Methods of Drug Delivery

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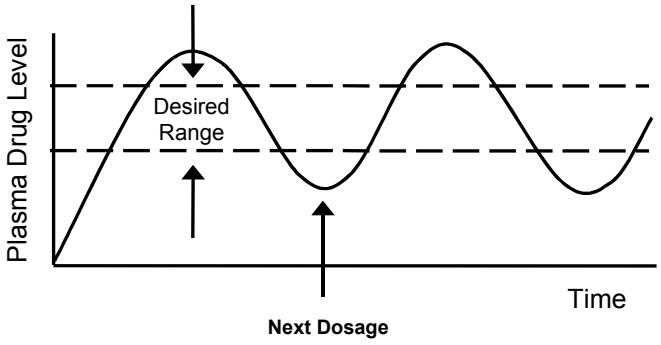
I. Introduction:

The means by which a drug is introduced into the body is almost as important as the drug itself. Drug concentration at the site of action must be maintained at a level that provides maximum therapeutic benefit and minimum toxicity. The pharmaceutical developer must also consider how to transport the drug to the appropriate part of the body and, once there, make it available for use.

As the name implies, a controlled-release drug delivery system serves two functions:

1. Drug delivery, involves the absorption and transport of the drug to a particular part of the body. This may be accomplished intravenously, transdermally, orally, by implantable reservoir, etc.
2. Controlled release governs the rate at which the drug is made available to the effect site once it has been delivered.

Traditionally, delivery systems have not incorporated means of controlled release. This means that the concentration of most drugs peaks and declines rapidly after each dose and will often be above or below the desired therapeutic range.

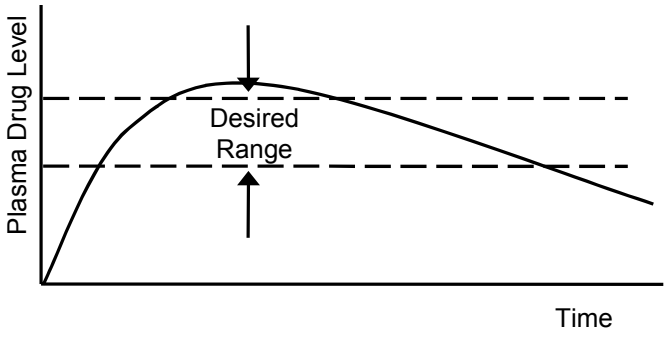


II. Sustained Release

Sustained release is an incremental improvement. It provides prolonged but not uniform release of drug and reduces the need for repeated dosing. Once the maximal level is reached, the amount of drug in the body decreases slowly so it will take longer to drop below the therapeutic range. Sustained release technologies in current use include

1. Complexes
2. Slowly dissolving coatings
3. Suspensions
4. Emulsions
5. Compressed tablets

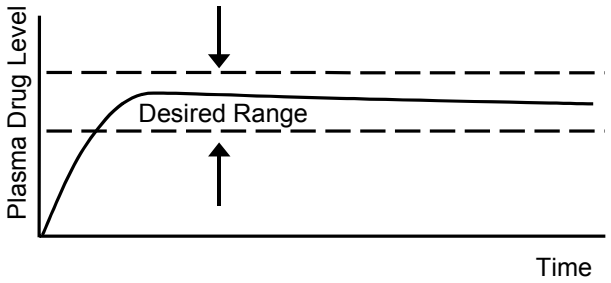
Release rates are strongly influenced by environmental conditions
Release rarely lasts longer than 12 hours; so the benefits are limited.



III. Controlled Release

This is a substantial advance over sustained release. Technologies include
1. Polymers
2. Pumps

Weakly influenced by local environment (fixed release pattern)
Release can occur over long periods



IV. Targeted (Controlled) Release

Controlled release technology designed to maintain relatively high concentrations at a specific site. Techniques include
1. Liposomes
2. Microspheres and microcarriers
3. Drug-carrier complexes (pendant systems)

V. What is driving growth of this technology?

Consider U.S. Annual Statistics
1. Adverse Drug Effects
   - 15% of hospital admissions
   - 100,000 deaths
   - $136 billion in health care costs
2. Patient Compliance
   - 10% of hospital admissions
3. 2001 Sales of Drug Delivery Systems
   - $20 billion

Multiple incentives for manufacturers to use controlled release:

