Chapter 9

Mechanisms of Controlled Release

Mechanisms of Controlled Drug Release

Physical Mechanisms

I. Dissolution
- **A. Encapsulated Dissolution (Reservoir) System**
- **B. Matrix Dissolution System**

II. Diffusion
- **A. Reservoir Devices**
  - **1. Nonporous Membrane**
  - **2. Microporous Membrane**
- **B. Monolithic Devices**
  - **1. Nonporous Matrix**
    - **a. Monolithic Solution**
    - **b. Monolithic Dispersion**
  - 2. Microporous Matix
    - c. Monolithic Solution
    - d. Monolithic Dispersion

III. Osmosis

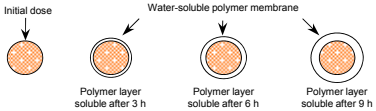
IV. Ion-Exchange

Chemical Mechanisms

V. Chemical Degradation

VI. Enzymatic Degradation

Encapsulated Dissolution (Reservoir) System



Dissolution of the polymeric material is the key to this mechanism; all of the polymers used must be water soluble or degradable.

Biodegradable polymers are hydrophobic and thus water insoluble; they break down into smaller units that are biocompatable.

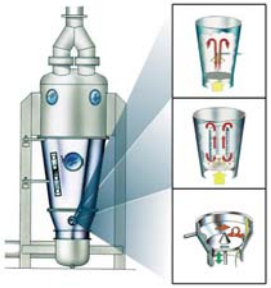
Encapsulated Dissolution (Reservoir) System

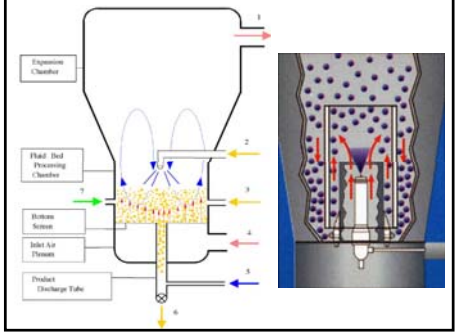
With a series of polymer thicknesses, the drug is released at discrete time periods—a repeat action dosage form that may not produce zero-order release.

With a spectrum of different polymer membrane thicknesses, zero-order release is possible.

Coated particles may be directly compressed into tablets or filled into capsules.

Fluid-Bed Wurster Coater





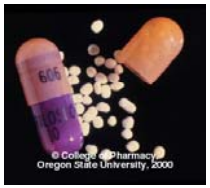
Spansules

Resaid® (phenylpropanolamine & chlorpheniramine)

Green, red, and white spherical beads within a capsule. Each color of beads represents a different coating level. Some beads release the drug immediately. Some beads release after a short while, some after a longer while.

Enteric Coated Prilosec® 10 mg

The beadlets contained in this capsule are large and irregular in shape when compared to other products. The granules are enteric coated because omeprazole is rapidly degraded in acid media. Absorption of omeprazole begins after the granules leave the stomach.



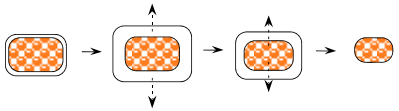
SODAS Verelan® SR (verapamil)

Spheroidal Oral Drug Absorption System

Small, visually identical white beads within an opaque capsule. A proportion of the beads is uncoated for bolus effect. The remainder consist of a drug core coated with rate-controlling polymers. Drug release is independent of food and pH.

Naprelan (Naproxen Sodium)

This system is a combination of the SODAS technology and the Hydrodynamic Cushion. This system allows the SODAS beads to be placed in tablet form providing for a higher dose than can be obtained from capsules. A coating to prevents disruption until it reaches the stomach where the tablet disintegrates and the beads are released into the GI tract. (30% of the drug is initially released within 30 min and the remaining is controlled-release over 24 h).



