Chapter 10
Transdermal Controlled Release Dosage Forms

Transdermal Drug Delivery
- First approved by FDA in 1980
- Effective for many drugs
  - Local effect
  - Systemic effect
  - Direct to the blood stream
  - Avoids GI
    - No first-pass effect
    - Avoids pH swings

Transdermal Limitations
- Difficulty of permeation
- Highly efficient physical & chemical barrier
- Skin irritation (contact dermatitis)
- Excipients and absorption enhancers
  - May increase percutaneous absorption
- Technical development problems
  - Batch-to-batch variations
  - Migration of active during storage
  - Crystallization

Transdermal Limitations

Criteria of Drug Selection
- High potency
  - Typical dosages are ~5 mg
  - Patch cannot exceed 50 cm² (7 cm x 7 cm)
  - Effective when delivered slowly over a long period

Criteria of Drug Selection
- Clinical need
  - Narrow therapeutic window
  - Extensive first-pass effect orally
  - Multiple dosing
  - Unpleasant side effects from short half-life
  - Highly fluctuating plasma levels

Criteria of Drug Selection
- Non-irritating
- Unreactive with patch components
- Must have an advantage over oral dosage form

Criteria of Drug Selection
- Physiochemical properties
  - Molecular weight < 500
    - Nicotine 162.23
    - Estradiol 272.37
    - Testosterone 288.41
  - Hydrophobic drugs are absorbed more easily
    - \( K_{octanol/water} \approx 10–1000 \)

Criteria of Drug Selection
- Non-irritating
- Unreactive with patch components
- Must have an advantage over oral dosage form

Criteria of Drug Selection
- The skin is the rate determining factor for most commercial systems
  - Zero order for membrane controlled
  - Zero order for monolithic systems
  - Non-zero order for alcohol-containing systems
- GRAS surfactants are typically used to enhance permeation and penetration

Enhancers and Excipients
Anionic Surfactants

- Sodium lauryl sulfate (sodium dodecyl sulfate, SDS)
  $$\text{C}_{12}\text{H}_{25}\text{NaO}_4\text{S}$$

- Sodium oleate
  $$\text{C}_{18}\text{H}_{33}\text{NaO}_2$$

Cationic Surfactants

- Dodecylamine hydrochloride
  $$\text{C}_{12}\text{H}_{28}\text{ClN}$$

- Cetyltrimethyl ammonium bromide
  $$\text{C}_{18}\text{H}_{40}\text{BrN}$$

- Stearylamine hydrochloride
  $$\text{C}_{18}\text{H}_{40}\text{ClN}$$

Nonionic Surfactants

- Linolenyl alcohol
  $$\text{C}_{18}\text{H}_{30}\text{O}$$

- Polyoxyethylene sorbitol
  $$\text{C}_{46}\text{H}_{92}\text{O}_{24}$$

Penetration Enhancers

- Reduce skin barrier function
- Trigger corrective response in skin
- Irritation level reflects extent of perturbation
- Response determines feasibility and acceptability
- Can significantly influence product form
- Lack of control on permeation
- Variability among users is high

Scopolamine Transdermal Patch

- Clinically proven to prevent motion sickness
- In clinical studies, 5 out of 6 people did not report drowsiness
- Larger-lasting, one patch lasts up to 3 days compared with a Dramamine tablet which only lasts up to 6 hours.