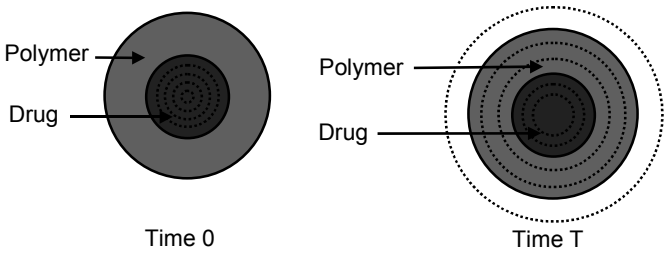
1. Therapeutic
   - Increase efficacy (more consistent exposure to adequate levels)
   - Decrease toxicity (more consistently avoiding toxic levels)
   - Increase compliance (less reliance on remembering pills, etc.)
2. Commercial
   - Increase patient and physician acceptance
   - Extend patent life (old drug sold in new patentable form)
   - Avoid costs of developing a new chemical entity

Polymeric Controlled Release Delivery Systems

Generally, 4 broad categories:

1. Diffusion controlled (reservoir systems, matrices)
2. Chemically controlled (bioerodable, pendant chain)
3. Solvent controlled (swelling, osmosis)
4. Externally activated or modulated

I. Reservoir Systems



1. Forms: capsules, microcapsules, hollow fibers, membranes
2. Most common polymers—silicone, eva, hydrogels
3. Advantages:
   - Zero-order release is possible with right geometry
   - Easy to control kinetics by design parameters
4. Disadvantages:
   - Must be implanted and removed
   - Impermeable to high MW drugs
   - Expense
   - Leaks can be dangerous (large quantity of drug soln.)

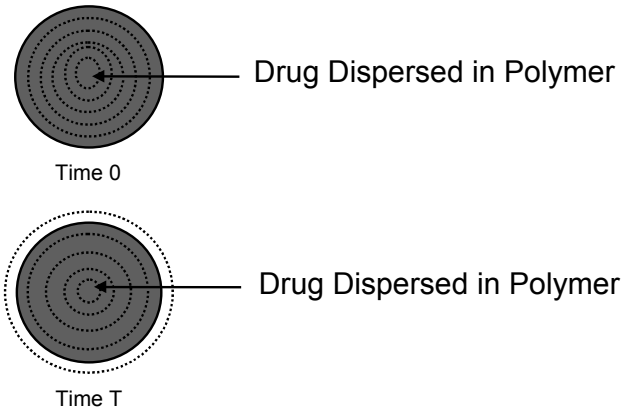
- $Flux = -D\frac{DC_m}{DX}$

Release rate for a <u>cylindrical</u> reservoir:

$$\frac{dM}{dT} = \frac{2\pi HDK(C_s - 0)}{\ln\left(\frac{R_o}{R_I}\right)}$$

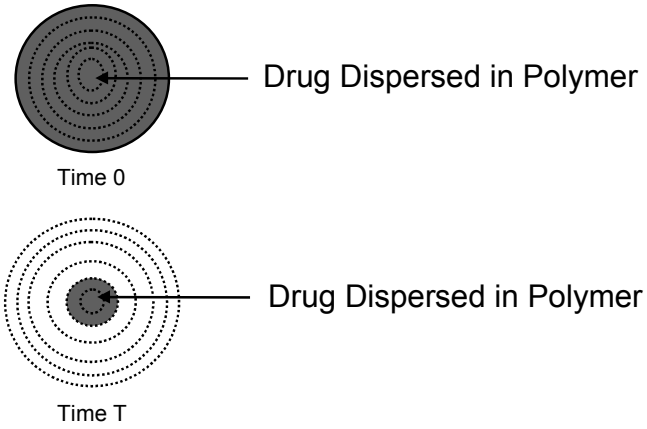
Where dM/dT = release rate
H = height
D = diffusion coefficient of drug in polymer
K = partition coefficient
C_s = drug solubility in surrounding media
R_o = outer radius
R_I = inner radius

II. Non-erodable Matrix



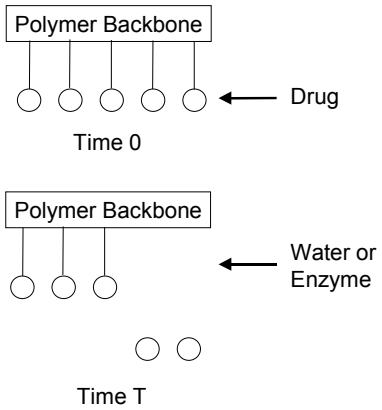
1. Advantages:
   - No leakage
   - Easily made
   - High MW compounds can be delivered
2. Disadvantages:
   - Not zero-order
   - Must be removed

III. Bioerodable Systems



1. Zero-order if only surface erosion occurs and surface area does not change with time
2. Examples include poly-lactic acid, polyaminoacids, polyorthoesters, and polyanhydrides
3. Advantages
   - removal is not a problem
4. Disadvantages
   - there are few biodegradable materials
   - release kinetics are often hard to control
   - by-products of degradation may cause toxicity or tissue damage