Dry tablet

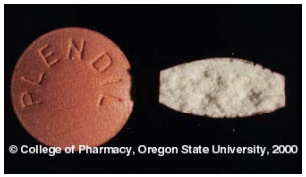
Drug reservoir coated with a gel-forming layer containing the API

Swelling and release of an initial dose from the gel layer

Drug release from reservoir and attrition of the gel layer

Erosion of the drug reservoir

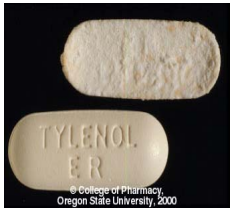
Plendil® 10 mg (felodipine)



Product is very similar to the hydrophilic matrix tablets except, only the surface of the tablet hydrates. As the drug is leached out of the surface of the tablets, the unhydrated portion of the tablet acts as a drug reservoir. The tablet slowly erodes away until all of the tablet is dissolved.

Tylenol® ER (acetaminophen)

Product is a bi-layered tablet consisting of 325 mg of immediate release acetaminophen and 325 mg of sustained release acetaminophen. The immediate release portion of the tablets rapidly disintegrates in water leaving a hydrophilic matrix.



Matrix Dissolution System

The drug is homogeneously distributed throughout the polymer matrix.

As the polymer matrix dissolves, drug molecules are released.

As the size of the matrix decreases, the amount of drug released decreases.

Drug release is nonzero-order.

Matrix Dissolution System

Micromatrix Systems

Small, spherical matrix systems prepared by microencasulation (Chapter 7).

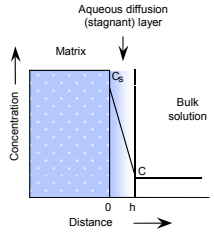
Macromatrix Systems

Tablets consist of an inner core, and outer coat, and a film coat.

Claritin® D (loratadine and pseudoephedrine)

This product provides 5 mg loratadine and 60 mg of pseudo-ephedrine in an immediate release layer. The inner layer is then a second dose of 60 mg pseudoephedrine that is coated to release after 6 h.

Dissolution Rate of Homogeneous Matrix System



The thickness of the stagnant layer *h* decreases with vigorous agitation.

The stagnant layer functions as a membrane through which the drug molecules have to diffuse.

The rate of drug release can be described by Fick's law (Chapter 6).

Dissolution Rate of Homogeneous Matrix Systems

Noyes–Whitney Equation

M = the total amount of drug dissolved

S = surface area of the exposed matrix

D = diffusion coefficient of the drug in the medium

$$M = \left(\frac{D \cdot S}{h}\right) \cdot (C_s - C) \cdot t$$

$$\frac{dM}{dt} = \left(\frac{D \cdot S}{h}\right) \cdot (C_s - C)$$

For small matrices consisting of uniformly sized particulates, it is much more convenient to consider the total weight.

Hixon–Crowell Cube Root Law

For small matrices consisting of uniformly sized particulates, it is much more convenient to consider the total weight.

Using the density (volume/weight) term in the Noyes–Whitney equation:

$$M_0^{1/3} = M^{1/3} = kt$$

where M_0 is the original mass of the particles and k is the cube root dissolution rate constant

Biodegradable Polymers

For oral delivery, there isn't a problem if the polymer does not degrade completely since there isn't a removal problem.

For implanted devices, it would be best if a second surgery is not needed to remove the device once all of the drug has been released.

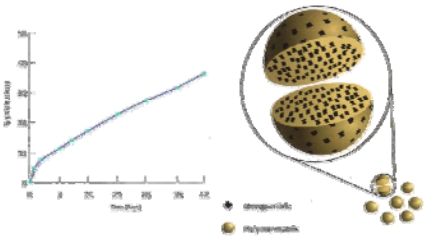
Thus, the polymers for implants must break down to nontoxic monomers that are eliminated in the blood stream.

Biodegradable polymers may be water soluble or not.

The most widely used biodegradable polymers are

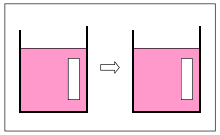
- **Poly(lactic acid)**
- **Poly(glycolic acid)**
- **Poly(lactic-co-glycolic acid)**

PLGA Protein Delivery Microparticles

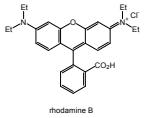


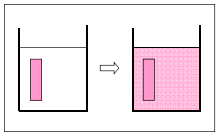
Diffusion-Controlled Drug Release

Serendipity



Judah Folkman observed that certain dyes were absorbed by silicon rubber and then subsequently released.

