# L13: Controlled Drug Delivery Systems

**May 17, 2018**

# Introduction & Definition

**Controlled drug delivery systems offer an approach to regulating both the duration and spatial localization of therapeutic agents.**

**Controlled drug delivery systems:**

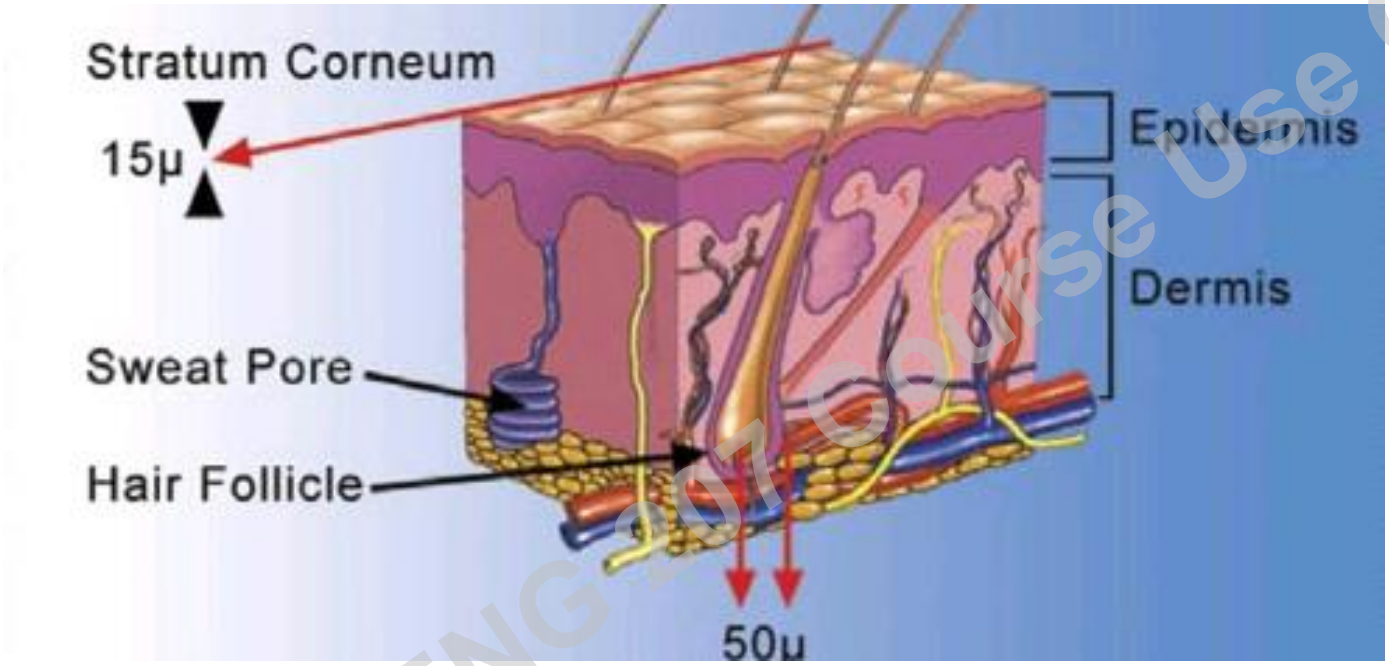
**--- Include a component that can be engineered to regulate an essential characteristic (e.g., duration of release, rate of release, or targeting).**

**--- Have a long duration of action (> 1 day)**

# Content

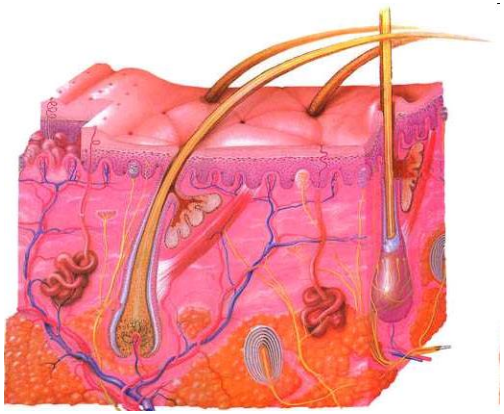
- Reservoir and transdermal delivery systems
- Matrix delivery systems
- Hydrogel delivery systems
- Degradable delivery systems
- Particulate delivery systems
- Responsive delivery systems