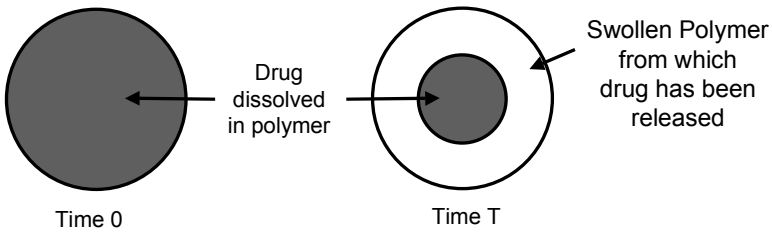
IV. Polymers with Pendant Drugs



1. Drug covalently attached to polymer
2. Advantage: very high drug loading

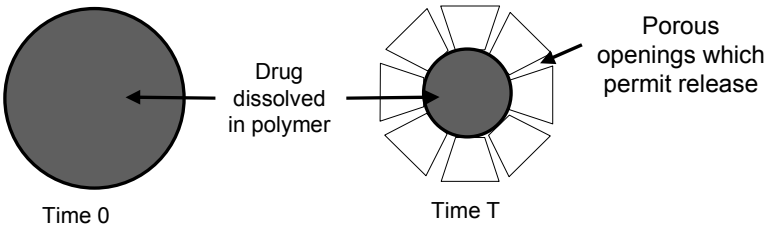
3. Disadvantage: new chemical entity - expense

V. Swelling Controlled Matrix



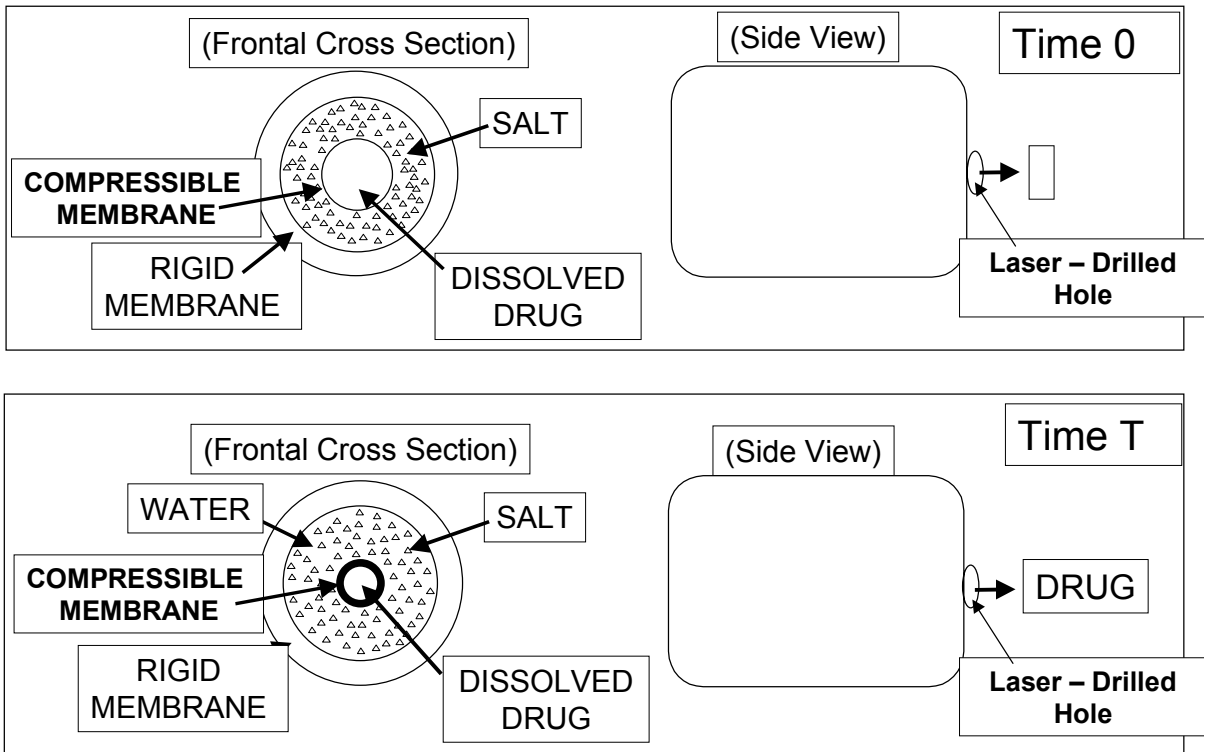
1. Drug is dissolved in polymer and is released when polymer swells
2. Advantage
   - no burst effect
   - reformulation of vehicle not necessary for different drugs
3. Disadvantage
   - Experimental systems—generally do not have water as permeant

