

TRANSDERMAL DRUG DELIVERY

Clinical and Regulatory Strategies



Jules T. Mitchel, Ph.D.
Target Health Inc., New York, NY



Otto Mills, Ph.D.
UMDNJ, Piscataway, NJ

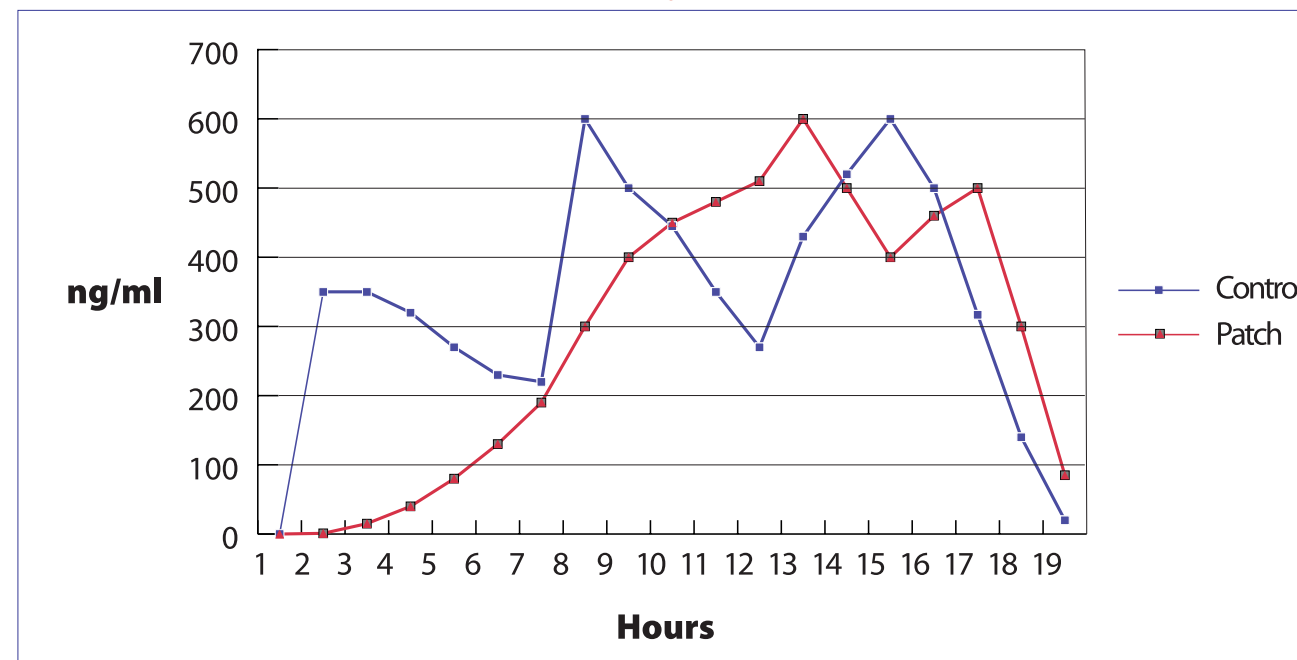
American Academy of Dermatology – 58th Annual Meeting
March 11-15, 2000
San Francisco, CA

Abstract:

Transdermal delivery of a drug product which is currently approved as oral dosage form, allows for the avoidance of first pass metabolism by the liver and the delivery of a more even level of the therapeutic agent over the course of 24 hours. Dermal patches are the most common form of transdermal delivery of drugs. To obtain FDA approval of a transdermally delivered drug, it is critical to involve the Food and Drug Administration (FDA) early in the development process. A strategy should be implemented to involve as much pharmacokinetic data as possible to demonstrate similar area under the curve but different maximum concentration and time to maximum concentration. To support the Investigational New Drug Application (IND), standard irritation and sensitization studies should be performed with the patch itself in animals, and if feasible, normal volunteers. There will be toxicology requirements, but the extent and timing of their implementation can be negotiated with the FDA. The dermatology division at FDA will review dermal aspects of the IND and New drug Application (NDA), but the primary review will occur at the division which handles the indication under study. Dose ranging studies will usually be required in Phase 2, but a single Phase 3 study could be negotiated.

Introduction:

When technically feasible, topical delivery of drug products for both local and systemic indications offer many advantages over the oral route. For the pediatric population, the advantages are obvious: ease of delivery, cooperative patient, compliance as well as the avoidance of first-pass metabolism. For the adult population, compliance and avoidance of first-pass metabolism are noted advantages. Topical delivery vehicles include creams, lotions, gels, etc. while transdermal drugs delivery uses patches, penetration enhancers, etc.



Transdermal delivery drug products:

- Avoid first pass metabolism by the liver
- Delivers a more even level of drug over time

To obtain FDA approval of a transdermally delivered drug:

- Involve the Food and drug Administration (FDA) early in the development process
- Develop a strategy to involve as much pharmacokinetic data as possible

Variables to Evaluate:

- Area under the curve
- Maximum concentration
- Time to maximum concentration
- Clinical efficacy

Regulatory Strategy to support the Investigational New Drug Application (IND) and NDA Submissions:

- Standard irritation and sensitization studies should be performed with the patch itself in animals/humans
- Negotiate the timing and implementation of the toxicology requirements
- The dermatology division at FDA will review dermal aspects of the IND and New drug Application (NDA)
- Primary review will occur at the division which handles the indication under study.
- Dose ranging studies will usually be required in Phase 2
- Single Phase 3 study could be negotiated

Conclusions:

Topical drug delivery offers the advantages of ease of delivery, a cooperative patient, increased compliance as well as the avoidance of first-pass metabolism. Disadvantages are the lack of, or reduced rates of absorption and cosmetic considerations. New patch technology and penetration enhancers may help to obviate some of these objections.

Bibliography:

- Hadgraft J. Passive enhancement strategies in topical and transdermal drug delivery. *Int J Pharm.* 1999 Jul 5;184(1):1-6. Review.
- Hadgraft J, et al. The selection and design of topical and transdermal agents: a review. *J Investig Dermatol Symp Proc.* 1998 Aug;3(2):131-5. Review.
- Kalia YN, et al. Transdermal drug delivery. Clinical aspects. *Dermatol Clin.* 1998 Apr;16(2):289-99. Review.
- Manitz R, et al. On mathematical modeling of dermal and transdermal drug delivery. *J Pharm Sci.* 1998 Jul;87(7):873-9.
- Rao PR, et al. Formulation and in vitro evaluation of polymeric films of diltiazem hydrochloride and indomethacin for transdermal administration. *Drug Dev Ind Pharm.* 1998 Apr;24(4):327-36.
- Weiss SR, et al. A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. *Transdermal Estradiol Investigator Group. Obstet Gynecol.* 1999 Sep;94(3):330-6.