Nitroglycerin Transdermal Patch

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosing Rate</th>
<th>Size</th>
<th>Units</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrek</td>
<td>0.2 mg/hr</td>
<td>8 cm²</td>
<td>30</td>
<td>$47.36</td>
</tr>
<tr>
<td>Nitrek</td>
<td>0.4 mg/hr</td>
<td>16 cm²</td>
<td>30</td>
<td>$54.01</td>
</tr>
<tr>
<td>Nitrek</td>
<td>0.6 mg/hr</td>
<td>24 cm²</td>
<td>30</td>
<td>$59.64</td>
</tr>
<tr>
<td>Nitrodisc</td>
<td>0.2 mg/hr</td>
<td>5 mg</td>
<td>30</td>
<td>$54.13</td>
</tr>
<tr>
<td>Nitrodisc</td>
<td>0.4 mg/hr</td>
<td>10 mg</td>
<td>30</td>
<td>$51.40</td>
</tr>
<tr>
<td>Nitro-Dur</td>
<td>0.6 mg/hr</td>
<td>15 mg</td>
<td>30</td>
<td>$53.50</td>
</tr>
<tr>
<td>Nitro-Dur</td>
<td>0.8 mg/hr</td>
<td>20 mg</td>
<td>30</td>
<td>$54.55</td>
</tr>
</tbody>
</table>

Sublingual tablet: Every 5 min

Estrogen Transdermal Patches

- Estraderm (1986)
  - Twice a week
  - Initially produced utilizing a skin absorption enhancer
  - Drug reservoir system of estradiol and ethanol gelled with hydroxypropylcellulose, an ethylene-vinyl acetate copolymer membrane for zero-order release, and an adhesive formulation of light mineral oil and polyisobutylene

- Climara® (3M & Berlex Labs)
  - First once a week patch

- Progynova® TS (Schering)
  - 100 μg/day for 7 days

- Fematrix® (Europe & Asia)
  - 3-4 or 7 days

- Menorest® (Noven)

Vivelle-Dot® is available in four dosage strengths (0.0375, 0.05, 0.075 and 0.10 mg/day). In the most commonly prescribed dosage strength (0.05 mg/day), Vivelle-Dot® is about the size and thickness of a postage stamp. By area, it is about one-third the size of Climara® (Berlex) and about one-quarter the size of Estraderm® (Novartis).
Estrogen Transdermal Patches

The Combipatch™ is a combination patch containing 17β-estradiol and norethindrone acetate, a progestogen. It is the first combination transdermal therapy system approved for marketing by the FDA.

Clonidine Transdermal Patch

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Programmed Delivery (mg/day over 1 week)</th>
<th>Size (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonipath 1</td>
<td>0.1mg</td>
<td>2.5</td>
</tr>
<tr>
<td>Clonipath 2</td>
<td>0.2mg</td>
<td>5.0</td>
</tr>
<tr>
<td>Clonipath 3</td>
<td>0.3mg</td>
<td>7.5</td>
</tr>
</tbody>
</table>

The plasma half-life of clonidine (a potent antihypertensive) is 10–20 hours. The half-life does not depend on the age or sex of the patient but is clearly prolonged in patients with severely impaired renal function.

Gelerosa TTS is programmed to release clonidine at an approximately constant rate for 7 days. The drug reservoir (clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide) is released through a microporous polypropylene membrane.

Clonidine flows in the direction of the lower concentration at a constant rate, limited by the rate-controlling membrane, so long as a saturated solution is maintained in the reservoir layer.

Fentanyl Transdermal Patch

The patch has a form-fill-and-seal drug reservoir and an ethylene-vinyl acetate membrane for the controlled delivery of the opioid.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Price</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testoderm¹ (testosterone transdermal system)</td>
<td>Alza Pharmaceuticals</td>
<td>6 mg/day</td>
<td>$3.40</td>
<td>Applied daily to scrotum</td>
</tr>
<tr>
<td>Testoderm with adhesive</td>
<td>Alza Pharmaceuticals</td>
<td>4 mg/day</td>
<td>$3.40</td>
<td>Applied daily to scrotum</td>
</tr>
<tr>
<td>Testoderm² TTS³ (testosterone transdermal system)</td>
<td>Alza Pharmaceuticals</td>
<td>5 mg/day</td>
<td>$3.60</td>
<td>Applied daily to skin, back, or upper buttocks</td>
</tr>
<tr>
<td>Androderm (testosterone transdermal system)</td>
<td>Scandia Biotech Pharmaceuticals</td>
<td>5 mg/day</td>
<td>$1.95</td>
<td>Applied daily to back, abdomen, upper arms, or thighs</td>
</tr>
</tbody>
</table>