VI. Osmotically Controlled System



1. Drug is dissolved in polymer and porous openings permit entry of fluid and release of drug along osmotic gradient

2. Advantage
- Osmosis is a constant driving force
3. Disadvantage
- Hard to achieve zero-order release unless put in an osmotic pump system



Specific Controlled Release Systems: Implants, Aerosol, Inserts, Brain Delivery, Oral Delivery

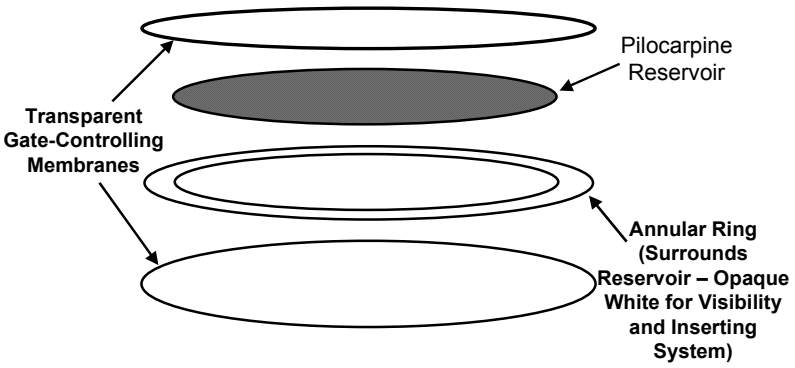
1. Potential Advantages:
- Drug levels are continuously maintained in a therapeutically desirable range
- Harmful side effects from systemic administration can be reduced or eliminated by local administration from a polymer-drug depot
- Drug administration may be improved and facilitated in underprivileged areas where good medical supervision is not available
- Administration of drugs which have short in vivo half lives may be facilitated greatly
- Continuous small amounts of drug may be less painful than several large doses of drug
- Patient compliance may be improved
- Drug delivery by this method is potentially less expensive and wasteful of the drug

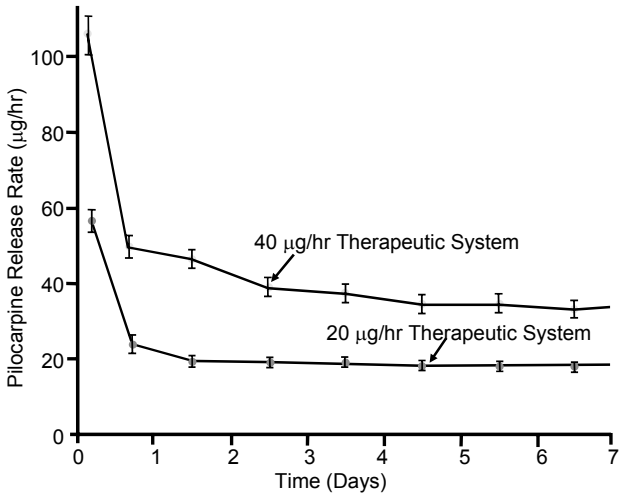
2. Potential Disadvantages:

- Toxicity or lack of biocompatibility of the polymer material used
- Production of harmful by-products from the polymer if it is degradable
- Surgical operations to implant the polymer in an appropriate location
- Discomfort to the user
- Expense of a particular polymer-drug formulation due to the cost of the polymer or the fabrication procedure
- Assurance of adequate safety features so that leaks or other factors leading to inadequate control are eliminated
- Difficulty of removal in the case of complications

A. Ocular Applications:

1. Glaucoma: Occusert





Occusert Advantages:

- Control of intraocular pressure with less drug and fewer side effects
- Convenience of once-a-week application
- Improved compliance
- Assurance of round-the-clock medication

Occusert Disadvantages:

- Retention
- Discomfort
- Leakage
- Expense
- Low initial acceptance, particularly by older patients

2. Artificial tears:

Goals:

- A wetting agent to stabilize the tear film and improve adherence to the corneal surface

Merck:

- Hydroxypropylcellulose

Advantages:

- Comfort

Disadvantages:

- Poor retention
- Discomfort
- Blurred vision
- Difficulty in insertion

B. Contraceptive Systems:

- Non-erodible subdermal implants
  - **Norplant** – silicone capsules containing Levonorgestrel. Implanted by trocar injections into forearm
    - 2 capsules, release rate = 3.8 μg/cm length/day = 70 μg/day TOTAL
    - Plasma level: 0.3ng/ml, 2-3 times higher in arm containing device
    - Effective with few side effects; perception in 3rd world that injection more effective than oral
    - Reasons for discontinuation:
      - Menstrual irregularity
      - Other factors: pain, appearance, feel

