

## Controlled Drug Delivery

### Evolution of Controlled Drug Delivery Systems

- 50-60s** Beginning (Delayed release, sustained release)  
Patience Compliance & Convenience  
Enhancement of Products
- 70s** Control of release kinetics
- 80s** Zero-order release  
Extension of product life (or patent life)
- 90s** Modulated release (Smart polymers)
- 00s** Nanotechnology  
Poorly soluble drugs, High mol wt drugs  
Systemic targeting  
Intracellular targeting

### Controlled Release Dosage Forms

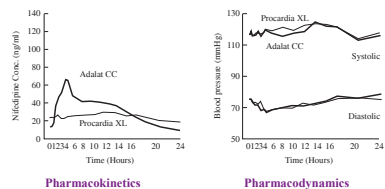
#### Reasons for development

A. Alternative to development of new drugs

1. High cost of developing new drugs
2. New tricks for old drugs



### B. Extension of Product Life (I.E., Patent Life) Procardia (bid) To Procardia XL (Once a Day)



Pharmacokinetics

Pharmacodynamics

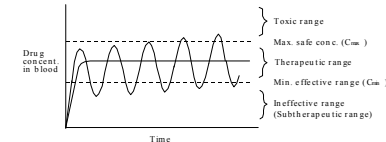
### C. Delivery Of Macromolecular Drugs (Protein Drugs, DNA, RNA)



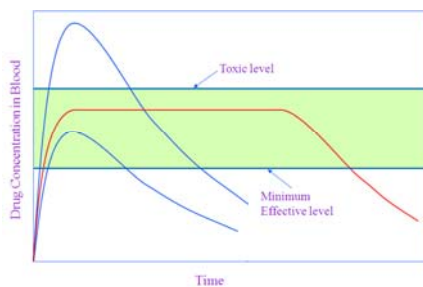
### Controlled Release Dosage Forms

#### Advantages

1. Maintenance of Optimum Concentration
2. Improved Efficacy with Less Drug
3. Minimal Side Effect



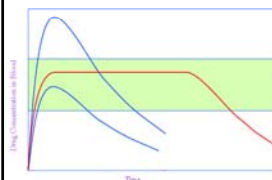
### Rationale of Controlled Drug Delivery Systems



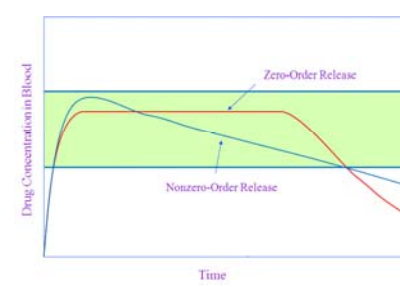
### Therapeutic Index (TI)

#### TI values of selected drugs

Drug	TI
Theophylline	$\infty$
Triphenylamine	19,000
Diphenhydramine	2,300
Chlorpheniramine	1,400
Penicillin	>100
Acetaminophen	20-40
Barbiturates	2-7
Quinidine	2-3
Digitoxin	1.5



### Zero-Order vs. Nonzero-Order Systems



### 4. Improved Patient Compliance & Convenience

Once-a-day  
Once-a-week



Once-a-month  
Once-a-year  
Once-a-decade



On-demand



Norplant: Made of Silicone rubber  
36 mg levonorgestrel.  
85 ug/day (later 30 ug/day) up to 7 years.

**Less Frequent Administration**

### Controlled Release Dosage Forms

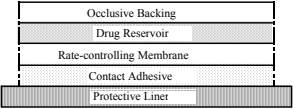
#### Disadvantages

1. Relatively high production cost
2. Dose dumping
3. Surgical operation
4. Difficulty in stopping drug release
5. Biocompatibility issue

### Major Components of Controlled Release Dosage Forms

1. Drug
2. Drug Delivery Module
  - Reservoir
  - Delivery Portal (Exit)
  - Energy Source
  - Rate Controller
3. Platform

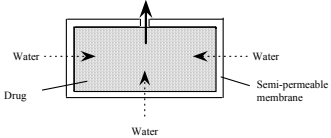
### Transdermal Patch



(not to scale)

