

Transdermal Drug Delivery System Regulatory Requirements (USA)

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To and Thru the Skin**

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Regulatory Authority Mission

**“Assure that
SAFE and EFFECTIVE
drugs are marketed in the
country and are available
to the People”**

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 Products

Drug Approval

<i>New Drug Application (NDA)</i>	<i>Abbreviated New Drug Approval (ANDA)</i>
Safety: Toxicity Studies <ul style="list-style-type: none">• Skin Irritation• Cutaneous Toxicity• Contact Sensitivity• Contact Photodermatitis	<ul style="list-style-type: none">• Skin Irritation• Cutaneous Toxicity
Efficacy: Clinical Studies <ul style="list-style-type: none">• Bioavailability Studies	<ul style="list-style-type: none">• Bioequivalence Studies
<ul style="list-style-type: none">• Manufacturing Controls	<ul style="list-style-type: none">• Manufacturing Controls
<ul style="list-style-type: none">• <i>In Vitro</i> Release Studies	<ul style="list-style-type: none">• <i>In Vitro</i> Release Studies

Transdermal Drug Delivery Systems

Advantages

- Avoid first pass metabolism
- Avoid GI side effects/disorders/degradation
- Can be easily removed from the body

Limitations

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

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

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

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 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.**

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

In Vitro Product Quality Tests

- **Compendial /Application tests**
 - **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**

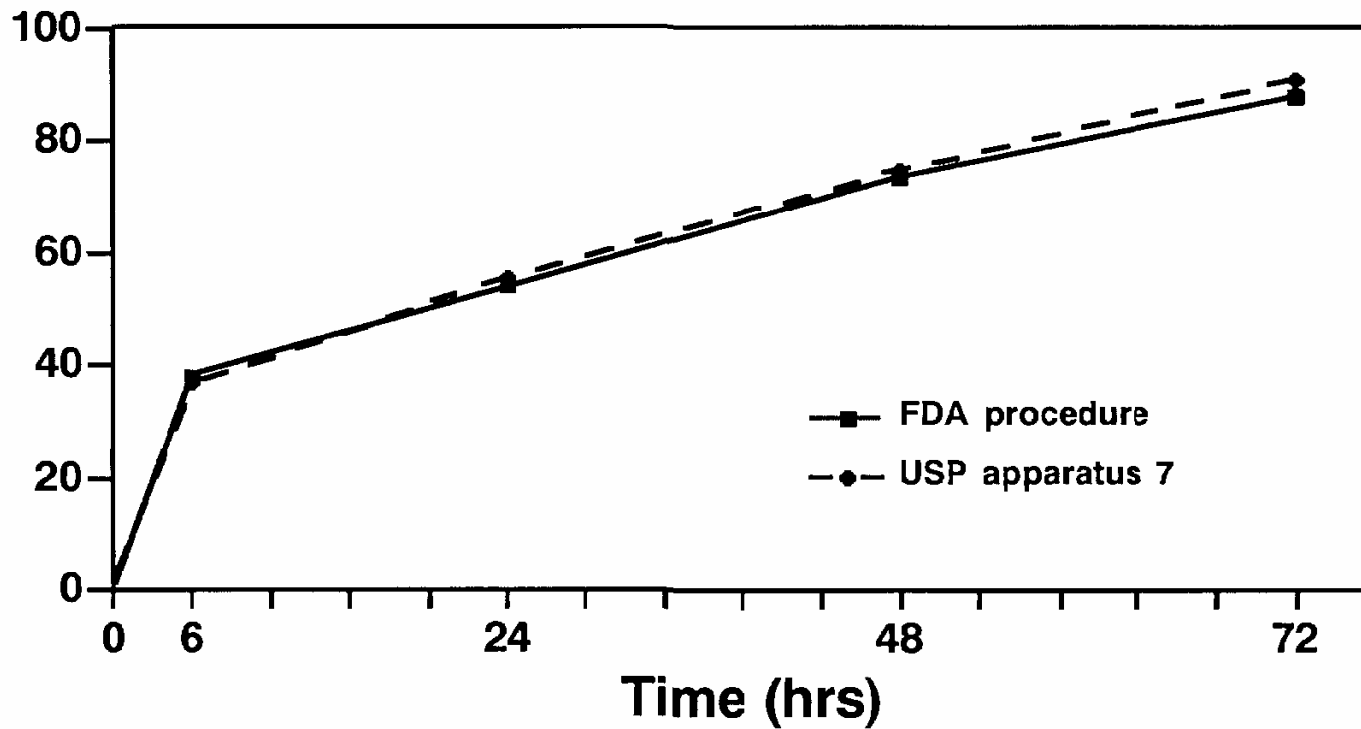
Paddle Over Disk Method

- **(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**

% Released



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**

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

- Drug
- Enhancer
- Adhesive
- Crystal inhibitor
- Drug delivery
 - Rate *vs* Duration
 - Efficiency
- Wear, Adhesion
 - Irritation, Ooze
 - Delamination
- Chemically stable
 - Should not change

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

TDDS - 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
- TDDS must be affordable!!!

Conclusions

Transdermal Drug Delivery System

Regulatory Considerations

1. TDS are regarded as new drugs

- **Scientific data (may be required) to substantiate clinical safety and efficacy.**
- **Bioavailability (blood and/or urine) level comparison employing known routes of administration.**
- **Clinical data (may be needed) to support labeling.**
- **Additional metabolism studies (may be needed).**

2. TDS are controlled release dosage forms

- **Demonstration of controlled release characteristics to support drug labeling.**

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