- Erodible subdermal implants:
  - Alza – Levonorgestrel and norethindrone : limited studies on norethindrone in humans shows zero-order release (allergic reactions observed)
  - Poly (ε-caprolactone): 6-month constant release
  - Injectable microcapsules – lactic/glycolic acid copolymer and rods
- Steroid releasing iuds (intrauterine device) –
  - Advantages: Less menstrual bleeding, improved compliance, and comparable pregnancy and expulsion
  - Disadvantages: Intrauterine inflammation, increased incidence of ectopic pregnancies
- Vaginal rings

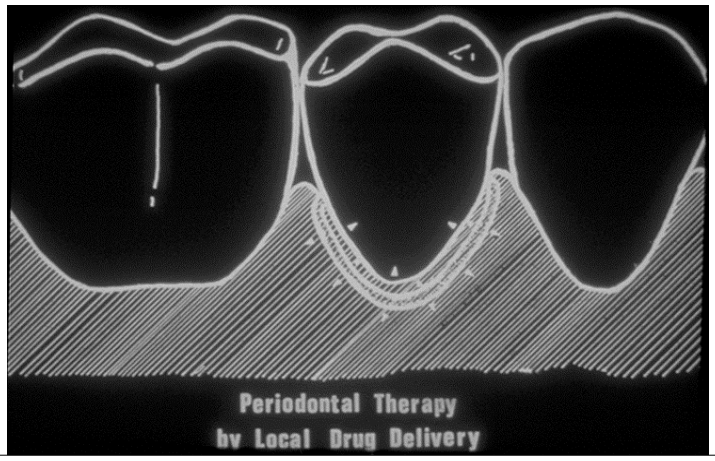
C. Periodontal Disease

- Percent with evidence of periodontal disease – 25%
- Percent requiring surgery – 2-3%

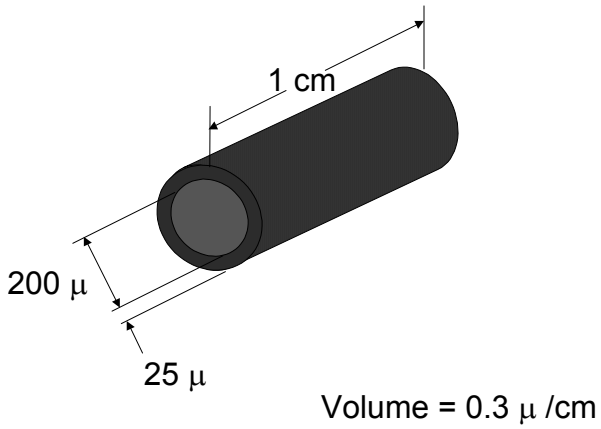
Current Therapy	Problems
None	Tooth Loss
Surgery	Pain, Expense
Oral Tetracycline	Nausea, diarrhea

1. Tetracycline hollow fibers:

- Are effective with less than 1/1000th of the dose
- Can be applied in less than 3 min. per tooth
- Barely visible, no local irritation
- Caused elimination of spirochetes



Placement of the drug-filled hollow fibers for local treatment of periodontal disease. Single strands of tetracycline-filled hollow fibers are placed around the tooth and gently pressed around the margin of the gingiva.



D. Coated intracoronary stents:

Problems to solve: atherosclerosis, restenosis
Polymers: ethylene-vinyl acetate, Pluronics
Drugs: Heparin, antisense DNA
Good initial results in animal models

- JOHNSON & JOHNSON
  - Drug- Sirolimus (Rapamune)
    - A lactone approved for renal transplant rejection
    - Polymer blend- acrylates used in bone cements, ocular lenses, and IUDS -poly(ethyl acrylate), n - butyl methacrylate

- Results
  - 100% effective 2 years later - no restentosis
- Survival
  - 94% at 12 months treated
  - 71% at 12 months Controls
- Other companies
  - Other companies use Taxol, Heparin, and other drugs

E. LHRH analogs

- Lupron – Takeda – Abbott
- One to four month release for advanced prostate cancer
- Injected through a 22 gauge needle: 75mg leuprolide acetate, 1.3mg gelatin, 66.2 mg DL lactic glycolic acid, 13.2mg D-mannitol

