

Chapter 10

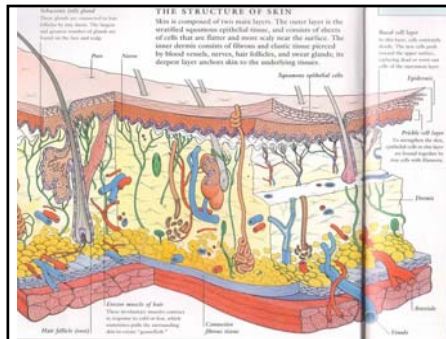
Transdermal Controlled Release Dosage Forms

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



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

- Physiochemical properties
 - Molecular weight < 500
 - Nicotine 162.23
 - Estradiol 272.37
 - Testosterone 288.41
 - Hydrophobic drugs are absorbed more easily
 - K_{octanol/water} 10-1000

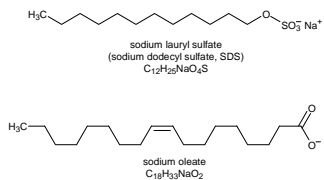
Criteria of Drug Selection

- Non-irritating
- Unreactive with patch components
- Must have an advantage over oral dosage form

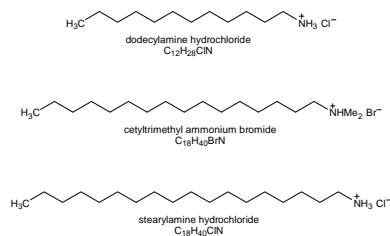
Enhancers and Excipients

- 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

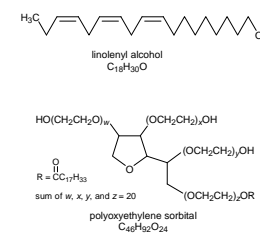
Anionic Surfactants



Cationic Surfactants



Nonionic Surfactants



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
- Longer Lasting, one patch lasts up to 3 days compared with a Dramamine tablet which only lasts up to 6 hours.



Transderm Scop® (1.5 mg scopolamine) - \$5 per patch
Dramamine (50 mg dimenhydrinate) \$7.33 / 24 tablets

Nitroglycerin Transdermal Patch



Product	Dosing Rate	Size	Units	Cost
Nitrek	0.2 mg/hr	8 cm ²	30	\$47.36
Nitrek	0.4 mg/hr	16 cm ²	30	\$54.01
Nitrek	0.6 mg/hr	24 cm ²	30	\$59.64
Nitrodisc	0.2 mg/hr	5 mg	30	\$54.13
Nitro-Dur	0.1 mg/hr	2.5 mg	30	\$45.18
Nitro-Dur	0.2 mg/hr	5 mg	30	\$44.68
Nitro-Dur	0.3 mg/hr	7.5 mg	30	\$50.35
Nitro-Dur	0.4 mg/hr	10 mg	30	\$51.40
Nitro-Dur	0.6 mg/hr	15 mg	30	\$53.50
Nitro-Dur	0.8 mg/hr	20 mg	30	\$54.55

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

Estrogen Transdermal Patches

- Climara® (3M & Berlex Labs)
 - First once a week patch
- Prodynova® TS (Schering)
 - ~100 µg/day for 7 days
- Fematrix® (Europe & Asia)
 - 3-4 or 7 days
- Menorest® (Noven)



Estrogen Transdermal Patches



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 17-β estradiol and orethindrone acetate, a progestogen. It is the first combination transdermal therapy system approved for marketing by the FDA.

Clonidine Transdermal Patch

	Programmed Delivery in vivo per day over 1 week	Clonidine (mg)	Size (cm ²)
Catapres-TTS-1	0.1mg	2.5	3.5
Catapres-TTS-2	0.2mg	5.0	7.0
Catapres-TTS-3	0.3mg	7.5	10.5

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.

Catapres-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.



Dose (mcg/hr)	Size (cm ²)	Fentanyl content (mg)
25	1.0	2.5
50*	2.0	5.0
75*	3.0	7.5
100*	4.0	10.0

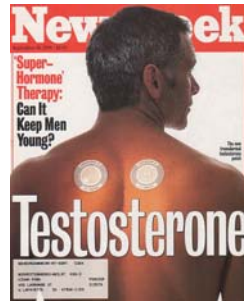
*For opioid-tolerant patients only.

