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Scientific and Regulatory Challenges of Transdermal Drug Delivery Systems (TDDS) and Relevance of Quality-by-Design (QbD) Approach to Their Development

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Talk Outline

- Major reported product quality problems
- Citizen petitions
- Significant innovations in patch design
- A roadmap for pharmaceutical development of TDDS
- Looking forward: QbD approaches
Major Product Quality Problems of TDDS

- Class I recalls of Fentanyl Reservoir patches from Innovator and generic manufacturers: (2004 to date)
- Problems of poor skin adhesion and cold-flow of an ADHD patch: 2006-2007
- Snowflakes (Drug crystallization) in a patch to treat Parkinson’s disease: 2008
- Safety concerns of a hormonal contraceptive patch (linked to quality drift?): 2003-2005

(FDA.gov, Medical News Today.Com and other internet sources)
Common Problems from Patients Perspective

- Patches do not stick
- Patches come off
- Patches leak
- Patches wrinkle
- Difficult to remove release liner from a patch
- Patch sticks inside the pouch
- Do not quite feel the effects of treatment
- Itchy feeling

*Potential misuse with band aid or other overlays*
Reactive Approaches to the Fix

- Increased sampling and end testing to weed out defective patches
- Changing drug coating rates
- Siliconization of inside of pouches and release liners to offset the problem of patch sticking due to cold flow
- Changing patch equilibration periods (curing) following manufacture
- Recommending use of overlays to offset stickiness problems
- Continuing with recalls
Flurry of Citizen Petitions

- Patch design for generics to be same as that of RLD
- Clinical trials for generic TDDS approvals
- Matrix patches not be approved because of safety
- Reservoir patches be removed from market as they carry manufacturing risk
- Require clinical studies using overlays to support their use on less sticky patches
Patch Design - Passive Patches

(a) Drug-in-adhesive: monolithic
- Impermeable backing
- Drug-adhesive matrix
- Rate-controlling membrane
- Adhesive
- Release liner

(b) Drug-in-adhesive: multilaminate

(c) Liquid reservoir
- Impermeable backing
- Drug-polymer matrix
- Drug reservoir
- Rate-controlling membrane
- Adhesive
- Release liner

(d) Polymer matrix
Reported Product Quality Defects, Complaints, and Recalls

Diagnosis: Design Risks & Manufacturing Risks

Inadequate Pharmaceutical Development Efforts

Manufacturing Controls & Monitoring?

Functional Testing to assure required performance?

ICH-Quality

Current Status of TDDS Vs FDA’s cGMP Initiatives for 21st Century

Dr. Nasr, FDA
Innovative Patch Designs

- Active delivery systems
  - Iontophoretic patches
  - Sonophoretic patches
- Microporation patches
- Abuse-deterrent patches
  - Antagonist layers
  - Taste-averting agents
  - Snort-averting agents
Evolution of Iontophoretic Drug Delivery Systems
Unique Advantages of TDDS

- Convenience and patient compliance
- Steady permeation of drugs across skin assures consistent serum levels.
- Lack of peaks and troughs
- Avoidance of first pass metabolism
- Patch may be quickly removed to stop drug’s undesired effects
  - Exception-Depot effect with some drugs
- Suited for delivery of drugs unstable in GI tract
- Ionic drugs may be delivered using active delivery technologies
- Less permeable and larger molecules may be delivered by microporation and other means of disrupting stratum corneum
Full Utility of TDDS Dosage Forms Requires Applications of Modern Science-based and Risk-based Approaches to Their Development
Factors Affecting Transdermal Delivery

- Patch adhesion
- Physical state of drug
- Rate-limiting membranes
- Penetration enhancers
- Occlusive overlays
- Skin temperature and condition
- Depot effect
- Skin irritation/sensitization

To maintain required flux rate across skin at all times
A Roadmap to TDDS Development