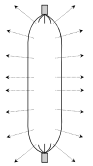




Diffusion-Controlled Drug Release

In 1963, Folkman and Long systematically studied the slow release of drugs, such as digitoxin, from the inside of silicon rubber tubing.

In 1966, other researchers showed that when progesterone-loaded silicon rubber tubing was implanted in cattle, it was able to prevent the animal from becoming fertile for more than a year.



Polymers

Cellulose (Ethylcellulose)
Chitin
Collagen
Nylon
Poly(alkylcyanoacrylate)
Polyethylene
Poly(hydroxyethyl methacrylate)
Poly(hydroxypropylethyl methacrylate)
Poly(methyl methacrylate)
Poly(vinyl alcohol-co-methacrylate)
Poly(vinyl chloride)
Polyisobutene
Polyurethane
Silicon rubber

Diffusion-Controlled Drug Release

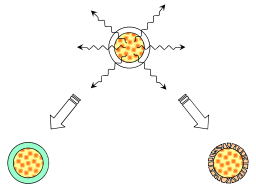
Drug molecules need to diffuse through a polymer membrane or matrix to be released.

Devices can be divided into two classes:

Reservoir—the drug is surrounded by a polymer membrane

Monolithic—the drug is distributed throughout a polymer matrix

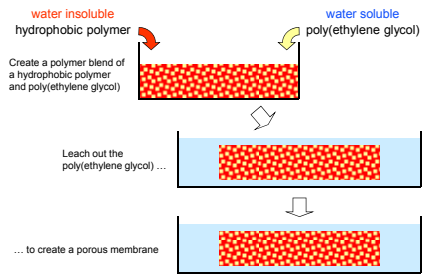
Reservoir Systems



Nonporous
Drug must diffuse through polymer

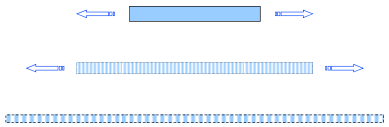
Microporous
Drug is released through micropores (usually filled with water or oil)

Microporous Membranes



Microporous Membrane

Stretching a polymer membrane can form micropores



Stretching porous polyethylene or polypropylene films is used to create microporous membranes used in transdermal patches

Mololithic Devices

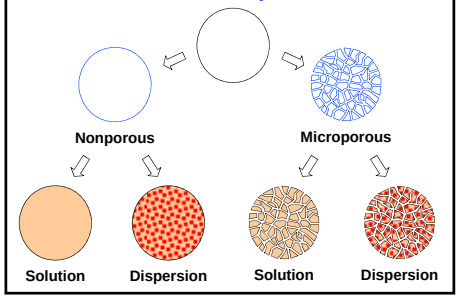
Solution—the drug is loaded in the polymer by soaking the polymer in a solution of the drug.

The drug concentration inside the polymer cannot be higher than the drug solubility.

Dispersion—the drug is loaded in the polymer at concentrations higher than that of a solution.

Extra drug exists as particles within the polymer.

Monolithic Systems



Diffusion through a Polymer

Drug molecules must diffuse through the polymer membrane or polymer matrix to be released.

The diffusion depends on the size of the drug and the size of the pores of the polymer (space between the polymer chains).

The actual pore size or space between the polymer chains may be somewhat smaller than the size of the drug molecules, but because of thermal motion and Brownian motion, the drug molecules can diffuse through the polymeric membrane or matrix.

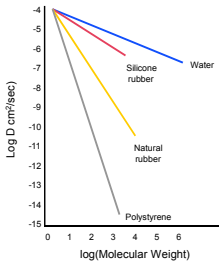
Diffusion through a Polymer

The local movement of the polymer chains may provide the local microscopic viscosity, which could be quite low.

The local movement of the polymer chains is a critical factor that determines the diffusion coefficient of a drug within that polymer.

In a rubbery polymer, chains can move relatively freely; glassy polymers have only limited movement.

Diffusion Coefficient Relationships



Diffusion in polymers is much more sensitive to the molecular weight of the drug.