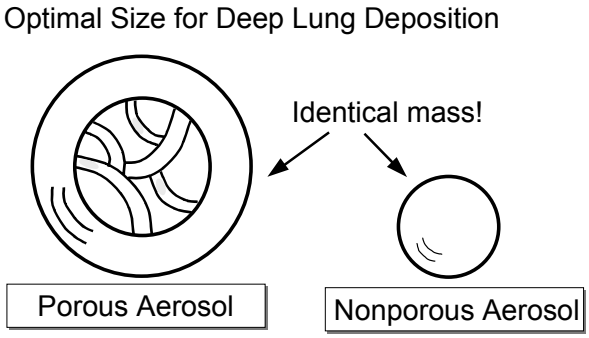
F. Glioblastoma Multiforme

- Statistics-Uniformly Fatal Disease

Treatment	*Median Life Expectancy (weeks)*
None	4
Surgery	16
Surgery and radiation	40
Surgery, Radiation and Chemorx	50

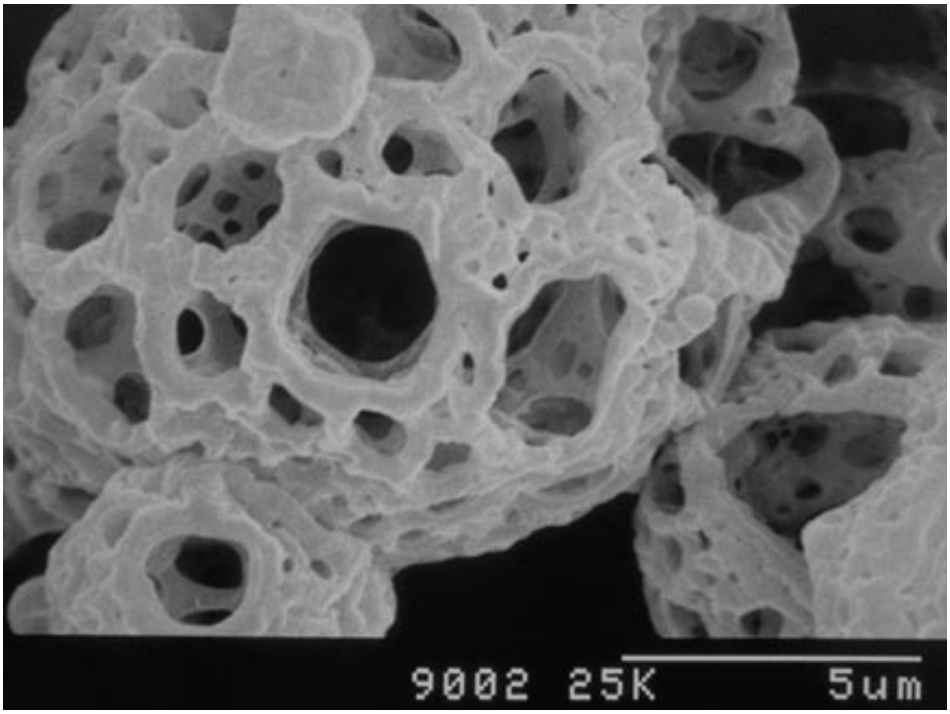
- Principles of therapy:
  - Line the surgical cavity with BCNU polymer
  - BCNU half-life = 12 minutes
  - Polymers protects BCNU from degradation
  - Polymer localizes drug, reducing systemic toxicity