- Drug selection and its polymorph control
- Adhesive selection (DoEs)
- Assessing and optimizing penetration enhancer(s)
- Crystal seeding studies
- Selection of patch design
- Stability assessment for compatibility, cold flow and crystallization
- Adhesion test battery to measure rheological and tape properties
- Flux studies using diffusion cells and preclinical animal models
- Flux studies in humans and establishment of IVIVR/IVIVC using flux rates measured by diffusion cells
- “Wear studies” as part of BE study arms to assess skin adhesion, cold flow, and effect of overlays
- Provisions for product quality defect reporting and analysis of defective patches
Pharmaceutical Development

- Rationale for component selection
  - Drug, its physical properties, polymorphism
  - Permeation enhancers
  - Adhesive
  - Solubilizers
  - Viscosity inducing agents (tackifiers)
  - Anti-oxidants
  - Release liners, backing layers, rate-controlling membranes

- Patch design and development

- Process design and development

- Basis for process scale up (continuous process)
Release Liners, Backing Layers, Rate-control Membranes

- Physical dimensions
- Degree of porosity and pore diameter
  - AQLs for pinholes Tensile
- Tensile and Elongation modulus
- MVTR/OTR (e.g. 10-20 g/m²/day)

Important attributes linked to process parameters- roll force, line speed, substrate tension and registration, and lamination pressure
Quality risks: fold-over defects, incorrect heat seal thickness, leakage, evaporation
Quality Target Product Profile (QTTPP) for Patches

- Adhesion to skin through intended duration of use (1-7 days) without additional overlays
- Easy removal from skin with no adhesive traces on skin
- Maintains the required drug flux throughout the wear period
- Use of overlays does not result in changes in drug flux
- No skin irritation and allergic reactions.
- Works under physically active lifestyle
- Moisture resistance (skin wearability, sweating, showers, sauna, etc.)
Franz Diffusion Cell for Skin Permeation Studies
Formulation optimization
  › Drug to penetration enhancer ratio
  › Additives
  › Crystallization inhibitors

Manufacturing changes

Effects of temperature and occlusion

Stability assessment of thermodynamic changes (crystallization), polymer cross-linking etc. impact drug flux

Scope to establish IVIVR/IVIVC to claim biowaivers
  › During IND stages
  › Major CMC changes
Deliberate Attempts to Prevent Cold Flow and Creep Properties

- Formulation optimization by DoEs
- Adhesion selection and control of its degree of cross-linking
  - resin component
  - polymer component and functional groups
  - molecular weights
  - resin-to-polymer ratios
- Addition of cohesive strengthening agents
  - nonionic surfactants,
  - fatty acid esters of glycerol,
  - metallic salts of fatty acids,
  - metallic salts of phosphoric acid

Undesired plasticizing effects of co-solvents, excipients, high drug loads, penetration enhancers on adhesive
Major Failure Modes

- Adhesion Failures (All designs)
- Leaks (Reservoir patches)
  - Stringer leak defects (heat seal area)
  - Fold over defects (heat seal area)
  - Misaligned cut defects (reservoir area)
- Cold flow (Matrix patches)
  - Leaves behind dark edges on skin
  - Develops wrinkles
  - Patch moves across the skin
  - Patch sticks to the inside of pouch
    - Patches elongate when forced out
  - Over-stick to release liners
  - Adhesive chips off with the release liner
CQAs for Pressure-sensitive Adhesives

- Tape properties
  - Tack: a measure of wettability
  - Shear/Creep resistance: a measure of resistance to flow
  - Adhesion strength: a measure of force required to peel

- Rheological properties
  - Viscous modulus ($G'$)
  - Elastic modulus ($G''$)
  - Intrinsic Viscosity ($\eta^*$)

- Glass transition temperature (Tg)
- Molecular weight distribution
- Permeability
- Compatibility
- Stability
- Leachables
Rheologic measurements on native adhesive and the drug-in-adhesive formulation to assess changes in the visco-elastic properties of adhesive

- Elastic or storage modulus ($G'$)
- Viscous or loss modulus ($G''$)
- Ratio of viscous to elastic modulus ($\tan \delta$)
- Intrinsic or complex viscosity