Diffusion coefficients of drugs in polymers are small and decrease sharply with molecular size.

The diffusion coefficient is determined primarily by the size of the drug molecule.

Diffusion Coefficient

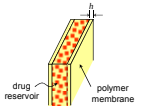
The dependence of the diffusion coefficient on the molecular weight of the drug molecule can be given by the expression:

$$D = k(\mathrm{MW})^n$$

where k is the diffusion coefficient of a polymer and n is dependent on the media.

~0.5	water
~0.6	silicon rubber
~2	natural rubber
~5	polystyrene

1-Dimension Reservoir Device (Slab)

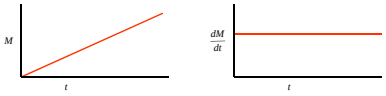


$$M = \frac{D \cdot K \cdot \Delta C \cdot S \cdot t}{h}$$

$$\frac{dM}{dt} = \frac{D \cdot K \cdot \Delta C \cdot S}{h}$$

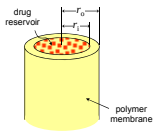
$\Delta C = C_s - C$

K = partition coefficient



Drug release is zero order

2-Dimensional Reservoir Device (Cylinder)

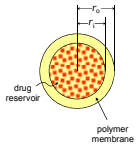


$$M = 2\pi \cdot D \cdot K \cdot \Delta C \cdot \ln\left(\frac{r_o}{r_i}\right) \cdot t$$

$$\frac{dM}{dt} = 2\pi \cdot D \cdot K \cdot \Delta C \cdot \ln\left(\frac{r_o}{r_i}\right)$$

Drug release is zero order

3-Dimensional Reservoir Device (Sphere)



$$M = 4\pi \cdot D \cdot K \cdot \Delta C \cdot \left(\frac{r_o r_i}{r_o - r_i}\right) \cdot t$$

$$\frac{dM}{dt} = 4\pi \cdot D \cdot K \cdot \Delta C \cdot \left(\frac{r_o r_i}{r_o - r_i}\right)$$

Drug release is zero order

Poly(ethylene-co-vinyl acetate) (EVA Copolymer)

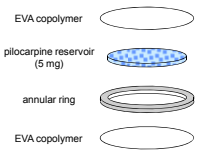
EVA permeability properties can be controlled readily by changing the content of the vinyl acetate.

The release rate can be tailored to the application.

The release rate is related to the glass-transition temperature and crystallinity of the copolymer.

- Polyethylene has a crystallinity of 70%.
- The crystallinity becomes 0% when 60% vinyl acetate is present.

Pilocarpine



Ocusert® is a flat wafer slow-release form of pilocarpine.

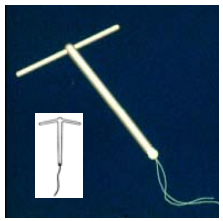
One wafer is placed in the corner of the eye once a week.

Pilocarpine (5 mg) is slowly released over a period of about a week (20 μg/h).

Progestasert® IUD

The cross piece is a tube of EVA copolymer that contains progesterone crystals suspended in a silicon fluid.

Daily release is ~65 μg/d for 1 y.



Silicon Rubber

Silicon rubber has a very high permeability for steroids, which have low water solubility.

Because of the low solubility, the boundary–layer effect is significant in this delivery system.

A typical diffusion coefficient of a steroid through silicon rubber is 5×10^{-7} cm²/s; a maximum flux of 200 μg/cm² is possible.

Norplant® Subdermal Implant

Norplant® implants are six matchstick-size silicon rubber rods inserted into the upper arm.

Each rod contains 36 mg levonogestrel.

Insertion takes about 7–10 min after a local anesthetic is given.

The system releases 85 μg/d initially, which declines to 30 μg/d during its useful life (up to 7 y).

Generation II Norplant devices contain the drug as a solid dispersion in a silicon elastomer matrix and only 2 units are required.

Micro-K® (KCl Controlled Release)

Small crystals of potassium chloride microencapsulated with a polymeric ethylcellulose coating.

Encapsulated crystals are filled in a hard gelatin capsule.

Provides controlled release of K^+ and Cl^- ions over an 8–10 h period.