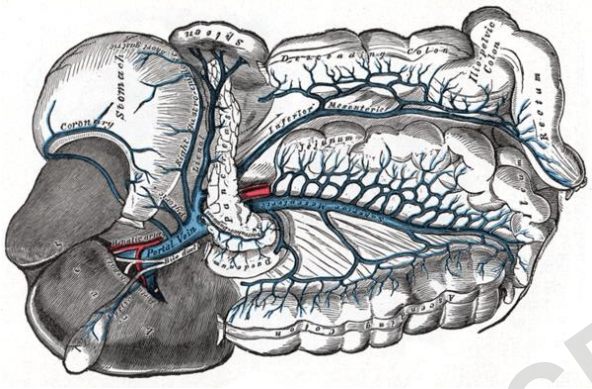
# I. Reservoir and Transdermal Delivery Systems

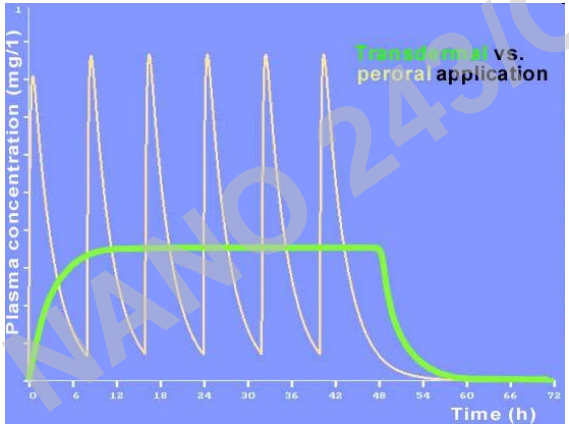



**Schematic representation of a cross section through human skin.**
**Stratum corneum**, located on the outer surface of the skin, is a non-living layer of keratin-filled cells surrounded by a lipid-rich extracellular matrix that provides the primary barrier to drug delivery into skin.
The **epidermis** below is a viable tissue devoid of blood vessels.
Just below the dermal-epidermal junction, the **dermis** contains capillary loops that can take up transdermally administered drugs for systemic distribution.

# Advantages of Transdermal Delivery



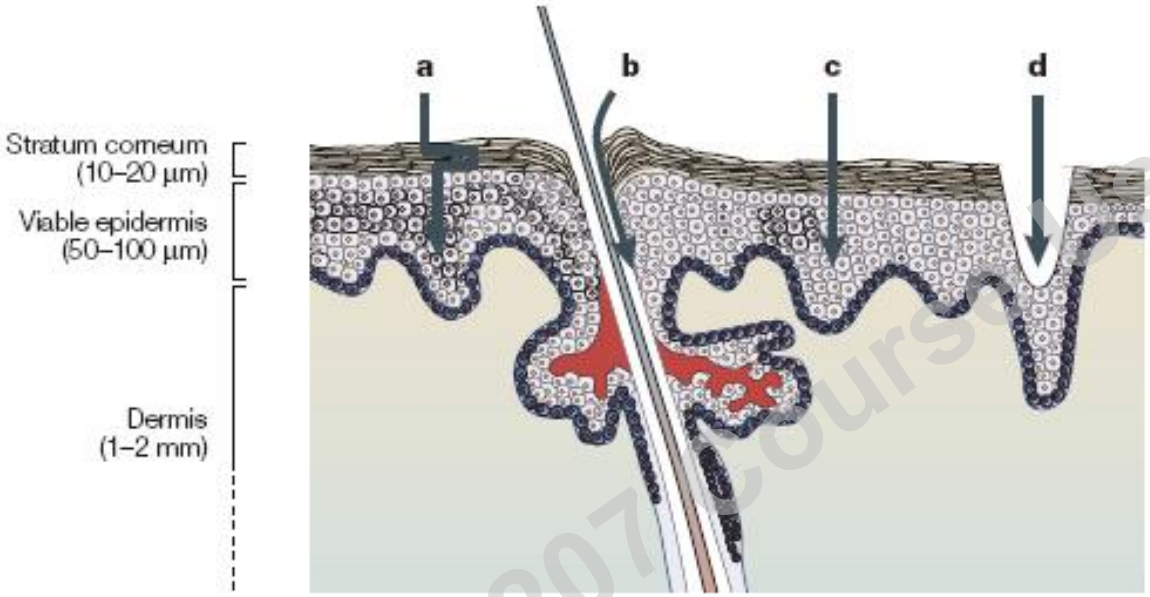





**After transdermal application, the drug penetrates through the skin and reaches the systemic circulation. Transdermal systems are advantageous for several drugs because:**