Fentanyl Transdermal Patch

- The reservoir contains the drug in an aqueous ethanolic solution that has the dual purpose of enhancing the permeation of ethanol through the skin and reducing the amount of fentanyl by limiting its solubility.

Oral 24-hour morphine (mg/day)	DURAGESIC dose (mcg/hr)
45 – 134	25
135 – 224	50
225 – 314	75
315 – 404	100
405 – 494	125
495 – 584	150
585 – 674	175
675 – 764	200
765 – 854	225
855 – 944	250
945 – 1034	275
1035 – 1124	300

600 mcg/24 hr



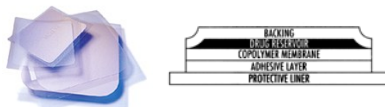
Testoderm®



TESTODERM® WITH ADHESIVE is composed of three 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 fluorocarbon diacrylate-coated polyester that must be removed before application covers the adhesive stripes and the adhesive-free area of the drug film

Testoderm

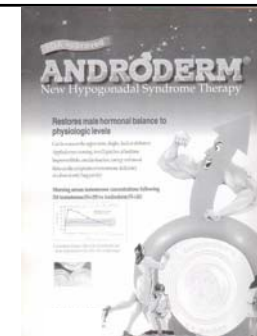


TESTODERM® TTS is composed of the following layers:

- a flexible backing of transparent polyester/ethylene-vinyl acetate copolymer film
- a drug reservoir of testosterone and ethanol gelled with hydroxypropyl cellulose
- an ethylene-vinyl acetate copolymer membrane coated with a layer of a polyisobutylene adhesive formulation that controls the rate of release of testosterone from the system
- a protective liner of silicone-coated polyester covers the adhesive surface that must be removed before application

Testoderm

Patches	Manufacturer	Dosing	Price	Administration
Testoderm® (testosterone transdermal system)	Alza Pharmaceuticals	6 mg/day 60 cm ² patch	\$3.40	Applied daily to scrotum.
		4 mg/day 40 cm ² patch	\$3.40	Applied daily to scrotum.
Testoderm with adhesive® (testosterone transdermal system)	Alza Pharmaceuticals	6 mg/day 60 cm ² patch	\$3.40	Applied daily to scrotum
Testoderm TTS® (testosterone transdermal system)	Alza Pharmaceuticals	5 mg/day 60 cm ² patch	\$3.60	Applied daily to arm, back, or upper buttocks
Androderm® (testosterone transdermal system)	SmithKline Beecham Pharmaceuticals	5 mg/day (two 2.5-mg, 37 cm ² patches, or one 5-mg, 44 cm ² patch)	\$1.95 \$3.40	Applied daily to back, abdomen, upper arms, or thighs



Fatigued?
Depressed mood?
Low sex drive?
Could be your testosterone is running on empty.

Ask your doctor if AndroGel is right for you.
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AndroGel
(testosterone gel) 1% Ointment
Testosterone restored

Salicylic Acid Patch

Trans-Ver-Sal

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, *Artemisia vulgaris*, is placed over an inflamed or affected area on the body.
- The cone is placed on an acupuncture point and burned.
- The cones is removed before burning the skin.
- The purpose is to stimulate and strengthen the blood and the life energy, or *qi*, of the body.

Moxibustion

Mugwort (*Artemisia vulgaris*)

CC1=C(C)C(=O)C1

β -thujone

Surgery or acupuncture? Antibiotics or herbs? BOTH ARE BETTER. More and more M.D.s are mixing ANCIENT MEDICINE and NEW SCIENCE to treat everything from the common cold to heart disease.

The Healing REVOLUTION

Jasmine gets acupuncture.
• "No animal says, oh, yes, please."

Acupuncture can work, and it's not just wishful thinking

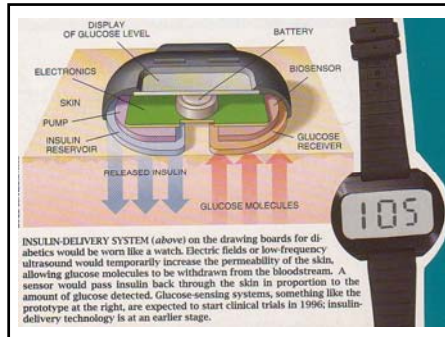
Acupuncture may be the answer. Wei Shengchu demonstrates in China, inserting 1,138 needles into his head.