2. Drug Delivery Module
  - Rate Controller
  - Energy Source
  - Delivery Portal (Exit)
  - Reservoir
3. Platform

### Oral Osmotic (Oros) System



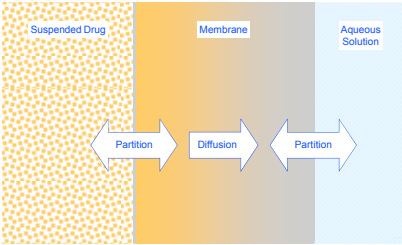
2. Drug Delivery Module
  - Rate Controller
  - Energy Source
  - Delivery Portal (Exit)
  - Reservoir
3. Platform

### Controlled Drug Delivery

#### Mathematical Models

### Solution-Diffusion Membranes

#### Nonporous, Homogeneous Polymer Membranes

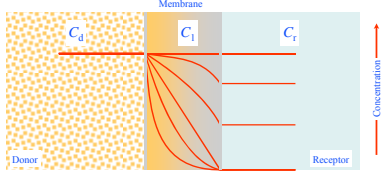


### Diffusion through a Membrane

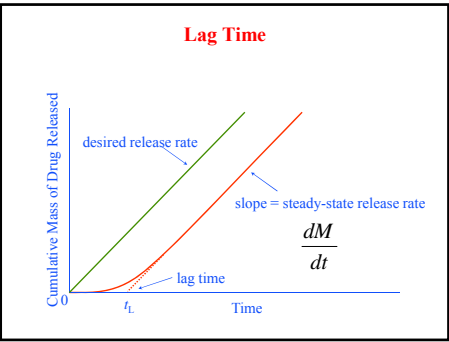
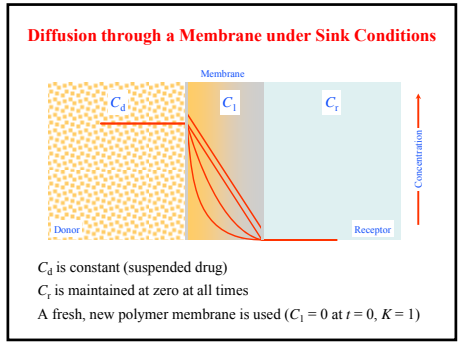
Important phenomena in controlled drug release

- Lag time
- Burst effect
- Diffusion through a polymer membrane
- Diffusion through a polymer membrane under sink conditions

### Diffusion through a Membrane



Concentration on the donor side  $C_d$  of the polymer membrane remains constant  
The concentration on the receptor side  $C_r$  is zero at  $t = 0$   
Concentration in membrane  $C_1$  is zero at  $t = 0$  ( $K = 1$ )



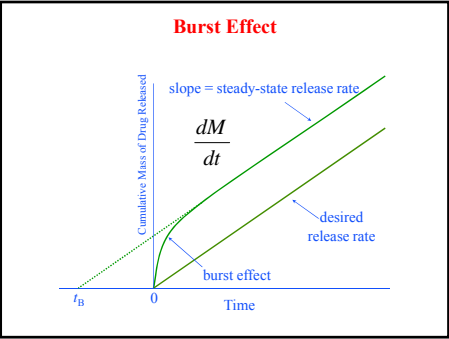
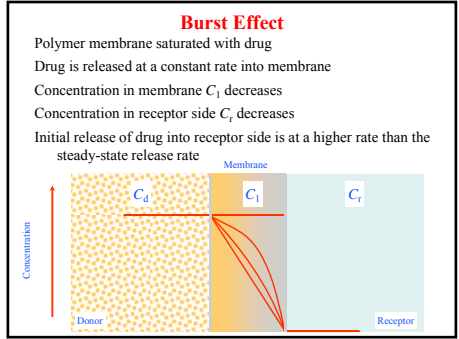
### Lag Time

Cumulative amount of drug released through membrane

$$M = S \cdot D \cdot K \frac{\Delta C}{h} (t - t_L)$$

Lag time may be expressed in terms of the diffusion coefficient and the membrane thickness

$$t_L = \frac{h^2}{6D} \Rightarrow M = S \cdot D \cdot K \frac{\Delta C}{h} \left( t - \frac{h^2}{6D} \right)$$