G. Advantages of Porous Aerosols for Inhalation Therapy

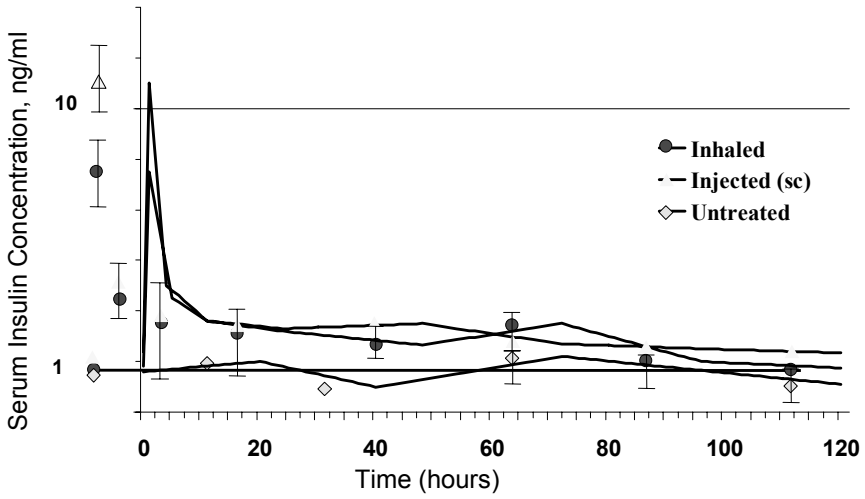


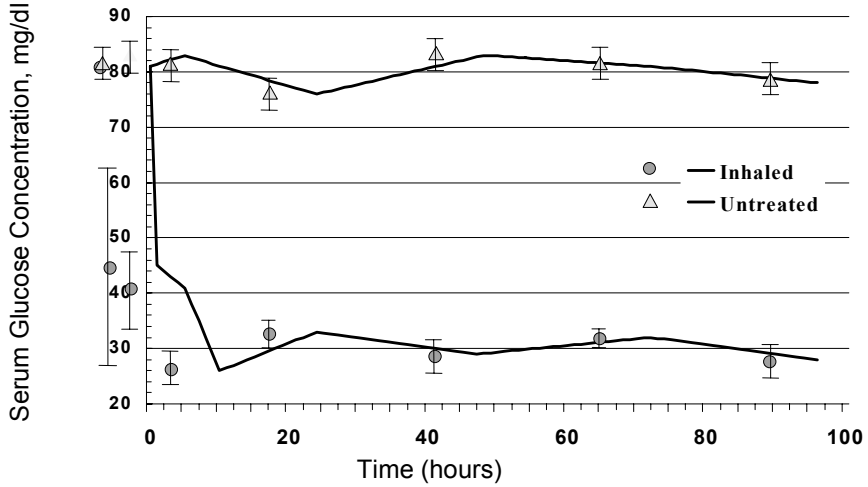
Advantages of large size for therapeutic aerosols

- Easier aerosolization and flowability
- Less prone to phagocytosis



Aerosol insulin:





Implanted Pumps

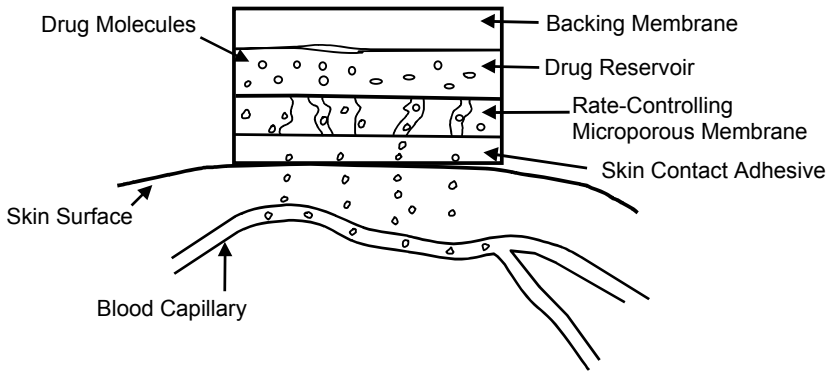
1. Advantages:
   - Can release drug directly into venous or arterial blood
   - Large volumes possible
   - Some are refillable
   - Releases drugs independently of the drugs' properties

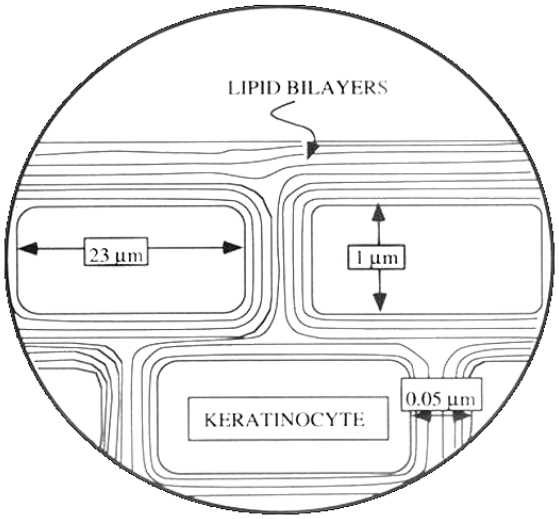
2. Disadvantages:
   - Expense
   - Need for surgical implantation
   - Contents are in solution
   - Difficult to reformulate