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

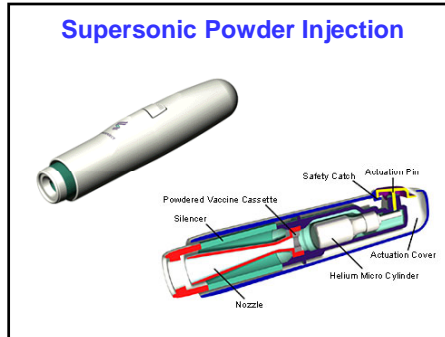
- The GlucoWatch® Biographer can measure glucose levels automatically every 20 min
- Consists of two integrated parts
 - Biographer
 - AutoSensor
- An extremely low current is used to pull glucose through the skin.



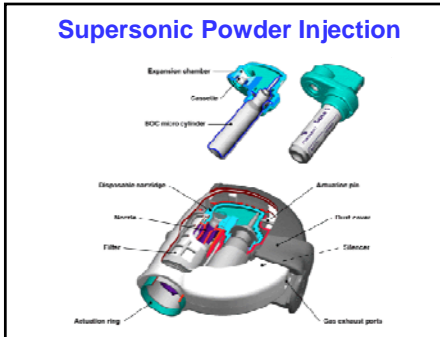
PowderJect®

- 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.

Supersonic Powder Injection



Supersonic Powder Injection



DNA Vaccines

Category / Product	Status	Partner
Hepatitis B Prophylactic	Phase I	GlaxoSmithKline
Hepatitis B Therapeutic	Phase I	GlaxoSmithKline
HIV Therapeutic	Preclinical	GlaxoSmithKline
HIV Prophylactic	Preclinical	GlaxoSmithKline
HPV Therapy for Genital Warts	Preclinical	GlaxoSmithKline
Undisclosed Infectious Disease	Preclinical	GlaxoSmithKline
Influenza	Preclinical	PowderJect
Herpes Simplex Virus	Preclinical	PowderJect

Human Vaccines

Vaccine type	Pathogens/diseases with licensed vaccine
Polysaccharide	pneumococcus, meningococcus, typhoid VI
Polysaccharide conjugate	haemophilus influenzae B
Native subunit	diphtheria, tetanus, pertussis
Recombinant subunit	hepatitis B, lyme disease
Inactivated whole pathogens	influenza, pertussis, rabies, Japanese encephalitis, polio, hepatitis A
Live attenuated	mumps, measles, rubella, rotavirus, cholera, polio, chickenpox, yellow fever, tuberculosis, vaccinia

Jet Injections

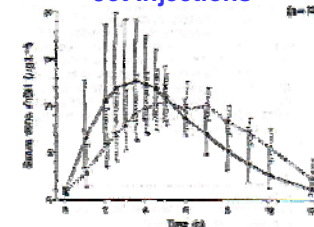
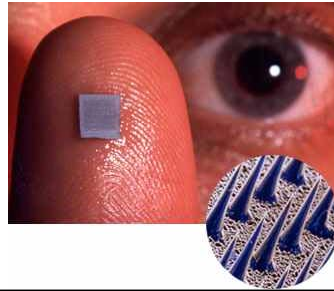


Fig. 5 Plasma concentrations of DNA (pneumococcal DNA) after jet injection (—○—) and needle-injection (---□---). The jet injection was below the lower limit of quantification (1.1–10 µg ml⁻¹) in all subjects at 88–38 min after dosing.

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

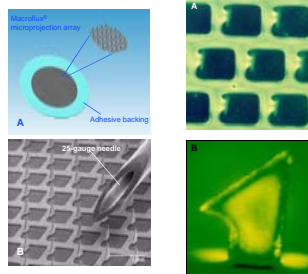


Alza's Macroflux™ Technology

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



Macroflux™



Macroflux™



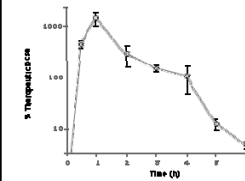
Macroflux™ skin interface technology incorporates a thin titanium screen with precision microprojections that, when applied to the skin, create painless, superficial pathways through the skin's barrier layer to allow for transportation of macromolecules.