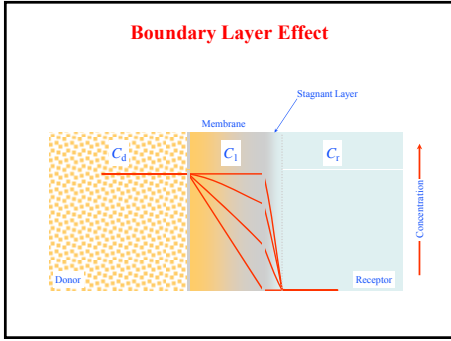
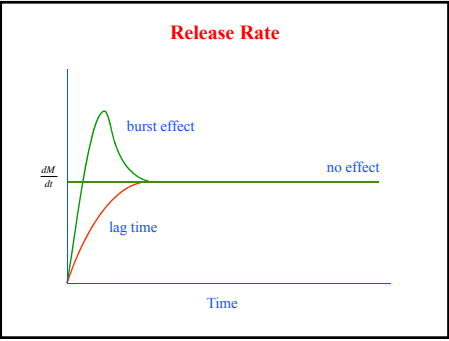
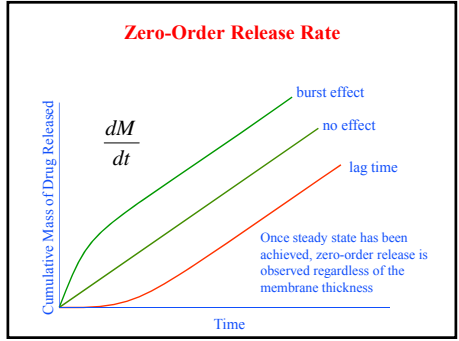
### Burst Effect

Cumulative amount of drug released through membrane

$$M = S \cdot D \cdot K \frac{\Delta C}{h} (t + t_B)$$

Burst effect may be expressed in terms of the diffusion coefficient and the membrane thickness

$$t_L = \frac{h^2}{3D} \Rightarrow M = S \cdot D \cdot K \frac{\Delta C}{h} \left( t + \frac{h^2}{3D} \right)$$



## 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
    - Monolithic Solution
    - Monolithic Dispersion
  2. Microporous Matrix
    - Monolithic Solution
    - Monolithic Dispersion

#### III. Osmosis

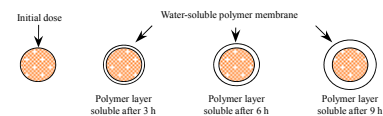
#### IV. Ion-Exchange

### Chemical Mechanisms

#### V. Chemical Degradation

#### VI. Enzymatic Degradation

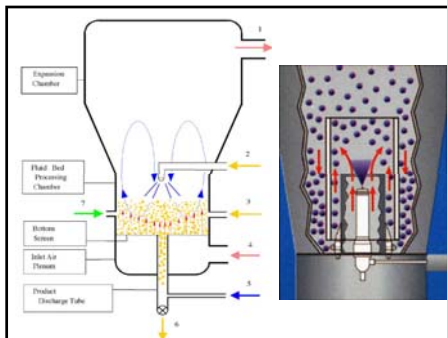
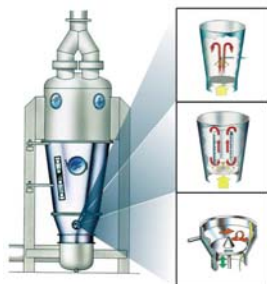
## Encapsulated Dissolution (Reservoir) System



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 biocompatible.

## 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.



## 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.

## 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.

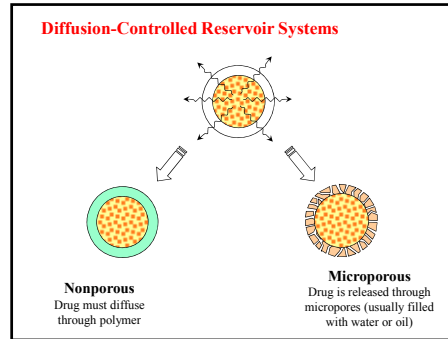
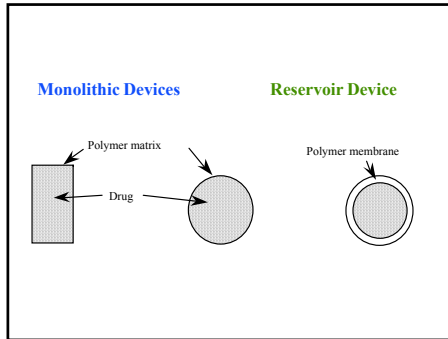
Thus, the polymers for implants must break down to nontoxic monomers that are eliminated in the blood stream.

