School of Pharmacy

Faculty of Medicine

The Chinese University of Hong Kong

Workshop in Celebration of 25th Anniversary of the School of Pharmacy

Biopharmaceutics of Modified Release Products and Challenging Drug Molecules

Design and Regulatory Assessment of Transdermal Drug Products

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Transdermal Drug Products

- Are intended for the treatment or prevention of a systemic disease.
- Are absorbed through the skin (percutaneous absorption) into blood circulation and transported to target tissues to achieve therapeutic effect.

Transdermal Drug Delivery Systems

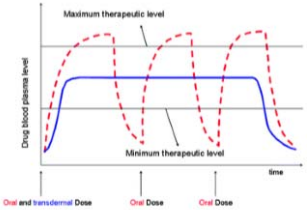
Advantages

- Avoid first pass metabolism
- Avoid GI side effects/disorders/degradation
- Can be easily removed from the body
- Provides continuous systemic drug delivery

Limitations

- Low molecular weight (500 daltons)
- Lipophilic in nature
- Low dose

Transdermal Drug Delivery System



- Provide continuous systemic drug delivery over the proposed wear period
- Avoid first-pass metabolism
- No dose dumping
- Unwanted effects can be terminated

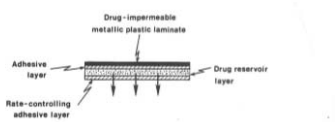
Transdermal Drug Delivery System

TDS consists of four basic elements:

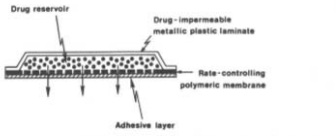
1. A reservoir of drug
2. Film or laminate which acts as a backing
3. A skin adhesive layer (adhesive,crosslinker, tackifier)
4. A protective liner (release Liner).

- TDS system may also contain additives such as solubilizers, plasticizers and skin penetration enhancers whcih meddiate drug delivery.
- The drug may be in solution, suspension, emulsion or as an adsorbate.

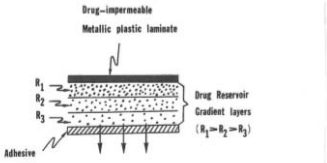
Design of Transdermal Delivery Systems



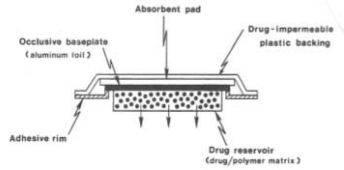
Cross-sectional view of an adhesive dispersion-type transdermal drug delivery system, showing major structural components.



Cross-sectional view of a membrane-moderated transdermal drug delivery system, showing major structural components.



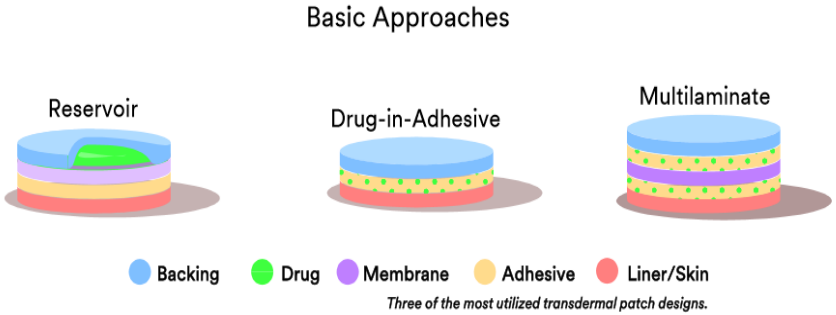
Cross-sectional view of a drug reservoir gradient-controlled transdermal drug delivery system, showing major structural components.



Cross-sectional view of a matrix-diffusion-controlled transdermal drug delivery system, showing major structural components.

Types of Transdermal Systems

Transdermal System Designs



Three of the most utilized transdermal patch designs.

Transdermal Drug Delivery System

There is no epidemiologic data available to determine whether Safety & Efficacy with transdermal route of administration will be different than the oral route.

Transdermal Drug Delivery System

TDS are controlled release dosage forms and are regarded as new drugs and require full New Drug Application as a basis of drug approval.