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 electrotransport 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.

Macroflux™

Performance of Macroflux™ Transdermal Systems
Peptide-Coated Macroflux™ Patch Delivers Target Dose Rapidly



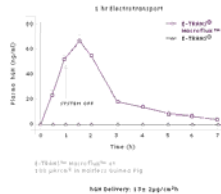
In preclinical animal tests, peptide-coated Macroflux™ can deliver a bolus dose with peak therapeutic plasma levels observed within one hour after administration.

Reference: Nelson, J.G. et al. (1998) *Journal of Pharmaceutical Sciences*, 87(12), 1485-1491.

Macroflux™

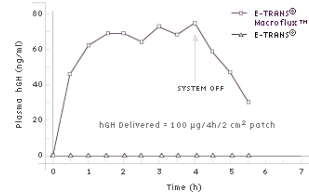
E-TRANS® Macroflux™ Delivers Human Growth Hormone In Vivo

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.



Macroflux™

4 hr Electrotransport

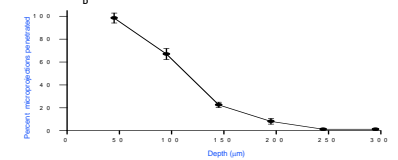


hGH Delivered = 100 µg/4h/2 cm² patch

E-TRANS™ Macroflux™ at 100 µA/cm², 2cm² patch in Hairless Guinea Pig

hGH Delivery: 132 2µg/cm²h

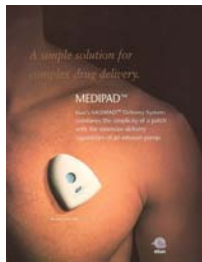

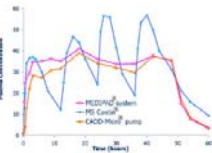
Macroflux™



Medipad™

A simple solution for transdermal drug delivery.


Medipad™ contains a reservoir of drug, a reservoir of gas, and a reservoir of an electrolyte.

Medipad™



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.

Veterinary Products

WORKINGKNOWLEDGE

Killer Drops

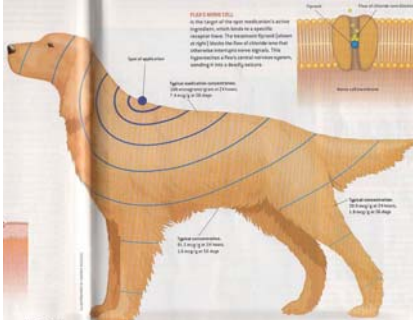
"SPOT" FLEA TREATMENTS mix with a pet's skin oils. A few drops disperse readily. Tests by maker Meril on midsize dogs given the recommended dose of the treatment fipronil show that concentrations quickly spread across the body. And although concentrations are low after 56 days, they are still high enough to kill fleas (95 percent of fleas die when exposed to 0.7 microgram per gram of fur).



Veterinary Products

INSECTICIDE

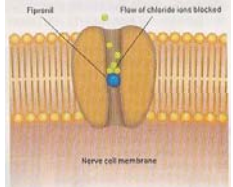
[blue] is stored in a hair's sebaceous gland, which can secrete the compound for a month or more.

Veterinary Products


Fipronil

FLEA'S NERVE CELL is the target of the spot medication's active ingredient, which binds to a specific receptor there. The treatment fipronil (shown at right) blocks the flow of chloride ions that otherwise interrupts nerve signals. This hyperexcites a flea's central nervous system, sending it into a deadly seizure.



Nicotine

- Chemical Name: S-3-(1-methyl-2-pyrrolidiny)-pyridine
- Molecular Formula: C₁₀H₁₄N₂
- Molecular Weight: 162.23
- Ionization Constants:
 - pK_{a1} = 3.04
 - pK_{a2} = 7.84
 - at 15 °C



S-(-)-nicotine

Nicotine Transdermal Patch

1992

Nicotine patch now available

A new method to help smokers kick their habit has become available by prescription in the United States. The system, called the nicotine transdermal system, consists of a patch that would be nonadhesive applied to a different area of skin each day. The patch contains some nicotine—the active, addictive, substance in cigarettes. The nicotine diffuses through the skin into the person's bloodstream and then travels to the brain, reducing his or her craving for a cigarette. Sold under a number of brand names, such as "Nicoderm" and "Habitrol", the system does not cure nicotine addiction. However, by using it to give up smoking, the addict does at least avoid one of the main health risks of cigarettes, which comes from the tar in cigarette smoke entering the lungs.