K-Dur® Microbusrt Release System

Small crystals of potassium chloride microencapsulated with a polymeric ethylcellulose coating.

Encapsulated crystals are granulated with crospovidone, hydroxypropyl cellulose, and microcrystalline cellulose.

Granules are blended with magnesium stearate and compressed into caplets.

The microcrystalline cellulose causes the caplets to disintegrate within seconds of reaching the stomach.

Theo-24®

First commercial product for 24-h theophylline therapy.

Developed by Searle, now sold by UCB Pharma, Inc.

Consists of small sugar and starch beads on which a thin coat of theophylline is applied.

The coated cores are then coated with an ethylcellulose layer with various thicknesses.

The beads are filled in hard gelatin capsules.

As the insoluble ethylcellulose coat slowly erodes, the soluble theophylline is released through the coating.

The starch swells and helps push the drug out.

The dissolving sugar helps carry the drug through the polymer layer.

Microporous Membranes

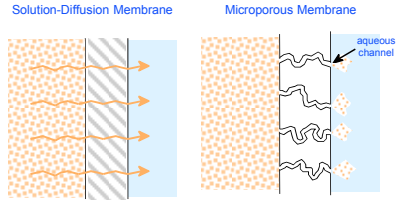
Reservoir Devices with Microporous Membranes

Diffusion through nonporous, homogeneous, dense polymer (solution-diffusion) membranes occurs between polymer chains

Diffusion through microporous membranes occurs through liquid-filled pores

- Water-filled pores for hydrophilic drugs
- Oil-filled pores for hydrophobic drugs

Reservoir Devices with Microporous Membranes



Microporous Membranes

Micropores typically are not straight and thus have longer path than thickness of membrane

Drugs must diffuse through a longer distance that membrane thickness

- The tortuosity τ must be considered
- The greater the tortuosity, the longer the path

Microporous Membranes

When drug is released only through micropores, the effective surface area of the membrane for drug release is greatly reduced

The fractional volume of membrane pores must be considered using the porosity ε parameter

Microporous Membranes

Drug release through nonporous membranes:

$$M = \left(\frac{SDK}{h}\right)\Delta Ct$$

Drug release through microporous membranes:

$$M = \left(\frac{\varepsilon SDK}{\tau h}\right)\Delta Ct$$

porosity — related to surface area

tortuosity — related to thickness

Microporous Membranes

Diffusion through pores may occur through the liquid in the micropores

- Diffusion coefficient D_0 of liquid
- Partition coefficient K_0 of liquid

$$M = \frac{\varepsilon}{\tau}\left(\frac{SD_0K_0}{h}\right)\Delta Ct$$

For water-soluble drugs through aqueous channels, $K_0 = 1$

Microporous Membranes

Microporous membranes may be prepared by making hydrophobic polymer membranes in the presence of water-soluble materials [*e.g.*, poly(ethylene glycol)]

After membrane is formed, the water-soluble materials are removed by dissolving them in aqueous solution

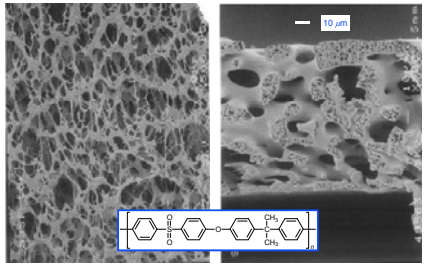
Microporous Membranes

Transdermal patch membrane

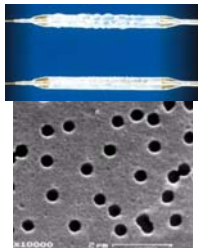
This microporous membrane was made by repeatedly stretching polypropylene film at high and low temperatures

The process creates minute, parallel rips in the film, spanned by microfibers that define an average pore size of several hundred Ångstroms

Microporous Membranes



Microporous Membranes



- An ultra-thin-walled PET balloon can be converted to a microporous membrane with hole sizes ranging from submicron to a few microns in diameter
- Hundreds of thousands or even millions of holes can be placed in a single balloon
- The pore size may be controlled precisely, enabling very small amounts of a drug to be infused over a well-defined area as large or as small as required
- Although these balloons contain millions of micro pores they are strong