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)

## Diffusion-Controlled Drug Release

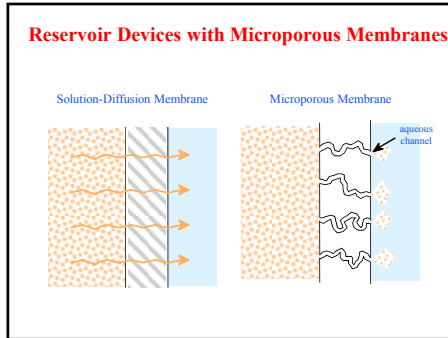


**Reservoir Devices with Microporous Membranes**

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



**Serendipity**

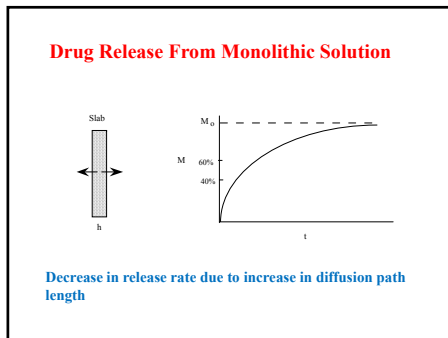
Judah Folkman observed that certain dyes were absorbed by silicon rubber and then subsequently released.

CC1=CC=C(C=C1)C(=O)O  
rhodamine B

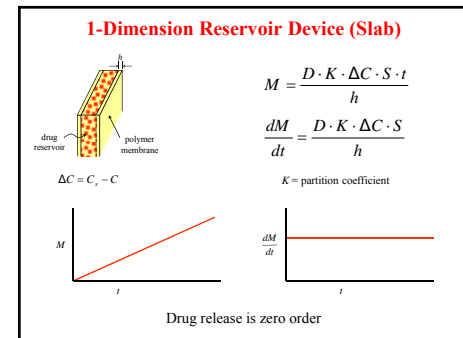
**Beginning**

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 used for Diffusion Controlled Release**
- 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)
  - Polysisobutene
  - Polyurethane
  - Silicon rubber



## 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 mg/d initially, which declines to 30 mg/d during its useful life (up to 7 years).

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



## 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.



## Monolithic Devices

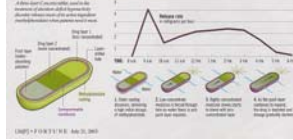
### Preparation

1. Crosslinking of Polymers  
Chemical and Physical Crosslinking
2. Molding  
Rubbery State at High Temperature
3. Solvent Casting  
Common Solvent for Polymer & Drug

## Osmosis-controlled Drug Release

## Osmosis-Controlled Systems

### Special delivery



### DUROS® implant technology DURECT



## TRANSPORT IN PLANTS

**OSMOSIS**

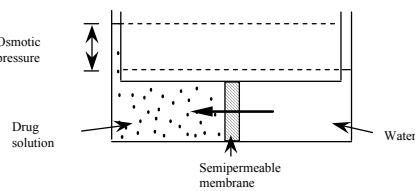
If you put a peeled potato in very salty water, water will be sucked out from its cells. If you put it in tap water, the cells will absorb water. This flow of water into and out of cells is called osmosis. During osmosis, water always flows through a semipermeable membrane. It always flows from the side that contains a bigger proportion of water molecules to the side that contains a lower proportion of water molecules and more dissolved substances.

*A cube of potato was left in very salty water for a day; it shrank slightly because water was sucked out of it by osmosis.*

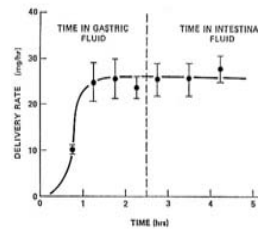
*A cube of potato of the same size was left in tap water for a day; it swelled slightly because water was absorbed by osmosis.*