The nicotine patch is applied to the skin.

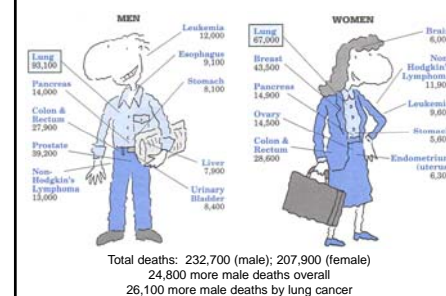
Nicotine Transdermal Patch



Nicotine Transdermal Patches

Product Name	Reservoir	Polymer	Release Rate	Company
Nicoderm®	EVA copolymer matrix (reservoir device)	Polyethylene	40 µg/cm ² /h (24 h)	Alza Marion Merrell Dow
Habitrol®	Methacrylic acid copolymer solution in a gauze (monolithic device)		29 µg/cm ² /h (24 h)	Lohmann Ciba-Geigy
ProStep®	Hydrogel (monolithic device)		130 µg/cm ² /h (24 h)	American Cyanamid (Elan-Lederle)
Nicotrol®			(16 h)	Parke-Davis (Cygnum-McNeil)

Annual US Cancer Deaths

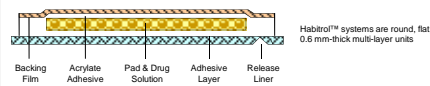


Nicotine Transdermal Patches

- 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.

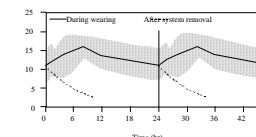
Habitrol™

- 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)



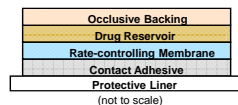
Habitrol™

- Two consecutive applications of Habitrol™ 21 mg/d system
- Nicotine concentrations peak $\sim 6-12$ h
- Decline of drug during last 12 h is determined by release through skin
- An open two-compartment disposition model with a skin depot



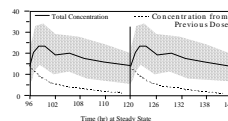
Nicoderm®

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



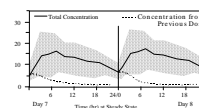
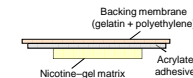
Nicoderm®

- Slow decline of plasma nicotine concentration during 4–24 h is determined primarily by release of nicotine from the system
- The absorption rate of nicotine from the skin depot to the blood is slower than the elimination rate
- Open two-compartment disposition model with skin depot



Prostep®

- Prostep® 22 mg/d system
- Nicotine concentrations increase to a peak $\sim 4-12$ h
- Open two-compartment disposition model with a skin depot





NRT Products			
Type	Name	Strength of nicotine available	Information
Patch	Nicorette	15 mg, 10 mg, 5 mg for use over 16 hours	Boxes of 7
	Nicotinell TTS	21 mg, 14 mg, 7 mg for use over 24 hours	Boxes of 2, 7 or 21 (21 mg), 2 or 7 (14 mg), 7 (7 mg)
	Niquitin CQ	21 mg, 14 mg, 7 mg for use over 24 hours	Boxes of 7 or 14 (21 mg), 7 (14 mg or 7 mg)
Gum	Nicorette	2 mg or 4 mg original or mint flavor	Boxes of 15, 30 or 105
	Nicotinell	2 mg or 4 mg original, mint or fruit flavor	Boxes of 12, 48 or 96 Chew for slowly for 30 minutes. Use a maximum of 15 pieces in 24 hours
Inhalator	Nicorette Inhalator	Mouthpiece with 10 mg cartridges	6 Cartridge starter pack and 42 cartridge refill
Lozenge	Nicotinell Lozenge	1 mg mint	Use 6-12 cartridges daily, boxes of 12, 36 and 96 Use a maximum of 25 lozenges in 24 hours
Sublingual Tablet	Nicorette Microtab	2 g tablets. Max of 40 tablets per day	Starter pack—2 x 15 tablet discs, refills of 7 x 15 tablet discs. Use a one or 2 tabs of once per hour to maximum daily dose of 80 mg
Nasal Spray	Nicorette Nasal Spray	0.5 mg nicotine spray per puff per dose. Max 32 puffs per nostril per day	200 spray dispenser. One spray per nostril twice an hour—max 64 sprays daily