Celgard®

Microporous polypropylene film (Celgard®) are used in disposable butane lighters

The microporous membrane replaces a costly and complex mechanical valve assembly used to maintain constant flow and flame height, regardless of ambient pressure and fuel level

Scopolamine Transdermal Patch

Scopolamine released at rate of 10 μg/h for 3 d

Scopolamine in reservoir of mineral oil

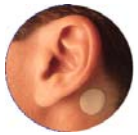
Multilaminate dosage form

Diffusion through oil-impregnated polypropylene film

Drug is also dispersed in the adhesive polymer (*e.g.*, polyisobutylene adhesive)

Scopolamine Transdermal Patch

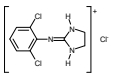
- Clinically proven to prevent motion sickness
- In clinical studies, 5 out of 6 people did not report drowsiness
- Longer lasting, one patch lasts up to 3 days compared with a Dramamine tablet which only lasts up to 6 hours



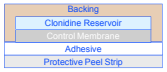
Transderm Scop® (1.5 mg scopolamine) ~ $5 per patch
Dramamine (50 mg dimenhydrinate) $7.33 / 24 tablets

CATAPRES-TTS®

- Clonidine, the active ingredient of CATAPRES, is active in very small doses (in the microgram range)
- The plasma half-life of clonidine is 10–20 h
- 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
- The protein binding, found to be 30-40% *in vitro*, has no influence on the pharmacokinetics

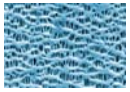


clonidine hydrochloride



	Programmed Delivery *In vivo* flux over 1 wk	Clonidine content (mg)	Size (cm²)
CATAPRES-TTS-1	0.1 mg	2.5	3.5
CATAPRES-TTS-2	0.2 mg	5.0	7.0
CATAPRES-TTS-3	0.3 mg	7.5	10.5

Celgard®

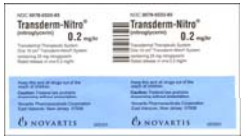


Parameter	Range
Porosity	30–60+ %
Pore Size	0.02 x 0.08 μm to 0.2 x 1.5 μm
Thickness	8–50 μm
Permeability, Gurley	5–100
Moisture Vapor Rate	4000–6000 gm/m²/day at 1 atm
Water Flow	20–400 L/m²/h at 10 psig
Tensile Strength Machine Direction	15–19 kpsi
Tensile Strength Transverse Direction	1.2–2.2 kpsi
Electrical Resistance	~ 2.0 ohm/cm²

- Microporous polypropylene film (Celgard®) is used to control insect pests (*e.g.*, Japanese beetle, whitefly, house fly, apple maggots)
- Active ingredients (e.g., hormones) can be released at a constant, predictable rate

Transderm-Nitro®

- Drug reservoir is a dispersion of nitroglycerin-lactose triturate (i.e., suspension) in silicone oil
- The drug release from reservoir is controlled by microporous EVA (ethylene–vinyl acetate) copolymer
- Nitroglycerin is delivered at dosage rate of 0.5 mg/cm²/d for relief of anginal attacks



nitroglycerin

Release Rate (mg/h)	Total NTG Content (mg)	Surface Area (cm²)
0.1	12.5	5
0.2	15	10
0.4	50	20
0.8	100	40

Estrogen Replacement

Oral administration often results in nausea, vomiting, headache, vaginal bleeding, and breast tenderness

Transdermal delivery eliminates most of these side effect

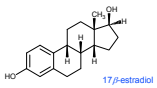
- Skin does not metabolize estradiol
- Only 5% of oral dose is needed to achieve the same blood plasma levels

Estrogen Replacement

Estrogen replacement is known to increase the risk of

- breast cancer
- uterine cancer
- hyperplasia or neoplasia
- gallstones
- blood clots
- high blood pressure

Estrogen Transdermal Patches



17β-estradiol

Estraderm (1986)

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

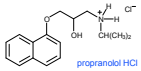
Fluoride Releasing Device

Hydrophylic polymer matrix containing NaF or Na_2PO_3F is coated with EVA (ethylene–vinyl acetate) copolymer by dip-coating in an EVA/chloroform solution

A thin button can be glued to one of the back molars for the prevention of tooth d

Controlled release of fluoride for 6–12 mo is possible.