Osmotic pressure

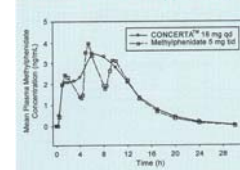
Drug solution



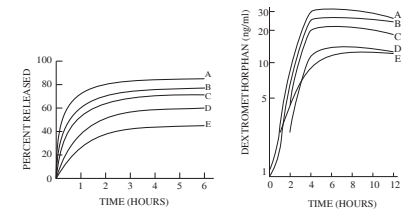
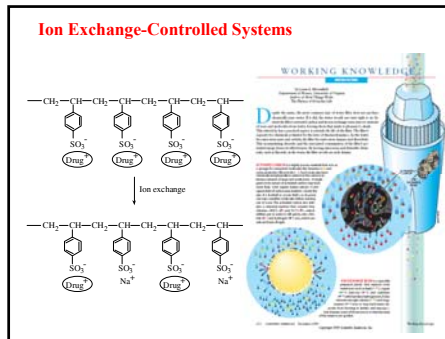
## TYPICAL DELIVERY RATE FROM OROS®



## Mean Plasma Methamphetamine Concentrations With Concerta and Immediate-Release Methamphetamine\*



## Ion Exchange-controlled Drug Release



## Pharmacogenetics

The study of genetic factors that influence response to drugs and the predisposition to develop adverse effects.

The correlation of the DNA sequence of genes to a drug response

## Pharmacogenomics

The implementation of large-scale genomic approaches to this question.

The study of the pattern of expression of genes involved in a drug response in a defined environment.



## Drug Delivery Routes

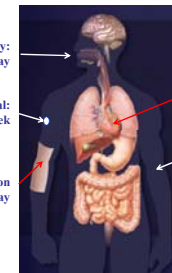
Oral Delivery:  
 < 1 min ~> 1 day

Transdermal:  
 1 day ~ 1 week

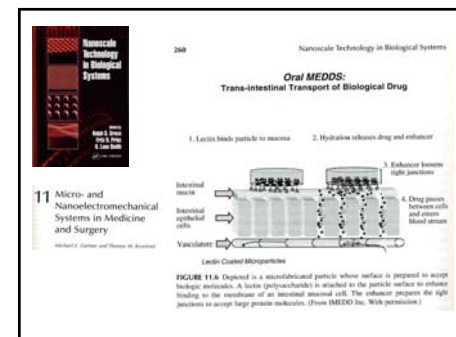
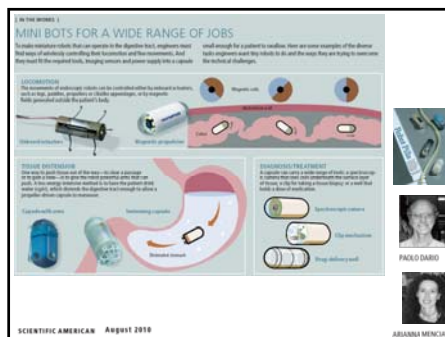
I.V. Infusion  
 ~ 1 day

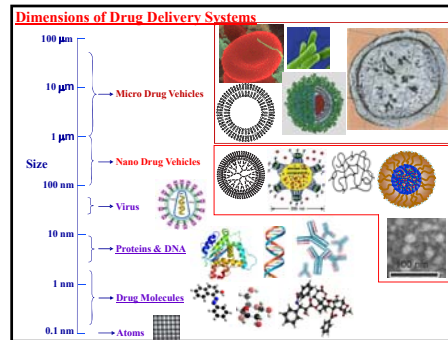
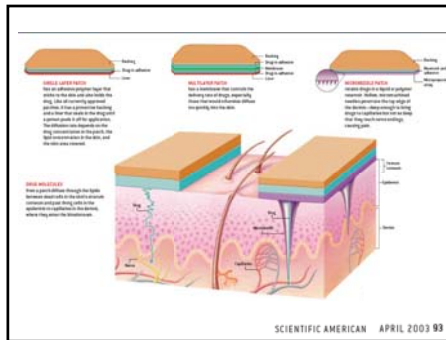
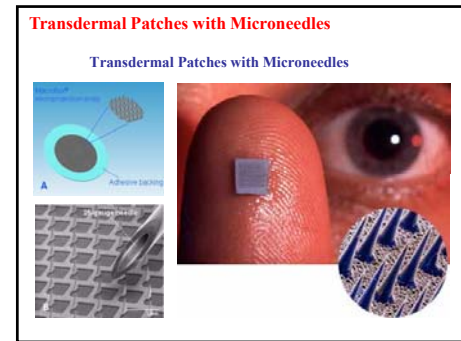
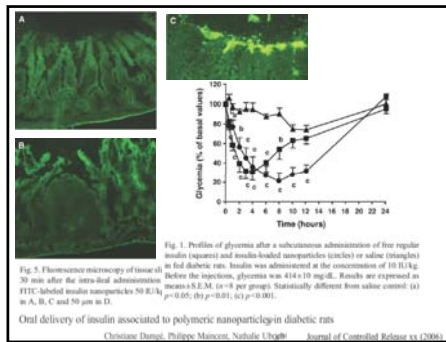
Localized Delivery:  
 1 month ~ 1 year