Nicotine Replacement Therapy

Pharmacologic Aid	Year Introduced	Delivers Nicotine Systemically	Availability
Bupropion HCl non-nicotine pill	1997	No	Rx
Nicotine inhaler	1997	Yes	Rx
Nicotine nasal spray	1996	Yes	Rx
Nicotine transdermal patch	1991	Yes	OTC/Rx
Nicotine gum	1984	Yes	OTC

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

CN(C)C(=O)c1ccc(Cl)cc1

bupropion HCl

23% PLACEBO (n=100)

49% ZYBAN (n=100)

just a PILL

Buspirone Transdermal Patch

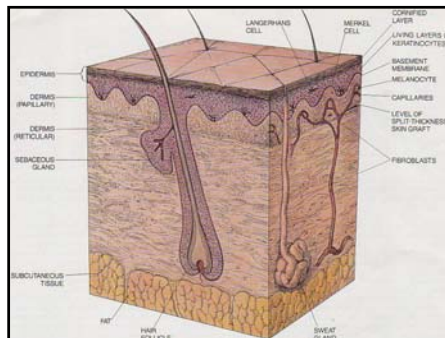
- Once-a-day transdermal patch
- Attention deficit hyperactivity disorder (ADHD) in children
- Open-label 8-wk study showed 70–80% of patients were "much improved or very much improved"
- Oral dosing is metabolized in the liver
 - Drug may be released erratically
 - Fluctuations increase risk of inconsistent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

CN1CCN(C1)CC2=CN=CN=C2

buspirone HCl

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.



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** ($< 1 \text{ mA/cm}^2$) 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 counter-ions when the electric field is applied.

Iontophoresis

- Ionization/Electrolysis Mechanism
 - **Drug must be ionized**
 - Electrode contains a solution of ions of the same polarity
 - Ions are repelled from the electrode into the body
 - Anions are repelled at the cathode
 - Cations are repelled at the anode
 - Chose drug with proper polarity

Iontophoresis

- Iontophoresis permeation is thought to occur through rare negatively charged **pores of 20–25 Å radius**.
 - Increases possibility of peptide delivery
- Iontophoresis is **not very efficient**
 - Only a fraction of the charge is used in drug delivery

Iontophoresis

- Skin is negatively charged at physiological pH (neutral at pH 3–4)
 - Enhances migration of cations at the anode
- **Electro-osmosis**
 - Water carries drug through skin
 - Other dissolved substances may also be carried through

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™

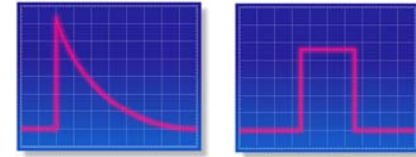
Numby Stuff™ electrodes teamed with Iontocaine® (brand of lidocaine 2% HCl with 1:100,00 epinephrine Topical Solution) provide clinically effective dermal anesthesia up to 10 mm depth in as little as 10 min. Numby Stuff™ is ideal prior to procedures that might otherwise be painful.



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



Exponential decay pulse produces a field that quickly rises to full strength, then gradually fades away.

The gentler alternative to the exponential decay pulse, the square wave quickly rises to full strength in a few millionths of a second, remains at that level for about a ten-thousandth of a second and then almost instantly declines.

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.



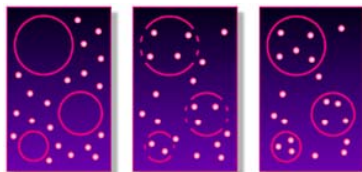
Electroporation

- 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



The electroporation process (from left to right): the drug or gene is mixed with the cells; a pulse is applied and pores form in the cells allowing the drug or gene to enter; after the pulse the pores reseal and the drug or gene remains in the cell.

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 Iontophoresis 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.



Sonophoresis