Inderal® LA



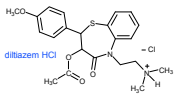
propranolol HCl

Inderal® LA (long acting) uses polymer coated controlled-release diffusion technology to achieve 12-h release of therapeutic levels of propranolol HCl for the treatment of hypertension

Inderal® LA consists of small beads contained in a gelatin capsule

- Each bead is coated with a porous membrane (ethylcellulose, hyddroxypropyl methylcellulose, and plasticizer)
- Polymer coating give a density > 1 and keeps the dose in the upper alimentary canal for a longer time

Cardizem® CD



diltiazem HCl

Cardizem® CD (vasodilator) is a once-a-day formulation based on the spheroidal oral drug absorption system (SODAS) technology

Consists of two populations of sustained release beads that differ only by the thickness of the polymer (ethylcellulose)

The ethylcellulose coating also contains water-soluble polymers that dissolve to create pores in the membrane

120mg, 24 h
180mg, 24 h
240mg, 24 h
300mg, 24 h

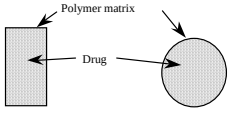
MONOLITHIC DEVICES

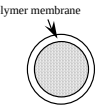
PREPARATION

1. CROSSLINKING OF POLYMERS
   CHEMICAL AND PHYSICAL CROSSLINKING
2. MOLDING
   RUBBERY STATE AT HIGH TEMPERATURE
3. SOLVENT CASTING
   COMMON SOLVENT FOR POLYMER & DRUG

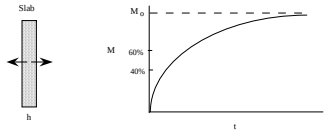
MONOLITHIC DEVICES

RESERVOIR DEVICE



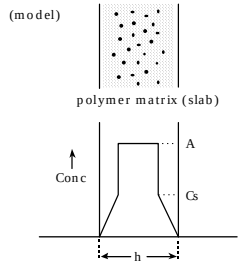


DRUG RELEASE FROM MONOLITHIC SOLUTION

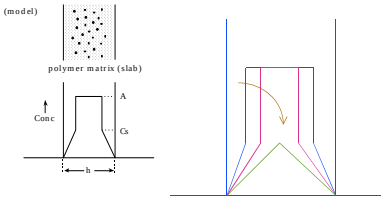


DECREASE IN RELEASE RATE
DUE TO INCREASE IN DIFFUSION PATH LENGTH

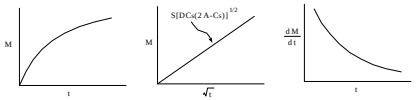
DRUG RELEASE FROM MONOLITHIC DISPERSION



DRUG RELEASE FROM MONOLITHIC DISPERSION



DRUG RELEASE FROM MONOLITHIC DISPERSION



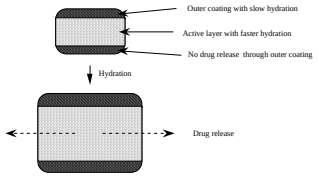
$$M = S\,[D\,Cs\,(2A - Cs)\,t\,]^{1/2}$$