A design-of-experiments may be undertaken to optimize the transdermal formulation

Stability assessment of formulation
Dynamic Mechanical Thermal Analysis (Rheologic measurements)

Source: Rheometrics
Methods of Testing Tack
ASTM D2979
ASTM D3121

Rolling Ball

Polykine Tester

Loop Tack

Thumb Tack
Shear strength (D3654, PSTC-107)

Dynamic Testing

Static Testing
Peel Force
D3330, PSTC 101

From Release Liner

From Solid Substrate (SST/HDPE)

Measure force (N)
(1kg = 9.8N)
9N = 102g = 1 apple

Calculate
N / mm width
(mN/mm)
Solubility Assessments

- Assessment of solubility of drugs in individual patch components
  - Adhesive
  - Additive
  - Penetration enhancer
  - Solvent
  - Plasticizer

- Solubility in the investigational formulations
Solubility Assessments Contd..

- Prepare different drug concentrations in adhesives
- Make patches and store at ambient (25oC) and elevated temperatures (e.g. 50oC)
- Monitor for drug crystal growth over a few weeks
Crystal Seeding Studies

- Prepare drug and adhesive mixtures with wide range of drug concentrations
- Seed drug crystals of all polymorphs onto the surface.
- Observe growth or dissolution of the seeded drug crystals
- Can be predictors of potential crystallization during storage
TDDS Manufacturing Process Development

General Process Flow Diagrams

**Reservoir System**
- Drug Formulation Mixing
- Gel Dispensing
- Lamination
- Seal reservoir and die-cut
- Primary Package (pouch)

**Drug-in-Adhesive System**
- Drug and Adhesive Mixing
- Coating and Drying
- Lamination
- Conversion – rolls to patches (die-cutting)
- Primary Packaging (pouch)
Processing Steps

- Raw material controls
- Adhesive mixing operations
- Adhesive coating and drying
- Gel dispensing (Reservoir)
- Patch sealing process (Reservoir)
- Conversion (Matrix)/Coupon cutting
- Primary packaging
Manufacturing Process Controls and Continuous Monitoring

- Controls to minimize air entrapment in drug-adhesive or drug-polymer mix.
- Controls to maintain drug homogeneity and viscosity of the drug-adhesive or drug-polymer mix in gel pots.
- Engineering controls to guide webs during lamination to prevent fold-over defects.
- Establishing sensors for continuous monitoring of critical operations and for weeding out defective patches.
  - E.g. patch registration, heat seal thickness, pinholes, drug in heat seal area, etc.
- At-line testing for pouch seal integrity.
- 100% inspections by Vision system.
Critical Process Controls for TDDS Manufacture

- Laminator speed: range and target (e.g. 15 ft/min)
- Laminator roll pressure: range and target (e.g. 90-250 lbs)
- Payout #1 tension: range and target (e.g. 55 lbs)
- Payout #2 tension: range and target (e.g. 2 lbs)
- Upper rewind tension: range and target (e.g. 40 lbs)
- Laminate roll size limits (e.g. do not exceed 1000 ft/roll)
Conclusion

- Current state of TDDS manufacturing does not assure adequate product quality and results in frequent recalls and raises concerns of safety and potential for suboptimal effectiveness.

- Enhanced pharmaceutical development efforts and quality-by-design principles are needed to assure product quality of TDDS.

- Pharmaceutical development efforts should include deliberate efforts to minimize undesired drug crystallization, cold flow, lack of adhesion.

- Adequate functional testing battery should be included in ensuring desired product performance for TDDS.

- Manufacturing process should include adequate sensors and vision systems to continuously monitor and weed out defective patches.

- Newer TDDS technologies designed for delivery of polar and ionic drugs are even more complex to manufacture and raise additional risks.

- Industry and FDA should work together to appropriately implement ICH Q8, Q9, and Q10 principles to these products while fostering drug development.