of transdermal delivery of 0.1mg per day of Fludrocortisone Acetate. Utilizing an in-vitro model, the study compares the delivery profile, the delivery rate, and the patch size of a Fludrocortisone Acetate drug-in-adhesive transdermal matrix system with that of the Vivelle-dot® transdermal system. The Vivelle-dot® transdermal system is FDA approved for delivering 0.1mg per day for 3.5 days of Estradiol from a 10cm² patch.

Methods

Transdermal Systems

The Fludrocortisone Acetate transdermal system was made with a backing layer, a drug-in-adhesive matrix layer, and a protective release liner layer. The protective release liner was a 5mil thick polyester film with a release surface that is coated with fluorocarbon. The backing film was a 2mil thick composite of polyester and ethylene vinyl acetate. The adhesive matrices had the coat weight of 10mg/cm² and were composed of a mixture of 2.3% Fludrocortisone Acetate, 14% permeation enhancer, 7.5% crystal inhibitor, 10% acrylic pressure sensitive adhesive, and 66.2% silicone pressure sensitive adhesive.

The Vivelle-dot® transdermal system was also made with a backing layer, a drug-in-adhesive layer, and a protective release liner. The transdermal system is provided by Noven Pharmaceutical Inc.

In-Vitro Study

Modified Franz diffusion cells were utilized for the evaluation of the in-vitro drug delivery. Five cells were used for each of the transdermal systems. These diffusion cells had a defined delivery area and receiving volume. The receiving solution was normal saline with an anti-microbial agent. The epidermis layer of human cadaver skin was used in the diffusion cells as the permeation barrier. The epidermis layer was separated from the dermis by heating the skin in hot water.

The diffusion cells were stored in an incubator at approximately 32°C. Samples were taken from the receiving solution at approximately 6, 22, 29, 46, 96, 54 and 70 hours from the initial time. HPLC was used to analyze for the Frovatriptan Acetate and Estradiol concentrations in the samples.

Figure 1

Comparison of Delivery Profiles

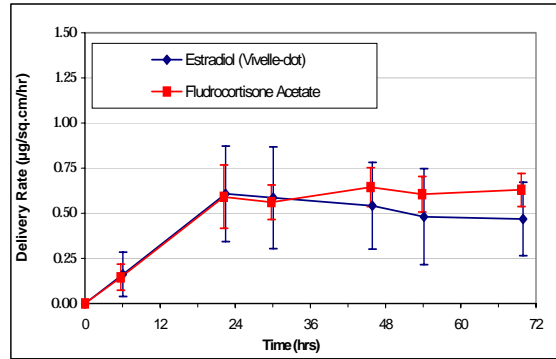


Figure 2

Comparison of Delivery Rates

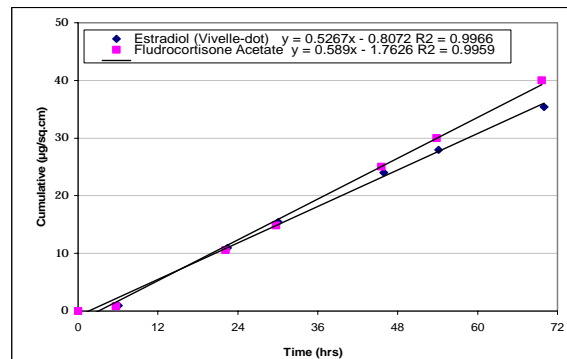


Table 1

	Average Delivery Rate (µg/cm ² /hr)	Delivery Ratio to Vivelle-dot	Patch Size for Delivering 0.1 mg/day (cm ²)
Vivelle-dot®	0.527	1.00	10.0
Fludrocortisone	0.589	1.12	8.8

Results

With the concentrations in the samples, the time when the samples were taken, the receiving volume, and the delivery area, the delivery rate and the cumulative amount were calculated and plotted. The results are in Figure 1, Figure 2 and Table 1.

The Delivery Profile

The comparison the delivery profiles, as illustrates in Figure 1, shows that the Fludrocortisone Acetate delivery rate was sustained over three days. The rate of the Fludrocortisone Acetate was increased for the first 24 hours; then it was sustained between 0.56 and 0.64µg/cm²/hr for the next 48 hours.

Comparing to the Vivelle-dot® transdermal system, the results indicate the delivery of the Fludrocortisone Acetate transdermal system was sustained better than the delivery of the Vivelle-dot® transdermal system.

The Delivery Rate

Figure 2 shows the cumulative permeation rate for drug delivery. Linear trend lines were utilized for the slope calculation, which indicate the average drug delivery rate. The results show that the Fludrocortisone Acetate delivery rate is 0.589µg/cm²/hr and the Vivelle-dot® delivery rate is 0.527µg/cm²/hr.

The Patch Size Estimation

The Vivelle-dot® transdermal system has been approved for delivering 0.1mg/day of Estradiol from a 10cm² patch. The delivery of Fludrocortisone Acetate is targeted at 0.1mg/day. The estimation of the Fludrocortisone Acetate patch size was estimated by normalizing the ratios of the Vivelle-dot® and the Fludrocortisone Acetate delivery rates. The ratio from Table 1 shows the delivery rate of Fludrocortisone Acetate was 12% higher than the Vivelle-dot®. The patch size of the Fludrocortisone Acetate was estimated at 8.8cm².

Conclusion

The results show it is feasible for transdermal deliver of 0.1mg/day of Fludrocortisone Acetate from an approximate 9cm² drug-in-adhesive-matrix transdermal system, with sustained delivery rate over three days.