

**ABSTRACT SUMMARY**

A transdermal delivery device incorporating the antiangiogenic compound 2-methoxyestradiol was evaluated by an in-vitro study of drug permeation through human cadaver skin. The compound was found to permeate the skin at a controlled rate for three days. 2-methoxyestradiol permeation properties were similar to 17β-estradiol, which is commercially available in patch form that provides continuous drug administration for up to one week.

**INTRODUCTION**

The use of angiogenesis inhibitors has become essential in the battle against cancer and other diseases. With the increased utilization of these therapeutic compounds, understanding has grown that efficacy of these agents can be optimized by maintaining constant plasma concentration of these drugs<sup>1</sup>. Transdermal patches are uniquely suited to facilitating this type of delivery over extended periods of time. Additionally, when compared to oral dosing, transdermal patches benefit from the elimination of first-pass metabolism with a reduction of systemic drug interactions and associated side effects.

Antiangiogenic compounds encompass a diverse range of molecular entities. Only compounds with molecular weights under 500 Da are typically deliverable from patches utilizing passive diffusion technology. 2-methoxyestradiol was selected as the initial compound for investigation of transdermal delivery of antiangiogenic entities as its molecular weight is 302 Da and it is conveniently compared to an FDA approved, transdermally administered compound: 17β-estradiol (272Da).

**MATERIALS**

The following materials were obtained from the indicated suppliers:

- 2-methoxyestradiol : Steraloids, Inc.
- 17β-estradiol : Diosynth, Inc.
- Scotchpak™ 9732 backing : 3M™
- Scotchpak™ 1022 release liner : 3M™
- Gelva® 788 : Cytec
- BIO-PSA® 7-4600 : Dow Corning Corp.
- Povidone K30 USP : BASF Corp.
- Oleyl Alcohol, NF : Croda Inc

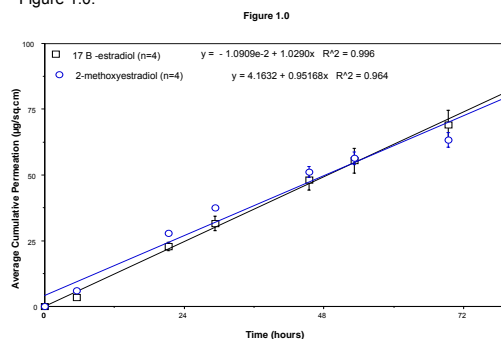
**EXPERIMENTAL METHODS**

Patches were formulated with a drug concentration of 1.6%. Adhesive and excipient concentrations were identical for both products. They were compared by in-vitro permeation study utilizing modified Franz cells with stratum corneum obtained from human cadaver skin by the heat separation technique. The receiving solution for this study was 0.9% NaCl with 0.01% NaN<sub>3</sub>. Franz cells were maintained at ~32°C for the duration of this study. Permeation samples were analyzed by HPLC using a Metachem Intertsil 5u ODS2 (150 x 046 column). The detector was set at 220 nm. Mobile phase 530:470:20 48mM TEA (H<sub>3</sub> PO<sub>4</sub> to pH=3.0); ACN: THF. Microscopic (25x) observation of patches was performed to evaluate saturation of drug in adhesive matrix.

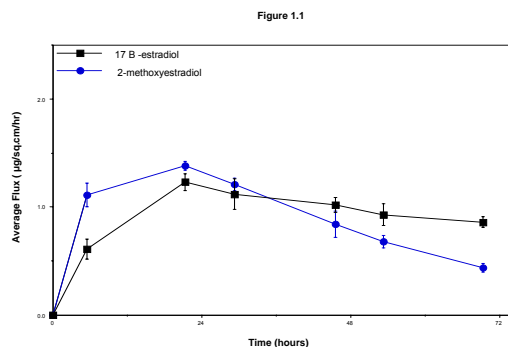
**RESULTS**

The patches maintained drug in a completely dissolved state with no crystallization of drug observed. Unexpected crystallization of drug can sometimes affect drug release from patches.

The cumulative drug permeation over a three day period for both 2-methoxyestradiol and 17β-estradiol matrices are displayed in Figure 1.0.



Additional analysis of the permeation data yields the flux rate over time for both drugs presented in Figure 1.1.



Both drugs continuously permeate over the 3-day duration of the study. The release of 17β-estradiol more closely approximates zero order, however, the actual in-vivo pharmacokinetics of transdermally administered 2-methoxyestradiol would dictate the desired permeation rates to obtain constant drug in plasma concentration. The manipulation of solubility parameters of the adhesive matrix components are typically adjustable to achieve most desired release profiles<sup>2</sup>.

**CONCLUSION**

2-methoxyestradiol was found to permeate through human cadaver skin for the entire duration of the three day study. Cumulative permeation of 2-methoxyestradiol over the three day period was nearly identical to 17β-estradiol. Assuming similar pharmacokinetics, prolonged transdermal administration of 2-methoxyestradiol in-vivo is expected to mimic the performance of commercially available transdermal 17β-estradiol products which provide steady concentrations of drug in plasma for up to a one-week duration.

Transdermal delivery devices provide a viable platform from which to investigate the affect of maintaining prolonged, constant plasma concentration of antiangiogenic or chemotherapeutic drugs. In addition to the recognized angiogenesis inhibitors, many chemotherapeutic drugs evidence antiangiogenic activity when dosed in a metronomic fashion<sup>3,4</sup>. Any of these established chemical entities that are amenable to incorporation into transdermal patches could be conveniently evaluated for their antiangiogenic activity at relatively constant concentrations for prolonged administration periods.

Additional investigation of active transdermal delivery techniques such as microporation and iontophoresis could facilitate the evaluation of the efficacy of steady state concentrations of antiangiogenic macromolecules already proven to be effective agents for oncology and ophthalmology indications [i.e. Avastin™ (bevacizumab), Macugen® (pegaptenib) etc.].

**REFERENCES**

- 1) Flokman, J. and Satchi-Fainaro, *Antiangiogenic Therapy: The Importance of Sustained Plasma Levels*. 32<sup>nd</sup> Annual Meeting and Exposition of the Controlled Release Society Miami Beach, Florida, U.S.A. June 18-22, 2005
- 2) Miranda, J. and Sablitsky, S. U.S. Patent 5,656,286 Solubility Parameter Based Drug Delivery System and Method for Altering Drug Saturation Concentration
- 3) Hanahan, D., Bergers, G., Bergsland E. *Less is more, regularly: Metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice* J. Clin. Invest. April 2000, Volume 105, Number 8, p.1045-1047
- 4) Man S., Bocci, G., Francia, G., Green S.K., Jothy, S., Hanahan, D., Bohlen, P., Hicklin, D.J., Bergers, G., Kerbel, R.S. *Antitumor Effects in Mice of Low-dose (Metronomic) Cyclophosphamide Administered Continuously through the Drinking Water* Cancer Research May 15, 2002 62, p.2731-2735

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