Toxicological and clinical studies

- Requirements based on drug entity, medical use and pharmacological class.

Safety studies

- Local irritation and systemic toxicity.

Efficacy studies

- For systems delivering new drug entity.
- New efficacy claims on marketed drugs.
- New medical claims
- Claims of superior efficacy.

Metabolism studies

Transdermal Drug Delivery System

Studies for the approval of NDA need to be customized and are largely based on:

- Critical nature of the active drug.
- Availability of marketed systemic dosage forms of the same active drug.
- Medical and biopharmaceutics rationale.
- Literature data on drug entity.
- Agency experience with the drug and/or drug delivery system.

Transdermal Drug Delivery System

Biopharmaceutics Considerations

- Define bioavailability (rate and extent)
- Define pharmacokinetics
- Establish reproducibility of TDS
- Evaluate sites of drug administration for optimizing drug delivery.

Bioavailability Determinations of TDD Systems

- Fentanyl Transdermal System
  - Blood level compared to IV dose
- Nicotine Transdermal System
  - Blood level compared to IV dose and chewable gum
- Testosterone Transdermal System
  - Clinical Efficacy and Safety Studies
  - Blood level compared to placebo and different dosage strengths

Transdermal Drug Delivery System
Evaluation

In vivo performance

- Safety (including dermal toxicity)
- Efficacy
- BA/Pharmacokinetics

In vitro performance

- Quality control (to assure batch-to-batch uniformity)

Transdermal Drug Products
Considerations for a Generic Product (ANDA)

- BE to a reference product - *In vivo* measurement of active moiety
- Reproducibility/consistency of drug release
- Inter/Intra subject variability
- Depot effect
- Body site
- Approved adhesive
- Approved inactive ingredients
- Skin irritation/patch adhesion

Transdermal Drug Delivery System
Evaluation

In vivo performance

- Safety (including dermal toxicity)
- Efficacy
- BA/Pharmacokinetics

In vitro performance

- Quality control (to assure batch-to-batch uniformity)

Transdermal Drug Delivery System

In Vitro Product Quality Tests

- Compendial /Application tests (USP <3>)
  - Identification, assay, content uniformity, …
  - Adhesive test
  - Leak test
  - Stability test

In Vitro Product Performance Tests

- In vitro release test

Transdermal Drug Delivery System

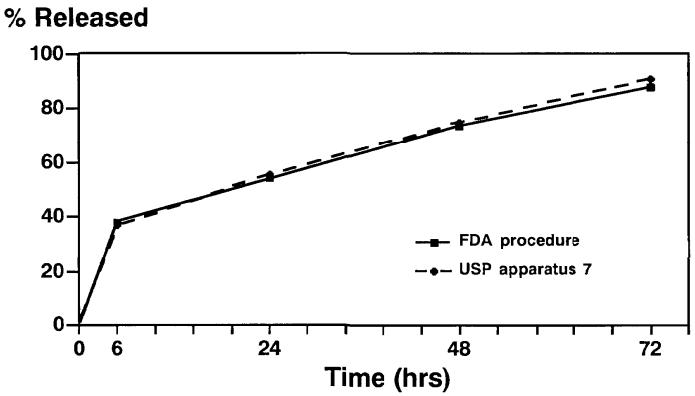
In Vitro Release Test

Paddle Over Disk Method

- **(FDA Method) - Watchglass-Patch-Teflon Mesh Sandwich and Paddle Method**
- **(USP Method) - Stainless Steel Disk-Adhesive-Patch-(Cuprophan Membrane) Problems - (i) Patch may come loose during the run, (ii) interference in HPLC analysis from adhesive**

Pharmacopeial Forum. 14: 3458-3462 and 4430-4431, 1988.

