Transdermal Drug Delivery

December 3rd, 2015

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Why skin?

- Largest organ in the body
- Readily accessible (Large surface area)
- Huge market potential (app $ 13 billion 2010 and expected to increase.

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Functions of skin

Skin

1. Containment function
2. Protective function
   - Microbial barrier
   - Chemical barrier
   - Mechanical barrier
   - Heat barrier
3. Temperature regulation
4. Excretory

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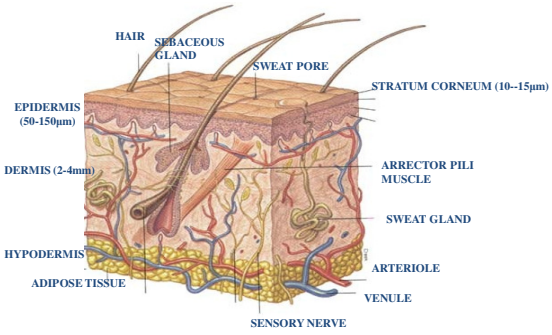
ANATOMY OF SKIN



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The Stratum Corneum

- The stratum corneum, being keratinized tissue, behaves as a semipermeable artificial membrane, and drug molecules penetrate by passive diffusion. It is the major rate-limiting barrier to transdermal drug transport.

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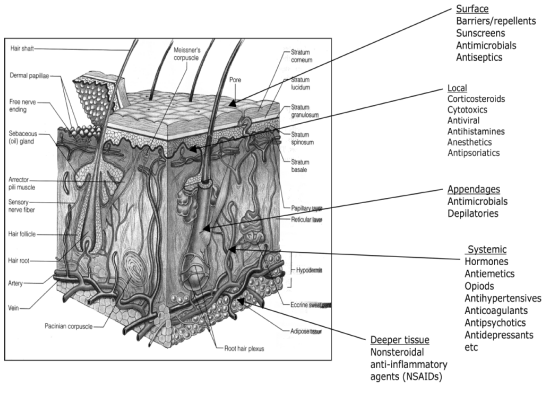

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Transport Pathways

SC is brick and mortar model - Pathways

- Paracellular pathway: via the lipid intercellular matrix
- Transcellular pathway: across keratinized cells
- Transappendageal pathway: across hair follicles and sweat ducts

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Benefits of Transdermal Drug Delivery

1. Controlled delivery rate into systemic circulation.
2. Substitute for oral administration.
3. Maintain efficacious plasma levels: 1 to 7 days.
4. More reliable and predictable blood levels.
5. Avoids first-pass metabolism.
6. Improved patient compliance, non invasive.
7. Increases efficacy and, typically, decreases toxicity compared to oral delivery.

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Factors affecting percutaneous absorption

1. Drug concentration.
2. Area of application.
3. Affinity to skin than the vehicle.
4. Molecular weight 500 dalton or less.
5. Hydrated skin favors percuatneous absorption.
6. Application site thin vs thick layer.
7. Longer contact time = greater drug absorption.

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Drug Candidates for TDD

1. Daily dose (< 20 mg/day)
2. Short half-life (nitroglycerin is 3 min)(reduce frequency of administration)
3. Molecular weight (< 500 Daltons)
4. Lipid solubility- partition coefficient
5. Non-irritating and non-sensitizing to skin.

Limitations of Transdermal Drug Delivery

- Only relatively potent drugs (usually less than 20 mg and ideally < 10 mg/day)
- Molecular size (<500 Dalton)
- Poor diffusion of large/hydrophilic molecules
- Skin irritation and contact dermatitis
- Lack of adhesiveness with certain TDDS
- Expensive

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Transdermal Drug Delivery

Advantage	Disadvantage
Uniform plasma levels.	Cost.
Bypass first pass metabolism.	Skin irritation.
Noninvasive i.e no pain associated with administration.	Lack of good adhesiveness.
Desired plasma levels can be maintained over longer duration.	
Increase patient compliance.	
Reduce frequency of administration.	
If adverse or overdose patient can easily remove the patch.	

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Enhancing Percutaneous Drug Absorption

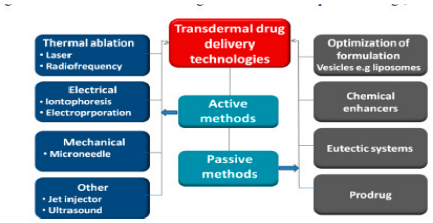

Figure 5. Approaches for enhancing drug transport across the skin.

Pharmaceutics **2015**, *7*, 438-470; doi:10.3390/pharmaceutics7040438

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Percutaenous Absorption enhancers

I. Chemical Enhancers.
II. Physical methods.
III. Mechanical methods.
IV. Optimization of formulation. (liposomes)

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Chemical Enhancers

- They act by :
  1. Increases skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum.
  2. Interaction with cellular proteins.
  3. Improved partitioning of drug co-enhancer or co-solvent into the stratum corneum.

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Classification of skin penetration enhancers

Alcohols	Ethanol, propanol
Fatty alcohols	Myristyl alcohol, cetyl alcohol, stearyl alcohol
Fatty acids	Myristic acid, stearic acid, oleic acid
Fatty acid esters	Isopropyl myristate, isopropyl palmitate
Polyols	Glycerol, propylene glycol, polyethylene glycol
Anionic surfactants	Sodium lauryl sulfate
Cationic surfactants	Benzalkonium chloride
Amphoteric surfactants	Lecithins
Non-ionic surfactants	Spans®, Tweens®, poloxamers

Physical & Mechanical Methods

Iontophoresis	Heat or thermal energy
Electroporation	Thermal Ablation
Sonophoresis	Microneedles

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Physical Methods

1. Iontophersis: delivery of charged chemical compound across the skin membrane using an electrical field.
2. Sonophoresis: a high frequency ultrasound influences the integrity of the stratum corneum and is used to enhance transdermal drug delivery.