Testoderm® is composed of the following layers:
- a soft flexible backing of polyester
- a testosterone-containing film of ethylene-vinyl acetate copolymer
- thin and narrow adhesive stripes composed of polyisobutylene and colloidal silicon dioxide partially cover the surface of the drug film
- a protective liner of fluoroelastomer-coated polyester that must be removed before application covers the adhesive stripes and the adhesive-free area of the drug film

Testoderm® with adhesive is composed of three layers:
- a soft flexible backing of polyester
- a testosterone-containing film of ethylene-vinyl acetate copolymer
- a protective liner of fluoroelastomer-coated polyester that must be removed before application covers the adhesive stripes and the adhesive-free area of the drug film

Testoderm TTS® (testosterone transdermal system) is composed of the following layers:
- a drug reservoir of testosterone and ethanol gelled with hydroxypropyl cellulose
- an ethylene-vinyl acetate copolymer membrane coated with a layer of polyethylene and colloidal silicon dioxide that controls the rate of release of testosterone from the system
- a transdermal delivery system that includes a protective liner of adhesive-coated polyester that must be removed before application covers the adhesive surface that must be removed before application

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- an ethylene-vinyl acetate copolymer membrane coated with a layer of polyethylene and colloidal silicon dioxide that controls the rate of release of testosterone from the system
- a protective liner of adhesive-coated polyester that must be removed before application covers the adhesive surface that must be removed before application
Salicylic Acid Patch

Site Specific Wart Removal for adults and children.
Available in three sizes:
• 6 mm PediaPatch for small warts on children and adults
• 12 mm AdultPatch for medium warts on hands and feet
• 20 mm Plantar Patch for plantar warts on feet

Exothermic Enhancement

• Wax — the drug is contained in a low-melting fat (e.g., cacao butter) and is released when the base is softened by body temperature.
• Laser energy-enhanced transdermal transport — brief pulses from an Ar–F laser (193 nm) increases skin permeation rate by more than 100 times.

Moxibustion

• Moxibustion is a technique used in traditional Chinese medicine in which a stick or cone of burning mugwort, Artemesia vulgaris, is placed over an inflamed or affected area on the body.
  - The cone is placed on an acupuncture point and burned.
  - The cone is removed before burning the skin.
  - The purpose is to stimulate and strengthen the blood and the life energy, or qi, of the body.

Mugwort (Artemesia vulgaris)

Moxibustion

HiPrO β-thujone

Skin Stripping

• The stratum corneum is removed by using adhesive tape.
• Relatively large molecules, such as insulin, can be absorbed through the stripped skin.
• Reproducibility may be a problem.
Reverse Iontophoresis

- Used for the extraction of information from the body
- Electrical current causes ions and other molecules to move in both directions under both electrodes.
- Able to sample analyte within the body, such as glucose, even though it is not charged (electro-osmosis).

GlucoWatch® Biographer

- The GlucoWatch® Biographer can measures glucose levels automatically every 20 min
- Consists of two integrated parts
  - Biographer
  - AutoSensor
- An extremely low current is used to pull glucose through the skin.

PowderJect®

- Involves the acceleration of dry, solid powder-formulations of medicines to high speed, using a transient high-velocity helium gas jet, for injection into any physically accessible tissue.
- Particles must have suitable properties and fall in a specific size range.
- Particles may consist of pure medicine or advanced formulations containing additional inert ingredients to dilute or stabilize the product.
- Can be used to deliver traditional small molecules, peptides, proteins, vaccines, or even DNA.