- **The drug does not reach the gastrointestinal tract. Thus, it can not be inactivated or produce side effects in this area.**
- **The drug does not undergo first pass metabolism in the liver, therefore less drug needs to be delivered.**
- **Sustained and controlled plasma levels can be obtained, avoiding peak levels which might produce side effects.**
- **The patient compliance is improved. The patient can easily control whether or not to take the medicine.**
- **The patient can immediately stop the administration by removing the patch.**

# Current Status of Transdermal Delivery



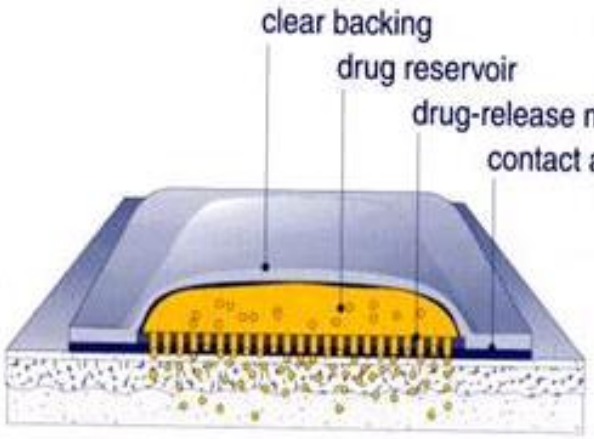

(a) Transdermal diffusion, possibly in the presence of a **chemical enhancer**, takes place by a tortuous route across the stratum corneum, winding around cells and occurring along the interfaces of extracellular lipid bilayers.

(b) Low-voltage electrical enhancement by **iontophoresis** can make transport pathways through hair follicles and sweat ducts more accessible.

(c) High-voltage enhancement by **electroporation** has been shown to occur via transcellular pathways made accessible by disrupting lipid bilayers.

(d) **Microneedles** and thermal poration create micron-scale holes in skin to provide pathways for drug transport.

# Transdermal Patches




**(1) Liner - Protects the patch during storage.**

**(2) Drug - Drug solution in direct contact with release liner.**

**(3) Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.**

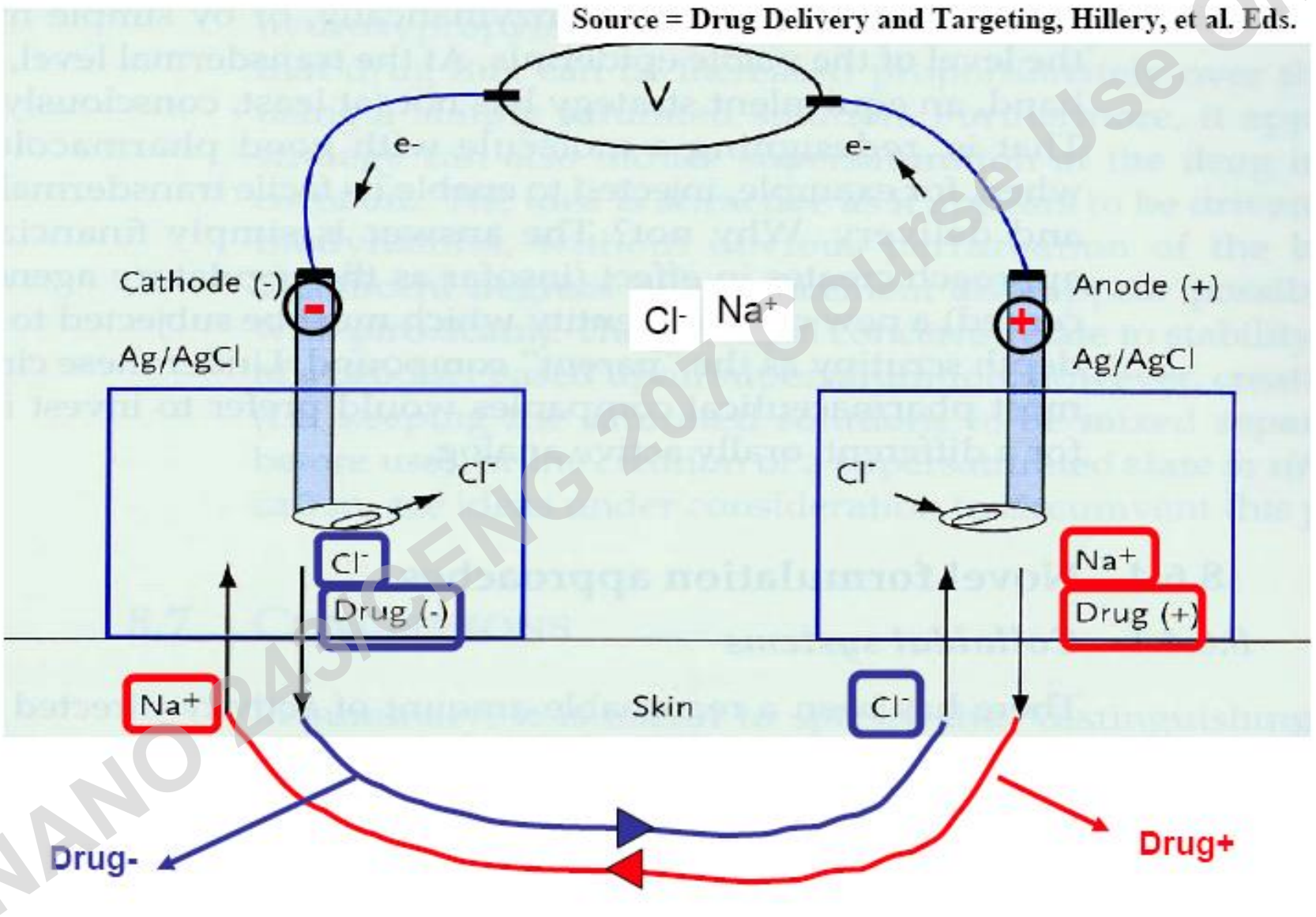
**(4) Membrane - Controls the release of the drug from the reservoir and multi-layer patches.**