Transdermal Systems

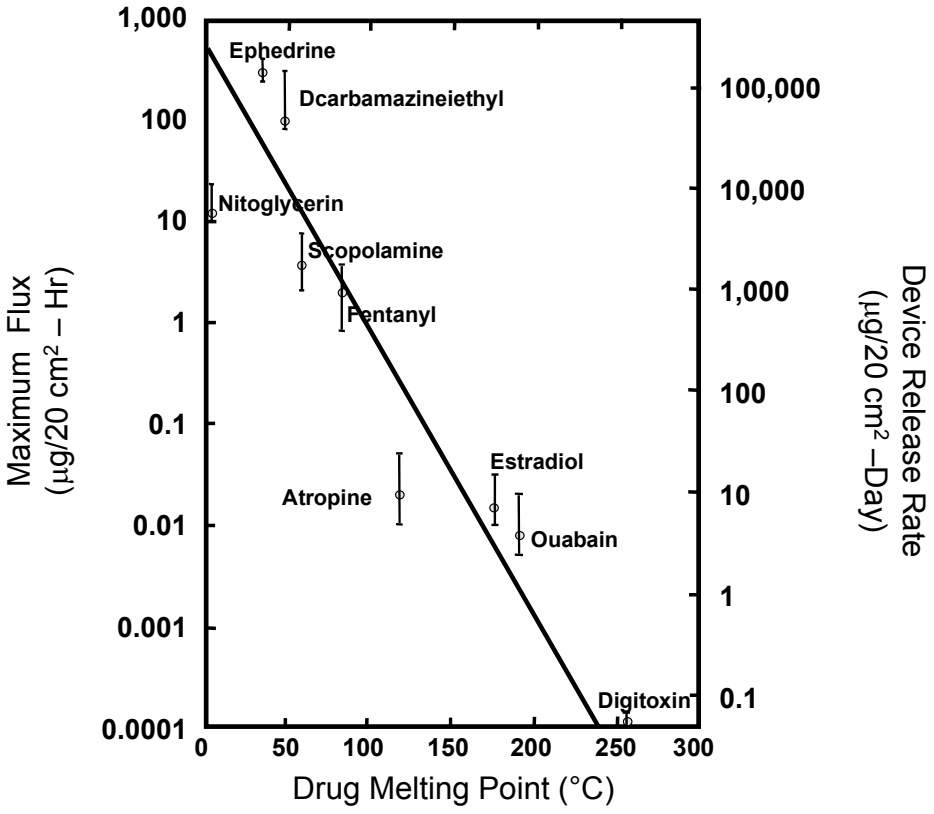
1. Skin generally impenetrable (principal resistance is stratum corneum)
2. Permeability correlates with drug's water solubility, molecular weight, and oil/water partition coefficient
3. Useful for drugs with low dose requirement, high skin permeability
4. Permeability can be enhanced by certain compounds
5. The system provides simple localization. It is easy to apply and remove.
6. Reduces first pass metabolism
7. Drawbacks: lag time to achieve effect (2-6 hours or more) in some cases; drug in skin may sustain effect even if device is removed

General rules for transdermal product:
1. Water solubility > 1 mg/ml
2. Oil solubility > 1 mg/ml
3. Molecular weight < 1000
4. Dose < 10 mg/ml
5. No requirement for rapid onset





Ordered Lipid Bilayers Make Stratum Corneum Impermeable



Transdermal Products:

1. **Scopolamine: Transderm Scop**
   - Multilaminate systems (0.2 mm thick)
   - Microporous polypropylene – rate limiting barrier
   - 2.5cm^2 surface area – delivers 0.5 mg over 3 day period
   - Reservoir contains 1.5mg of scopolamine in mineral oil and polyisobutylene
   - Adhesive contains 200 mcg priming dose

Site Of Permeation	*Total Drug Permeated after 22 hrs. (mg/cm2)*
Post Auricular	475
Back	300
Chest	275
Stomach	250
Forearm	150
Thigh	40

Donor Solution: Scopolamine free base in mineral oil after 4.7 mg/gm at 30°C

2. **Nitroglycerin: Transderm - Nitro**

- Alza – CIBA
- Microporous membrane (ethylene-vinyl acetate copolymer(rate limiting barrier)
- Delivers 0.5mg/cm^2/day
- Nitroglycerine adsorbed on lactose and dispersed in a colloid suspension of silicone dioxide
- Reservoir contains 5 times the amount delivered
- About 8% of nitroglycerine diffused into adhesive layer during storage

Problems:
- Tolerance generally occurred (treadmill test used) – mechanism unknown
- Even doses 10 times higher than conventional fail to overcome tolerance
- Patches still useful for patients with high frequency (more than 7 a week) of anginal attacks
- On-off patches may be useful

3. **Catapres - TTS® -1 :** Clonidine

4. **Other systems:**
- Nicotine
  - Four systems commercialized
  - Unusual problem - too high a flux
  - Can use low permeable membranes like polyethylene to control flux
  - Need very dense backing membranes
  - 16 - 24 hour systems

- Fentanyl
  - Sizes up to 40 sq. cm
- Testosterone
  - ALZA - Scrotal delivery
  - Theratech – Watson uses enhancer
- Estradiol/Progesterone

Methods of Enhancement:

- Iontophoresis
  - Useful for polypeptide when stratum corneum is removed and will probably be useful for peptides
- Electroporation
  - Early stage, but very good
  - Potential - 10^4 increase in permeation
- Ultrasound
  - Eliminates lag time
  - Potential - 10^5 increase in permeation
- Prodrugs
  - Make lipophilic
- Penetration Enhancers