Implants (IM, SQ):  
 1 month ~ 1 year

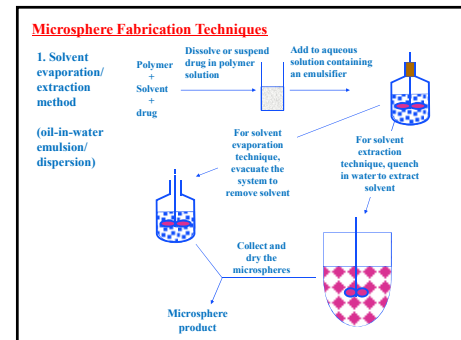
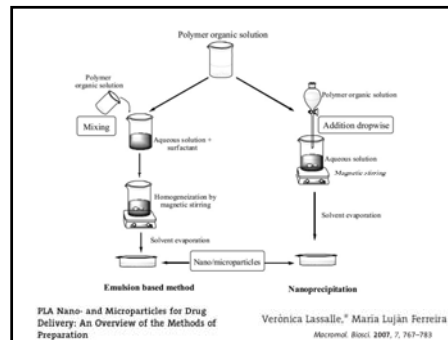
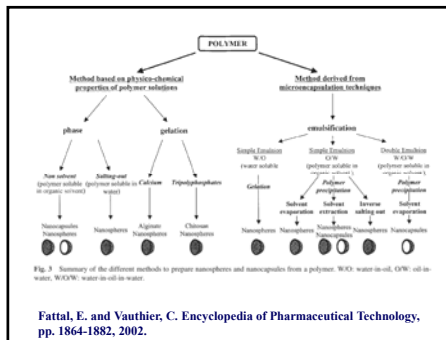


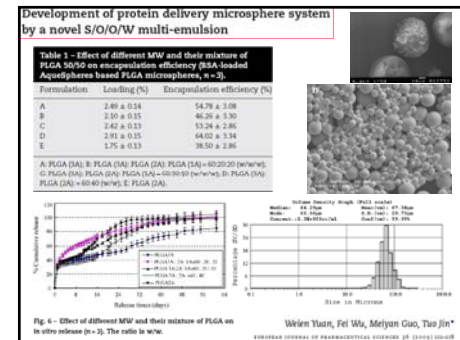
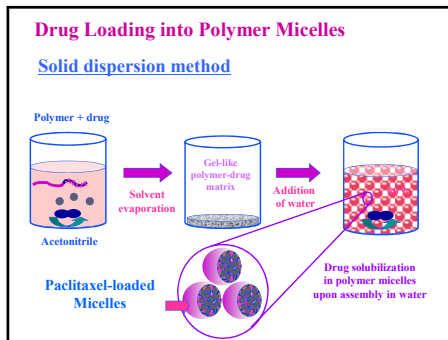
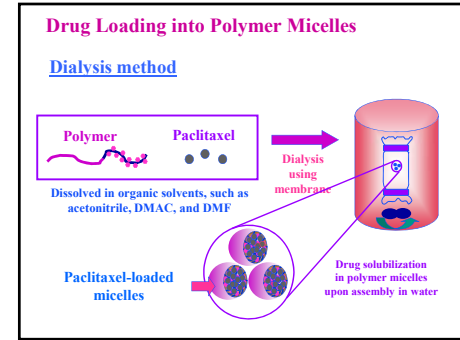
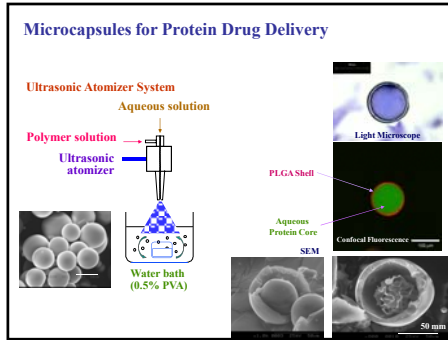
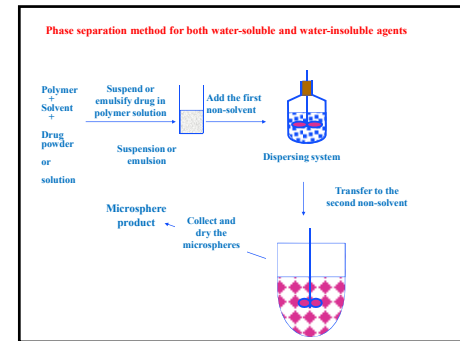
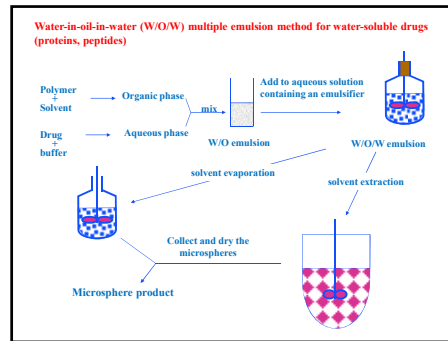
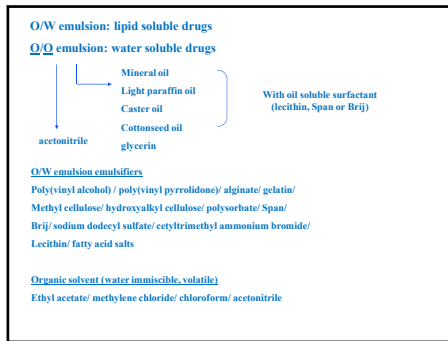
## Oral Delivery: Targeting to GI Tract

