Enhanced Transdermal Permeation Performance Utilizing Pro-drugs of Testosterone

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Abstract

A comparison of in-vitro permeation performance of transdermal delivery devices containing testosterone and pro-drugs of testosterone to Testoderm is reported. In-vitro permeation testing utilizing stratum corneum from human cadaver skin was performed upon drug-in-adhesive (DIA) matrix patches. Patches contained testosterone, pro-drugs (testosterone acetate or testosterone enanthate) or mixtures of testosterone with pro-drugs. Both pro-drugs mixed with testosterone to yield eutectic mixtures, which facilitated increased drug solubility and produced increased permeation performance. Mixtures utilizing the more permeable pro-drug, testosterone acetate, resulted in the greatest increase in total drug permeation.

1. Purpose

Compare in-vitro permeation performance of transdermal delivery devices containing testosterone and pro-drugs of testosterone to Testoderm.

2. Methods

2.1 Materials

Testosterone – Upjohn
Testosterone acetate – Sigma Chemical Co.
Testosterone enanthate- Sigma Chemical Co.
Silicone BIO-PSA® 7-4502 – Dow Corning
Kollidon® (PVP) K-30 – BASF
Dipropylene Glycol - Dow Chemical
Oleyl alcohol – Croda Inc.
Acrylic Gelva 788 – Surface Specialties

2.2 Adhesive Matrix Preparation

All experimental formulations utilize identical amounts of an acrylic pressure sensitive adhesive, oleyl alcohol, dipropylene glycol and polyvinylpyrrolidone. Silicone pressure sensitive adhesive and drug(s) make-up the remainder of each matrix. Drug contents are recorded in the following table.

	Formulation								
	1	2	3	4	5	6	7	8	9
Testosterone*	2	2	3	4	-	2	3	4	-
Testosterone Acetate	-	5	5	5	5	-	-	-	-
Testosterone Enanthate	-	-	-	-	-	5	5	5	5

* Single entity testosterone formulations created with 3% and 4% testosterone crystallized. Permeation studies of testosterone only formulations are included for demonstration of the affect of overloading drug in this type of DIA matrix.

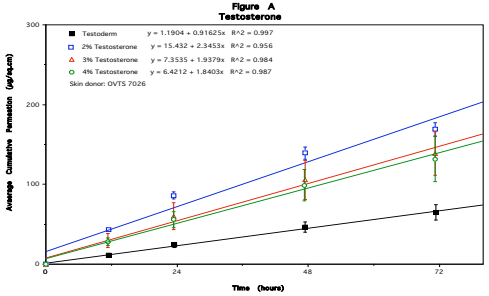
Patches were produced by casting polymer blends on 3M Scotchpak 1022 release liner, drying for 5 minutes at RT, then 5 minutes at 92°C in a convection oven. Dried matrix was laminated to the polyester side of 3M Scotchpak 9732 backing and had a coat weight of 10.0 ± 1.0 mg/cm^2.

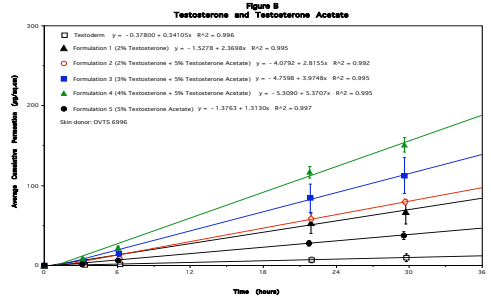
2.4 Human Cadaver Skin Permeation Study

Stratum corneum was obtained from split thickness, cryopreserved cadaver skin by the heat separation technique. 0.5 cm^2 circular patches (n=3) were cut from adhesive laminate, placed on stratum corneum and mounted on modified Franz cells that were magnetically stirred at ~300 rpm and maintained at 32°C. The receiving solution was 7.5 ml of 0.9% NaCl, which was replaced at each sample point. The permeation samples were analyzed by HPLC using a Supelcosil C-18-DB, 3.3 x 4.6cm, 5µm column. The mobile phase was 50:50 ACN: H2O with an injection volume of 50µl. The detection wavelength was 237nm.

3. Results

The following three figures illustrate the drug permeation single entity and drug / pro-drug mixtures. Pro-drug values are expressed as testosterone.





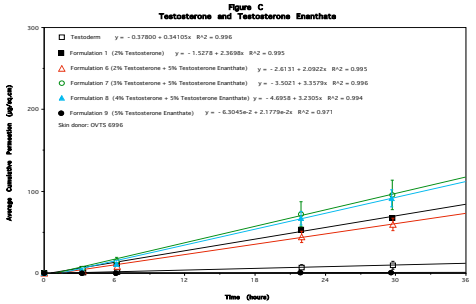


Figure A demonstrates the typical performance observed when a DIA patch is overloaded with drug. The excess drug crystallizes and is unavailable for permeation. Both pro-drugs formed eutectic mixtures with testosterone facilitating increased drug loading without crystallization. Figure B shows there was over a 200% increase in drug permeation from formulation 4 when compared to formulation 1. In contrast, the analogous formulation made with testosterone enanthate (8) yielded only a 50% increase in drug permeation over formulation 1 as seen in figure C.

All matrices permeated at a much higher rate than Testoderm. Projection of in-vivo performance from this data is precluded by the fact that Testoderm is designed to be applied to scrotal skin.

4. Conclusion

Both types eutectic mixtures can promote increased drug permeation. Eutectic mixtures formulated with two permeable entities, in this case the combination of testosterone and testosterone acetate, were much more effective at improving total drug permeation. As ester hydrolysis is a significant reaction occurring in the skin [1], use of dual permeating drug / pro-drug blends should enable significant improvements in transdermal testosterone permeation rates in-vivo.

REFERENCES

1) Bronaugh R.L, Kraeling M.E.K., Yourick J.J. and Hood H.L.Cutaneous Metabolism During In Vitro Percutaneous Absorption. Percutaneous Absorption 3rd Edition p.58-63 (R.L. Bronaugh and H.I. Maibach, ed.) Marcel Dekker, New York, 1999

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