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3. Electroporation: cells are temporarily exposed to high intensity of electric pulse that leads to the formation of aqueous pores in the lipid bilayers of the stratum corneum.
4. Thermal Ablation: heat is applied to the surface of the skin via laser or radiofrequency to deplete the stratum corneum at the site of heating, without damaging underlined epidermis.

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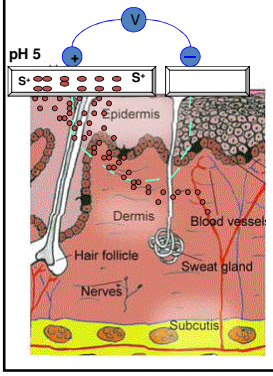
TRANSDERMAL IONTOPHORESIS



Enhancing the transport by application of the electrical current

Mechanical Methods

5. Tape stripping: removing of the stratum corneum layers by repeated application of adhesive tape.
6. Microneedles: minimalyy invasive drug delivery system has a potential to be used as an alternative to hypodermic and SQ needle.

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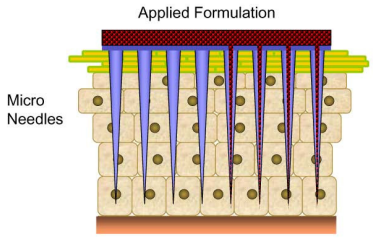
Microneedles



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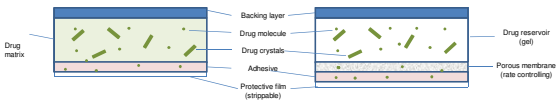
Design of Transdermal Drug Delivery Systems

1. **Monolithic systems: Matrix**

2. **Membrane controlled transdermal system: Reservoir**

Commercial TDDS



Matrix TDDS

Reservoir TDDS

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Transdermal Drug Delivery

Passive

- Matrix (Oxytrol, Vivelle Dot)
- Reservior (Androderm, Duragesic)

Active

Iontophoresis	Heat or thermal energy
Electroporation	Thermal Ablation
Sonophoresis	Microneedles

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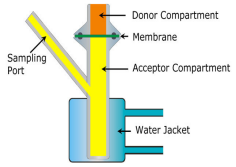
Percutaneous Absorption Studies Models

1. In vivo studies in humans and animal models.
2. In vitro studies utilizing human or animal whole skin, dermis or epidermis in diffusion cells Fig 11.1



http://www.skin-care-forum.basf.com/en/articles/skin/publication-year/2001/strategies-for-skin-penetration-enhancement/2004/08/12?id=5b9a9164-6148-4d66-bd84-6d76bd6d111&mode=Detail

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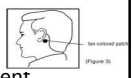
Challenges

1. Flux sufficient but TDDS manageable size.
2. Adequate skin adhesion.
3. Adequate shelf life stability.
4. Non-irritating.
5. Aesthetically pleasing.
6. Easy to handle and use.
7. Comfortable.
8. Product cost.

Transdermal Products



Scopolamine (Transderm Scop) (1st product)

Continuous release of drug over 3 days to prevent nausea, vomiting of motion sickness and nausea of certain anesthetics and analgesics used in surgery.Patch is placed behind ear.

Clonidine

Catapres TTS: provides 7 days of continuous antihypertensive therapy

Nitroglycerin

- Several nitroglycerin patches available (Deponit, Nitro-Dur)

Testosterone

Testoderm: Patch is placed on scrotum in treatment of testosterone deficiency.

Androderm: Patch is placed on back, abdomen, upper arms, or thighs for treatment of testosterone deficiency.

Nicotine

Several nicotine patches available on market from various manufacturers (Nicoderm, Habitrol, Prostep, Nicotrol)

Aid to smoking cessation

Typically, 21 mg/day over 24 hrs for 4-8 wks followed by weaning doses of 14 mg/day for 2-4 wks and then 7 mg/day for another 2-4 wks

Fentanyl (Duragesic)

Transdermal therapeutic system providing continuous 72-hour systemic delivery of potent opioid analgesic; indicated in patients with chronic pain requiring opioid analgesia.

Oxybutynin (Oxytrol)

Oxytrol is available as a 39 cm^2 system containing 36 mg of oxybutynin. This medication is used to treat an overactive bladder. This medication is an antispasmodic. Used as two patches per week.

(Ortho-Evra)

- Transdermal contraceptive system
- Contains 6 mg of norelgestromin and 0.75 mg of ethinyl estradiol in 20 cm^2 patch
- It is once a week patch

Novelle Dot

- Estradiol for post menopausal symptoms
- Smallest patch

Approved Iontophoretic Patches

- Iontocaine (lidocaine and epinephrine) 1996 – before IV injection
- Ionsys (Fentanyl) 2006 - pain
- Zecuity (sumatriptan) 2013 - migraine

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Proper Usage and Handling of Transdermal Patches

- General guidelines.
- Specific to drug guidelines.
- Placement
  - Abdomen, upper arm, back & thigh most common
  - Avoid hairy areas
  - Rotate sites
- Do not apply a heat pad!!

General Guidelines

- Once lining is pulled off, do not touch the sticky surface of the patch
- Do not apply to broken or irritated skin
- When applying a new patch, remove the old one! Do not apply two to compensate for a missed one. Wear only for the designated period of time
- Do not cut the patch!

https://quitsmokingcommunity.org/how-to-quit-smoking/smoking-cessation-tools/nicotine-patch/