

In-Vitro Transdermal Delivery of Phentermine

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Abstract

This study evaluates the feasibility of transdermal delivery of Phentermine from drug-in-adhesive transdermal systems. An in-vitro model was utilized for the evaluation of the permeation rates. Daytrana™, Methylphenidate transdermal system, was used as a control in the in-vitro study for the evaluation of the delivery rates and patch sizes estimation of the Phentermine transdermal systems. The results demonstrate Phentermine could be delivered at the rate of 30 mg in 9 hours from a 30 cm² transdermal system.

Purpose

Phentermine, an anorectic drug, has been used in treating obesity by appetite suppression. A dose of 30 mg Phentermine has been given orally at breakfast for obesity treatment; late evening medication is avoided because of a side effect, which is insomnia¹. Transdermal delivery has the advantage over the oral delivery in that the delivery can be stopped at any time by the removal of the transdermal patch. By removing the patch early or late in the afternoon, patients can control the medication being delivered into their body, hence optimizing the treatment and minimize side effects. This study evaluates the feasibility of passive transdermal delivery of Phentermine from the drug-in-adhesive matrix systems.

Methods

Transdermal Systems

Three Phentermine transdermal systems were 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 2 mil thick composite of polyester and ethylene vinyl acetate. The adhesive matrices of the three formulas had a coat weight of 10 mg/cm² and comprised of a mixture of 5%, 10%, or 15% Phentermine base with 1:1 ratio of acrylic and silicone pressure sensitive adhesives.

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 heat separation.

The diffusion cells were stored in an incubator at approximately 32°C. Samples were taken from the receiving solution at approximately 2, 4, 5, 7, and 12 hours from the initial time. HPLC was used to analyze for the Phentermine concentrations in the samples.

Figure 1

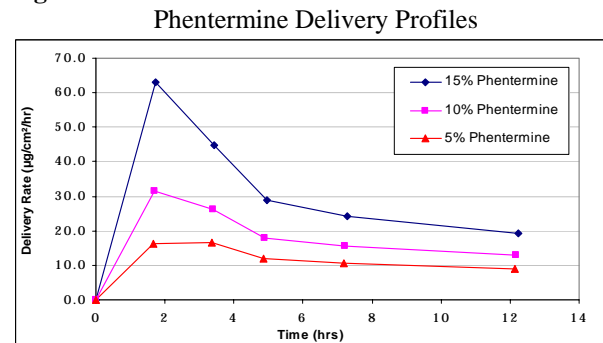


Figure 2

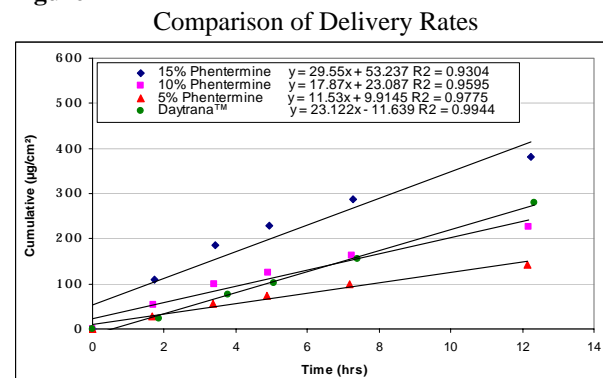


Table 1

Patch Sizes Estimation			
	Average Delivery Rate (µg/cm²/hr)	Delivery Ratio to Daytrana™	Patch Size for Delivering 30 mg/day (cm²)
Daytrana™	23.12	1.00	37.5
5% Phentermine	11.53	0.50	75.0
10% Phentermine	17.87	0.77	48.7
15% Phentermine	29.55	1.28	29.3

Delivery Rate Normalization

Because there is no in-vivo to in-vitro correlation established for Phentermine delivery rates, Daytrana™ delivery rate is utilized for normalization of the Phentermine delivery rates. Daytrana™, which is a FDA approved transdermal system for delivering 30 mg of Methylphenidate in 9 hours from a 37.5 cm² patch, was also comprised of a backing layer, a drug-in-adhesive layer, and a protective release liner. The in-vitro delivery rate of the Daytrana™ system was measured along with the delivery rate of the Phentermine formulations.

Results

The Delivery Profile

Figure 1 illustrates that the delivery rate is sustained at 5% Phentermine concentration; however, as the concentrations are increased to 10% and 15%, both the delivery rate and the peak is increased. The peak has a maximum at about 2 hours after patch application.

The delivery profile of the 15% Phentermine formula show that about 60% of the dose is delivered in the first four hours. The advantage of quick onset is to bring the blood level to the therapeutic window quickly for appetite suppression. The delivery rate then is slowed down for maintaining the therapeutic level.

The Delivery Rate

Linear trend lines were utilized for the slope calculation, which indicate the average delivery rates. Figure 2 shows the delivery rate of 5%, 10%, 15% Phentermine formula and the rate of Daytrana™ are 11.53µg/cm²/hr, 17.87µg/cm²/hr, 29.55µg/cm²/hr, and 23.12µg/cm²/hr. Delivery rates are increased as a function of the Phentermine concentrations.

The Patch Size Estimation

Based on the FDA approval data and the in-vitro delivery rate of the Daytrana™, the estimation of the patch sizes for delivering 30 mg of Phentermine in 9 hours is 75 cm² for the 5% formula, 50 cm² for the 10% formula, and 30 cm² for the 15% formula as shown in Table 1.

Conclusion

This study indicates that it is feasible for transdermal deliver of 30 mg of Phentermine from a 30 cm² over 9 hours from a drug-in-adhesive-matrix transdermal system. The transdermal systems could be applied to the body at 7:00 am and removed at 4:00 pm for obesity treatment.

REFERENCE

1) ADIPEX-P® (phentermine HCl 37.5 mg), Physicians's Desk Reference, 60th Edition, 2006, p.1216-1217

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