DNA Vaccines

<table>
<thead>
<tr>
<th>Category / Product</th>
<th>Status</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B Prophylactic</td>
<td>Phase I</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Hepatitis B Therapeutic</td>
<td>Phase I</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HIV Therapeutic:</td>
<td>Preclinical</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HIV Prophylactic:</td>
<td>Preclinical</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HPV Therapy for Genital Warts</td>
<td>Preclinical</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Undisclosed Infectious Disease</td>
<td>Preclinical</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Influenza</td>
<td>Preclinical</td>
<td>PowderJect</td>
</tr>
<tr>
<td>Herpes Simplex Virus</td>
<td>Preclinical</td>
<td>PowderJect</td>
</tr>
</tbody>
</table>

Human Vaccines

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Diseases with licensed vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide</td>
<td>Pneumococcus, meningococcus, typhoid V1</td>
</tr>
<tr>
<td>Polysaccharide conjugate</td>
<td>Haemophilus influenzae B</td>
</tr>
<tr>
<td>Native subunit</td>
<td>Diphtheria, tetanus, pertussis</td>
</tr>
<tr>
<td>Recombinant subunit</td>
<td>Hepatitis B, type disease</td>
</tr>
<tr>
<td>Inactivated whole pathogens</td>
<td>Influenza, pertussis, rabies, Japanese encephalitis, polio, hepatitis A</td>
</tr>
<tr>
<td>Live attenuated</td>
<td>Mumps, measles, rubella, rotavirus, cholera, polio, chickenpox, yellow fever, tuberculosis, vaccine</td>
</tr>
</tbody>
</table>

Supersonic Powder Injection

- Involves the acceleration of dry, solid powder-formulations of medicines to high speed, using a transient high-velocity helium gas jet, for injection into any physically accessible tissue.
- Particles must have suitable properties and fall in a specific size range.
- Particles may consist of pure medicine or advanced formulations containing additional inert ingredients to dilute or stabilize the product.
- Can be used to deliver traditional small molecules, peptides, proteins, vaccines, or even DNA.

Jet Injections

<table>
<thead>
<tr>
<th>DNA Vaccines</th>
<th>Human Vaccines</th>
<th>Jet Injections</th>
</tr>
</thead>
</table>
Microneedles
- The stratum corneum is an excellent barrier to the outside world, hence the need to poke a large needle through it to get to the bloodstream.
- Very small needles could deliver vaccines and medication to the tissue just below the stratum corneum.
- The medications would then diffuse from the tissue into capillaries.
- Since the outer skin doesn’t contain any nerve endings—the first extensive nerve layer is below the outermost capillaries—the small needles wouldn’t cause any pain.

Microneedles

Alza’s Macroflux™ Technology
Macroflux™ technology is designed to enable painless, convenient patient administration of therapeutic proteins and vaccines.

Macroflux™
Macroflux™ skin interface technology incorporates a thin titanium screen with precision microprojections that, when applied to the skin, create painless, superficial pathways through the skin’s barrier layer to allow for transportation of macromolecules.
This technology provides the option of dry-coating the drug on the micro-projection array for bolus delivery into the skin or using a drug reservoir for continuous passive or electrophoretic applications.
In addition, the creation of these pathways allows for better control of drug distribution throughout the skin patch treatment area and reduction in potential skin irritation.

Performance of Macroflux™ Transdermal Systems
Peptide-Coated Macroflux™ Patch Delivers Target Dose Rapidly
In preclinical animal tests, peptide-coated Macroflux™ can deliver a bolus dose with peak therapeutic plasma levels observed within one hour after administration.

E-TRANS® Macroflux™ Delivers Human Growth Hormone In Vivo
Macroflux™ technology can also enable the E-TRANS® transdermal delivery of recombinant human growth hormone (hGH). A short delivery pulse for 1 hour or continuous delivery for 4 hours both demonstrate rapid appearance of therapeutically relevant doses of hGH in plasma and the absence of a skin depot effect on system removal.
**Medipad™**

- Prior to use, the needle is invisible to the user.
- When the system is activated, the needle is advanced into the tissue at the proper depth and angle. Gas generation precisely controls drug release throughout the application time.
- Upon removal, the needle is automatically retracted and Medipad™ locks into the discard position for easy disposal.