$$dM/dt = (S/2)\;[D\,Cs\,(2A - Cs)]^{1/2}\;t^{-1/2}$$

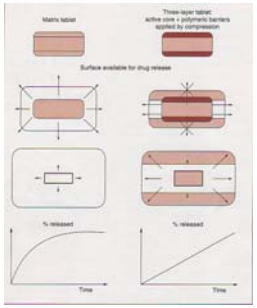
EXAMPLE
ON p. 169

DECREASE IN RELEASE RATE
DUE TO INCREASE IN DIFFUSION PATH LENGTH

DILACOR X: GEOMATRIX TECHNOLOGY



MC, EC
HPMC

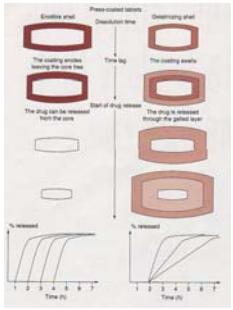


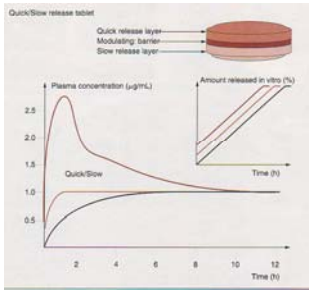
DELAYED RELEASE

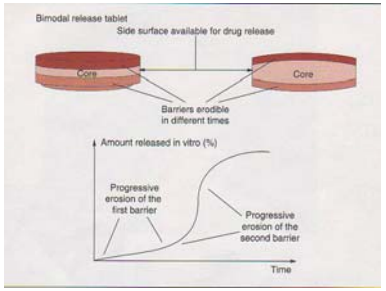
TAKING MEDICINE AT BEDTIME

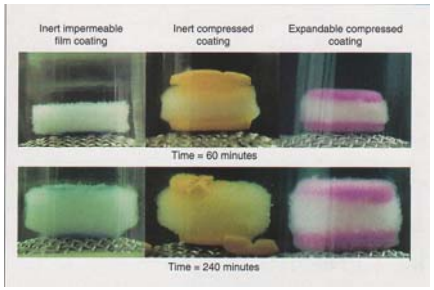
↓

DRUG EFFECT IN THE MORNING

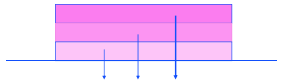






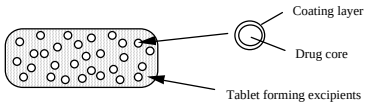


COMPLEX MONOLITHIC DEVICES
MULTIPLE LAYER MONOLITHIC DEVICES
DEPONIT SYSTEM



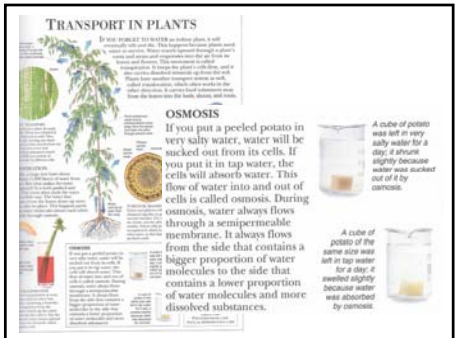
NEAR ZERO-ORDER RELEASE

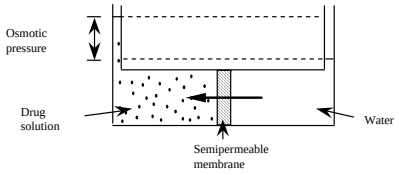
COMBINATION OF MICRORESERVOIR-MATRIX SYSTEM
P.177. TROPOL-XL TABLET

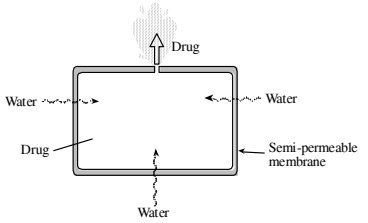


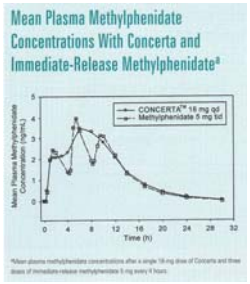
CHAPTER 9.

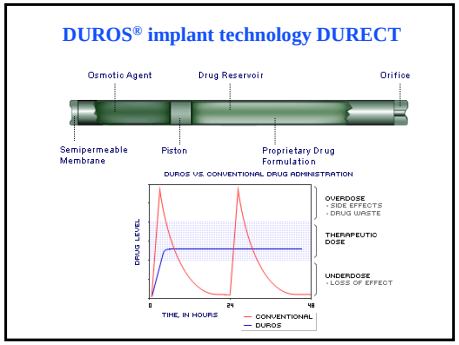
III. OSMOSIS-CONTROLLED DRUG RELEASE











CHAPTER 9.

IV. ION EXCHANGE-CONTROLLED DRUG RELEASE