IN VITRO RELEASE SCOPOLAMINE PATCH



Transdermal Drug Delivery System

In Vitro Release Test

Advantages

- **Simple, reproducible, stability indicating test**
- **Can be used for batch to batch uniformity**

Limitations

- **Difficult to have same release specifications for all brands of a given product**
- **Cannot detect changes in adhesive properties**

Generic TDS

- PE + BE = TE = TI

  PE – same API, same dosage form, same route of administration

  BE – Comparable rate and extent of bioavailability

  Adequate labeling and GMP
- Demonstration of non-inferiority for adhesion, irritation and sensitization
- Minimal residual drug after labelled period (FDA Guidance)

Transdermal Drug Products
Drug Approval

New Drug Application (NDA)	*Abbreviated New Drug Approval (ANDA)*
Safety: Toxicity Studies	
• Skin Irritation	• Skin Irritation
• Cutaneous Toxicity	• Cutaneous Toxicity
• Contact Sensitivity	
• Contact Photodermatitis	
Efficacy: Clinical Studies	
• Bioavailability Studies	• Bioequivalence Studies
• Manufacturing Controls	• Manufacturing Controls
• *In Vitro* Release Studies	• *In Vitro* Release Studies

Transdermal Drug Delivery System
Enhancers - Chemical

1. Mechanism of action
   - Mechanism and Duration
   - Specificity for enhancement (drug vs. excipients)
2. Biopharmaceutics and Pharmacokinetics
   - Fate of enhancer in the body
   - Drug with and without enhancer
   - Excipients and enhancer
3. Efficacy
   - Alteration in the time course and shape of drug and metabolite concentration effect
4. Safety
   - Alteration in time course and shape of drug and metabolite concentration toxicity
   - Local change and reversibility
   - Excipients effect

Transdermal Drug Delivery System
Enhancers - Chemical

Ideal properties of a chemical enhancer:

- Safe and nontoxic
- Pharmacologically inert
- Nonirritating and nonallergenic
- Duration of action predictable and reversible
- Chemically and physically compatible.

Transdermal Drug Delivery System
Enhancers - Chemical

Regulatory concerns

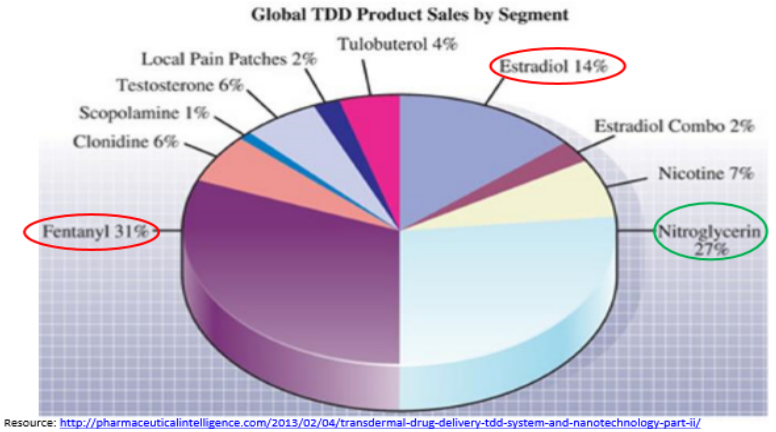
- Careful attention to biopharmaceutical, PK and PD issues to assess the effect of a specific enhancement method.
- Focus on the PK and PD effects of the enhancer alone, the drug alone, and the drug and enhancer in combination. Because a penetration enhancer may promote absorption of other excipients and of itself, certain PK and PD concerns may extend to excipients and enhancer itself.

Some of FDA Approved TDS in the Market

- Scopolamine (Scop®)
- Nitroglycerin (Nitro-Dur®)
- Testosterone (Androderm®)
- Estradiol (Climara®, Alora®, Vivel-Dot®)
- Estradiol/Norethindrone acetate (CombiPatch®)
- Estradiol/Levonorgestrel (Climara Pro®)
- Nicotine (Nicoderm®)
- Oxybutynin (Oxytrol®)
- Methylphenidate (Daytrana System®)
- Fentanyl (Duragesic®)
- Norelgestromin/Ethynyl Estradiol (Ortho Evra®)
- Selegeline (Emsam®)

TDS – Global Market

Global sales for potent TDDS significantly high



Resource: http://pharmaceuticalintelligence.com/2013/02/04/transdermal-drug-delivery-tdd-system-and-nanotechnology-part-ii/