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**Medipad™**

**Veterinary Products**

**WORKING KNOWLEDGE**

- *Killer Drugs*

**Veterinary Products**

- Medication is applied to the skin at the site of desired action.

**Nicotine**

- Chemical Name: S-3-(1-methyl-2-pyrrolidinyl)-pyridine
- Molecular Formula: C_{10}H_{14}N_{2}
- Molecular Weight: 162.23
- Ionization Constants:
  - pK_{a1} = 3.04
  - pK_{a2} = 7.84
  - at 15 °C

**Nicotine Transdermal Patch**

- The nicotine patch is applied to the skin.
Nicotine Transdermal Patches

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Reservoir</th>
<th>Polymer</th>
<th>Release Rate</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicoderm®</td>
<td>EVA copolymer matrix (reservoir device)</td>
<td>Polyethylene</td>
<td>40 μg/cm²/h (24 h)</td>
<td>Alza / Mentor-Menal Dow</td>
</tr>
<tr>
<td>Habitrol®</td>
<td>Methacrylic acid copolymer solution in a gauze (monolithic device)</td>
<td>25 μg/cm²/h (24 h)</td>
<td>Lohmann / Ciba-Geigy</td>
<td></td>
</tr>
<tr>
<td>ProStep®</td>
<td>Hydrogel monolithic device</td>
<td>130 μg/cm²/h (24 h)</td>
<td>Amercian Cyanamid / Elan-Lederle</td>
<td></td>
</tr>
<tr>
<td>Nicotrol®</td>
<td>monolithic device</td>
<td>16 h</td>
<td>Parke-Davis / Cygnus-McNeil</td>
<td></td>
</tr>
</tbody>
</table>

Annual US Cancer Deaths

- Total deaths: 232,700 (male); 207,900 (female)
- 24,800 more male deaths overall
- 26,100 more male deaths by lung cancer

Nicotine Transdermal Patches

- The distribution volume \( (V_d) \) following IV administration of nicotine is \(~120\ L\).
- The major elimination organ is the liver.
- The plasma clearance \( (PC) \) is \(1.2\ L/min\).
- The elimination rate constant, \( k_{el} \), is equal to the plasma clearance rate divided by the distribution volume \( (PC/V_d) \).
- There is no significant skin metabolism of nicotine.

Nicoderm®

- The nicotine is slowly released from the reservoir through the membrane
- \( k_{rel} \) is \(~20\ times\) smaller than skin absorption rate

Habitrol™

- The plasma nicotine concentrations are proportional to the dose for the three dosages.
- Nicotine kinetics are similar for all sites of application (neck, back, abdomen, side)

ProStep®

- Prostep® 22 mg/d system
- Nicotine concentrations increase to a peak \(~6\–12\ h\)
- Open two-compartment disposition model with a skin depot
### Nicotine Replacement Therapy

#### NRT Products

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Strength of nicotine available</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patch</strong></td>
<td>Nicorette</td>
<td>15 mg, 10 mg, 5 mg for use over 16 hours</td>
<td>Boxes of 7, 21 mg, 14 mg, 7 mg for use over 24 hours</td>
</tr>
<tr>
<td></td>
<td>Nicotinell</td>
<td>21 mg, 14 mg, 7 mg for use over 24 hours</td>
<td>Boxes of 7 or 14 (21 mg), 7 mg for use over 24 hours</td>
</tr>
<tr>
<td><strong>Gum</strong></td>
<td>Nicorette</td>
<td>2 mg or 4 mg original or mint flavor</td>
<td>Boxes of 15, 30 or 105</td>
</tr>
<tr>
<td></td>
<td>Nicotinell</td>
<td>2 mg or 4 mg original, mint or fruit flavor</td>
<td>Boxes of 12, 48 or 96</td>
</tr>
<tr>
<td><strong>Inhalator</strong></td>
<td>Nicorette</td>
<td>Mouthpiece with 10 mg cartridges</td>
<td>6 cartridge starter pack and 42 cartridge refill</td>
</tr>
<tr>
<td><strong>Lozenge</strong></td>
<td>Nicotinell</td>
<td>1 mg mint</td>
<td>Use 6-12 cartridges daily, boxes of 12, 36 and 96</td>
</tr>
<tr>
<td><strong>Sublingual Tablet</strong></td>
<td>Nicorette</td>
<td>2 g tablets</td>
<td>Max of 40 tablets per day, boxes of 12, 36 and 96</td>
</tr>
</tbody>
</table>
| **Nasal Spray** | Nicorette | 0.5 mg nicotine spray per puff  | Max 32 puffs per nostril per day, 200 spray dispenser, one spray per nostril per hour  