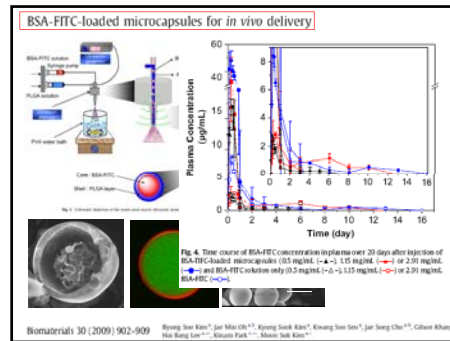
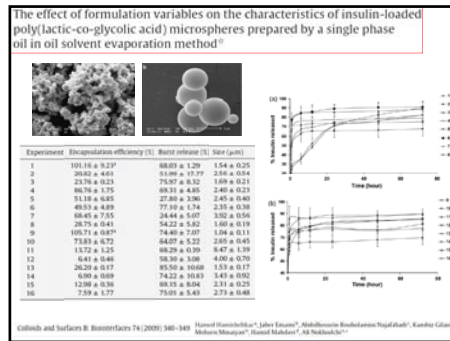





- Methods for Making Nano/Micro Particles**
1. Emulsion methods  
W/O/W, S/O/W, W/O/O, S/O/O
  2. Atomization methods  
Spray drying, spray freeze-drying  
Ultrasonic atomization  
Electrospray
  3. Nano/micro fabrication







**Protein Formulations**

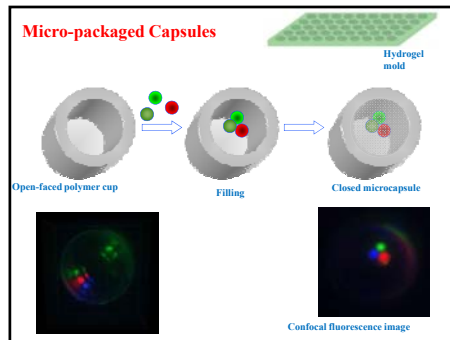
Proteins: Tertiary structure 

Factors to consider for formulation:

- Loading capacity
- Encapsulation efficiency
- Release profiles → *In vitro & in vivo* correlation
- Protein stability → **Bioactivity**

Polymers: Biodegradable polymers (Old or New?)

Scale-up production



**BIOMIMETICS**

“Study of Materials, Structures, and Processes designed through eons of evolution of life to inspire and improve the engineering & design of artificial materials, man-made structures & processes.”

(Marc J. Madou, *Fundamentals of Microfabrication. The science of Miniaturization*, 2<sup>nd</sup> Edition, CRC Press, 2002)

Artificial materials that function as biological entities do.