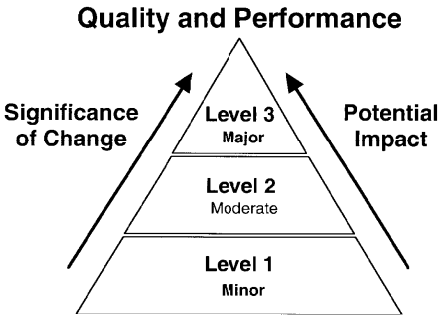
Guidances - References

- Residual drug in transdermal and related drug delivery systems (FDA, August 2011)
- Estradiol TDDS (FDA, Draft Sept 2015)
- Selegiline (FDA, October 2011)
- Rivastigmine (FDA, Draft Nov 2013)
- Scopalamine (FDA, October 2011)
- Guideline on quality of transdermal patches (EMA, June 2015)
- Topical and transdermal products – product quality tests (USP <3>)

TDS – Product Quality

- **Product Quality Tests**
  - Peel Adhesion Test
  - Release Liner Peel Test
  - Tack Test
  - Cold Flow Test
- **Product Quality Defects**
  - Leakage from Reservoir System
  - Adhesion Failures
  - Variability in Permeation
  - Drug Crystallization

Scale-Up and Post Approval Changes (SUPAC)



The hierarchy of scale-up and post approval changes and their significance on transdermal delivery system performance.

Pharm. Res. 14, 848-852, 1997.

Advances in TDD Systems

- Active Poration
- Thermal ablation
- Electrical ablation – Iontophoresis
- Ultrasound
- Radio frequency ablation
- Mechanical ablation – Micro needles

Advances in TDD Systems

- New Polymeric Technologies
  Can stick to dry or wet surfaces
- Micro channels for delivery of
  water soluble drugs and macro molecules
- Matrix controlled membrane systems
- Passport System
  Patch attached to a film of metallic filaments (Porator) → creates aqueous channels 30-50 micrometers for drug delivery

Transdermal Drug Delivery Systems

Active transdermal technology

- Mechanical Microporation – micro needles
  - To deliver small and large molecules through the skin (1 micron size), proteins and vaccines, high-dose hydrophilic drugs
- Creates temporary micropores - disruption of stratum corneum to create a passage

Transdermal Drug Delivery Systems Iontophoresis

Active transdermal technology

- For water soluble, ionized drugs
- Hybresis – Transdermal iontophoretic drug delivery system^{R} (IOMED). It consists of miniaturized, wireless dose controller that connects directly to the integrated drug delivery system.

Transdermal Drug Delivery Systems

- DOT Matrix
- Two polymers in its drug in adhesive blend – an acrylic that holds high concentration of drug in microcells and a silicone that holds the patch to the skin.
- Drives more drug through a smaller area
- Advantage – smaller, more wearable patches e.g., estrogen patch

TransDermaSal

- TransDermaSal Technology makes it possible to contain drugs in salt form in a nonaqueous transdermal patch formulation.
  - Fentanyl citrate
  - Oxybutynin HCl
  - Dichlofenac Na

DermaLight

- Adhesive / Polymer Technology
  - Pressure-sensitive adhesive technology
  - Increased adherence to the skin
  - Easy patch removal - Reduced skin irritation

Transdermal Drug Delivery System

Parameters

- Drug
- Penetration Enhancers
- Adhesive
- Crystal inhibitor
- Membrane
- Preservative
- Baking
- Release liner
- Size

Performance

- Drug delivery
- Wear
- Chemical stability
- Physical stability
- Economics

TDS - Optimization

- Optimum value for variables is controlled by multiple constraints
- Relationship between variables and performance attributes are often nonlinear
- Prototype performance must be tested after each carefully considered modification
- The art of product development is maintaining the desirable product attributes
- It requires fundamental understanding of many fields – chemistry, rheology, life science and problem solving skills, an inquisitive nature, patience and perseverance

Focus Focus Focus

Challenges

- Regulatory requirements are complex – drug + drug delivery device
- Improve drug delivery and dosing rate
- Develop technology / enhancers to deliver large molecules, in larger quantity
- TDS must be affordable!!!

Conclusions

- Regulatory requirements are complex
- Active and passive TDDS technologies have made strides
- Quality control and drug release specifications are dependent upon the drug delivery system.

Thank You