### Nicotine Replacement Therapy

#### Pharmacologic Aid

<table>
<thead>
<tr>
<th>Aid</th>
<th>Year Introduced</th>
<th>Delivers Nicotine</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion HCl, non-nicotine pill</td>
<td>1997</td>
<td>No</td>
<td>Rx</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>1997</td>
<td>Yes</td>
<td>Rx</td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>1996</td>
<td>Yes</td>
<td>Rx</td>
</tr>
<tr>
<td>Nicotine transdermal patch</td>
<td>1991</td>
<td>Yes</td>
<td>OTC/Rx</td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>1984</td>
<td>Yes</td>
<td>OTC</td>
</tr>
</tbody>
</table>

### Zyban® Sustained Release

- Zyban® (150 mg bupropion HCl) significantly reduced withdrawal symptoms as compared to placebo
  - Irritability, frustration, or anger
  - Depressed mood or negative affect
  - Difficulty in concentrating
  - Restlessness
  - Anxiety

### Buspirone Transdermal Patch

- Once-a-day transdermal patch
- Attention deficit hyperactivity disorder (ADHD) in children
- Open-label 8-wk study showed 70–80% of patients were “much improved or very much improved”
- Oral dosing is metabolized in the liver
- Drug may be released erratically
- Fluctuations increase risk of inconsistent symptom controls
- Associated with peak drug concentration in blood

### Physical, Biochemical, and Mechanical Approaches of Enhancing Transdermal Drug Delivery

#### Iontophoresis

- Iontophoresis — a mean of enhancing the flux of ionic compounds across a membrane by the application of an electric current.
- This technique has been reported useful for the enhancement of transdermal delivery of ionized drugs, including macromolecules.
- The skin is a multilayered organ delimiting the body constituted of several layers. The outermost layer, the stratum corneum, is the main barrier to drug transport.

#### Iontophoretic Drug Delivery System
### Iontophoresis Requirements
- A DC-powered dose controller designed and approved for iontophoretic drug delivery: microprocessor controlled with continuous self monitoring circuits
- A water-soluble drug that contains charged ions (many commonly used prescription drugs contain charged ions)
- Unbroken skin at the treatment site
- A drug delivery and grounding (dispersive) electrode

### Iontophoresis
- The application of electric current (< 1 mA/cm²) is able to increase the penetration of molecules through this barrier.
- The two principal mechanisms by which iontophoresis enhances molecular transport across the skin are:
  - Ionization/electrolysis — a charged ion is repelled from an electrode of the same charge
  - Electro-osmosis — the convective movement of solvent that occurs through a charged "pore" in response to the preferential passage of counterions when the electric field is applied.

### Iontophoresis Concerns
- Costly
- Drug stability
- Extent of skin metabolism
- Local irritation
- Deliver only small amounts per day

### IOMED's GelSponge®
- A primary function of an iontophoretic electrode is to ensure uniform skin wetting, which results in even current distribution and consistent drug delivery to the treatment site.
- IOMED’s GelSponge® iontophoretic electrodes incorporate a unique hydrogel drug containment element.

