

Abstract

To achieve a seven-day sustained delivery rate of Clonidine from a drug-in-adhesive transdermal system, this study evaluates the effect of the drug in crystalline form on the delivery profile. Three Clonidine drug-in-adhesive transdermal systems were made. One system was formulated with dissolved drug and the other two systems were formulated with dispersed drug crystals, which had the particle sizes of 75µm and 230µm. These systems were evaluated for in-vitro delivery profile. The results show that the delivery rate can be sustained by utilizing the drug in the crystalline form.

Purpose

Large and bulky reservoir transdermal systems can provide a sustained delivery rate for a long period of time. However, more comfortable and thin drug-in-adhesive matrix systems have difficulty maintaining the steady state delivery rate due to the depletion of the drug concentrations in the matrix. To overcome the difficulty, this study illustrates that utilizing the drug in the crystalline form can achieve a sustained delivery rate of Clonidine over seven days.

Methods

Transdermal Systems

The 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 5 mils thick polyester film with a release surface that is coated with fluorocarbon. The backing was 2 mils thick of polyester and ethylene vinyl acetate film. The adhesive matrices had the coat weight of 10mg/cm² and were formulated as follow.

The drug-in-adhesive matrix of Formula #1 was 5% Clonidine, 10% acrylic adhesive and 85% silicone adhesive. The Clonidine was completely dissolved in the adhesive matrix.

The adhesive matrix of Formula #2 was 5% Clonidine, 10% polyisobutylene, and 85% silicone adhesive. The crystalline drug had the average particle size of 75µm and was dispersed in the adhesive matrix.

The adhesive matrix of Formula #3 was 5% Clonidine, 10% polyisobutylene, and 85% silicone adhesive. The drug had the average particle size of 230µm and was also dispersed in the adhesive matrix.

In-Vitro Study

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

The diffusion cells were stored in an incubator at approximately 32 °C. Samples were taken from the receiving solution at approximately 12, 24, 48, 72, 96, 120, 144, and 168 hours from the initial time. HPLC was used to analyze for the Clonidine concentration. The results of the delivery rate are in Figure 1, Table 1 and Table 2 below.

Figure 1

In-Vitro Delivery Rate of Clonidine

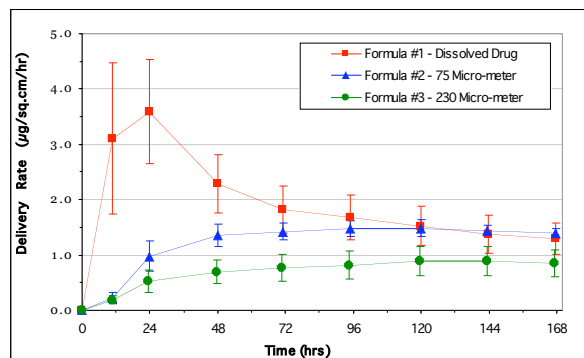


Table 1

Effect of Clonidine Particle Sizes on Delivery Rate

	Average Particle Size (µm)	Average Clonidine Delivery Rate (µg/cm ² /hr)
Formula #1	Dissolved	1.87
Formula #2	75	1.37
Formula #3	230	0.78

Table 2

Effect of Clonidine Particle Sizes on Sustained Delivery Rate

	Average Particle Size (µm)	Maximum Delivery Rate (µg/cm ² /hr)	Minimum Delivery Rate (µg/cm ² /hr)
Formula #1	Dissolved	3.59	1.30
Formula #2	75	1.49	1.39
Formula #3	230	1.12	1.08

Results and Discussion

To evaluate the average delivery rate, Table 1 shows that Formula #1, which was formulated with dissolved drug, has the highest average delivery rate, 1.87 µg/cm²/hr. In comparison between Formula #1 and Formula #2, the average delivery rate is decreased when the Clonidine is changed from dissolved to the crystalline form of drug. The average delivery rate is decreased further when the particle size of the crystals is increased as can be seen when comparing Formula #2 to Formula #3.

To evaluate the sustained delivery rate, Table 2 shows that Formula #1 has no sustained delivery rate. The delivery rate drops from 3.59 µg/cm²/hr at the maximum to 1.87 µg/cm²/hr at the minimum, which is a 64% change in the delivery rate. When crystalline drug is utilized in Formula #2, the delivery rate is significantly sustained. The rate drops only 7% from the maximum to the minimum. Formula #3 shows the delivery rate is sustained further, 4% drop from the maximum to the minimum, when the particle size of the crystals is increased.

To permeate through the skin effectively, the drugs need to be dissolved. The drug in Formula #1 was dissolved in the acrylic adhesive at the saturated concentration and ready to permeate. At the moment the patch touches the skin, the drug quickly diffuses through the skin, which resulted in a quick onset of delivery. As soon as the saturated concentration in the adhesive matrix is decreased, the delivery rate begins to decrease.

In Formula #2, the drug was un-dissolved, so it was not ready to permeate. When the patch touches the skin, the water from the skin begins to diffuse into the adhesive matrix and provides the medium for the drug to dissolve in. At this point the drug begins to diffuse out from the crystals, into the medium and into the skin. This process takes time but it provides a constant concentration of the drug in the medium, which results in a delay of the onset and a steady state of delivery.

When the particle sizes of the crystals are increased, the surface area, which the drug diffuses out from, is decreased and resulted in the decrease of the drug diffusion out of the patch. This is why Formula #3 has lower delivery rate than the Formula #2's.

Conclusion

This study shows the utilization of Clonidine in crystalline form for the development of a drug-in-adhesive matrix system provides a sustained delivery rate over seven days. Moreover, particle size of the crystals has a large effect on the average delivery rate; as the particle sizes were decreased, the delivery rates were increased.