### IOMED’s GelSponge®
- Once hydrated with medication, the hydrogel drug containment element becomes jelly-like and creates an effective conductive medium that contours to virtually any treatment site.
  - This ensures that the entire surface of the electrode is in contact with the skin.
  - The hydrogel drug containment element changes color as medication is added.
  - This indicates that the electrode is hydrated properly and that there are no dry spots.
  - If a dry spot exists, no medication is being delivered in that area and it creates an uneven distribution of the current.

### IOMED’s TransQFlex®
- IOMED’s new shape with Gel technology gives an added advantage over other transdermal drug delivery systems.
- This shape increases the conformability of drug delivery, especially to areas of the body that make traditionally shaped electrodes more difficult to use.
- TransQFlex® GelSponge increases the ability to treat patients more comfortably, while increasing the ease-of-use.
IOMED’s Numby Stuff™

Numby Stuff™ electrodes teamed with Iontocaine® (brand of lidocaine 2% HCl with 1:100,000 epinephrine Topical Solution) provide clinically effective dermal anesthesia up to 10 mm depth in as little as 10 min. Numby Stuff™ is ideal prior to procedures that might otherwise be painful.

Electroporation

- Drug delivery using transient (∼10 μs) high-voltage (∼1 V) electrical pulses.
- Briefly applying an electric field to a living cell causes a transient permeability in the cell’s outer membrane.
  - This permeation is manifest by the appearance of pores across the membrane.
  - After the field is discontinued, the pores close in approximately one to 30 minutes without significant damage to the exposed cells.

Electroporation

- Electron micrographs of cells before and after brief electric pulses confirm that electroporation causes pores to open in cells during the pulse and to close after the pulse ceases.

Electroporation

- Permeability and electrical conductance of lipid bilayers in either living cells or metabolically-inactive systems (e.g., liposomes) are known to rapidly increase by many orders of magnitude and duration.

Electroporation

- Electroporation therapy to treat cancer by inducing, by electrical pulses, increased permeability of the cell membrane of cancer cells so that chemotherapeutic drugs (drugs that otherwise cannot enter the cell effectively) can accumulate inside the cell at relatively high concentrations and kill the cancerous cells.
  - The amount of drug used per treatment is much lower than in conventional chemotherapy and causes no or few side effects for the patient.
  - Clinical trials are ongoing for late stage squamous cell carcinoma of the head and neck, liver and pancreatic cancer, other accessible solid tumors, melanoma and other skin cancers.

Electroporation

- Intradermal and transdermal delivery of drugs — quickly and effectively delivering drugs, DNA or cosmetic substances.
  - Present programs include treatments to combat pain, erectile dysfunction, skin damage and osteoporosis.
  - DNA delivery into cells and tissues for gene therapy — treating diseases caused by single or multiple gene deficiencies.
  - Genetronics is funding and supplying electroporation devices for a Phase I study being conducted by the Toronto Hospital with the goal of treating hemophilia.

Sonophoresis

- Sonophoresis has the advantage that the compounds do not have to be ionised.
- The best explanation for the movement through skin seems to be explained as cavitation of the skin cells and membranes.
- This process of cavitation occurs during the treatment but these cavities disappear after the treatment and histological examination of the skin has shown that the skin is normal after the treatment.
- These may in fact be the same pores as are induced by iontophoresis.
Sonophoresis

- Contrary to expectation, cavitation of the skin occurs better the nearer one is to audible sound.
- In fact in the range of the sounds that dolphins emit their sonic messages, the best cavitation and penetration of molecules through skin is obtained.
- This range is at most only 10% of the sound that is used in conventional ultra-sound machines.
- ~ 4000% better penetration after five minutes of sonophoresis at 20 KHz than with topical application.

Sonophoresis

- Directions for use: Clients are generally recommended to have 24 treatments, twice weekly, but it could take up to 50 to 60 treatments to see results in severe cases.
- Sonophoresis, especially combined with Iontophoresis, treatments for upper lip lines should be done twice a week for a minimum of 24 treatments, but may require as many as 50 treatments to give significant lightening of upper lip lines and pigmentation in severe cases.
- Clients should continue their regular home care Proactive or ionzyme range regimes.