**(5) Backing - Protects the patch from the outer environment.**

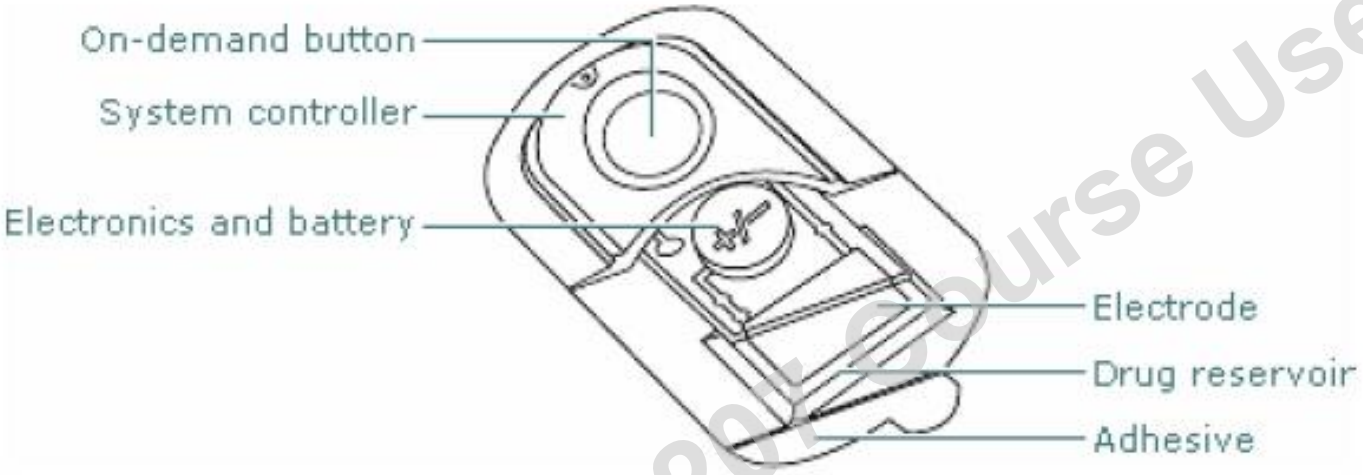

CombiPatch: A transdermal patch marketed by Novogyne Pharmaceuticals for hormone replacement therapy.


Nicotinell: A transdermal patch marketed by Novartis Pharmacological for smoking cessation

# Transdermal Iontophoretic Drug Delivery



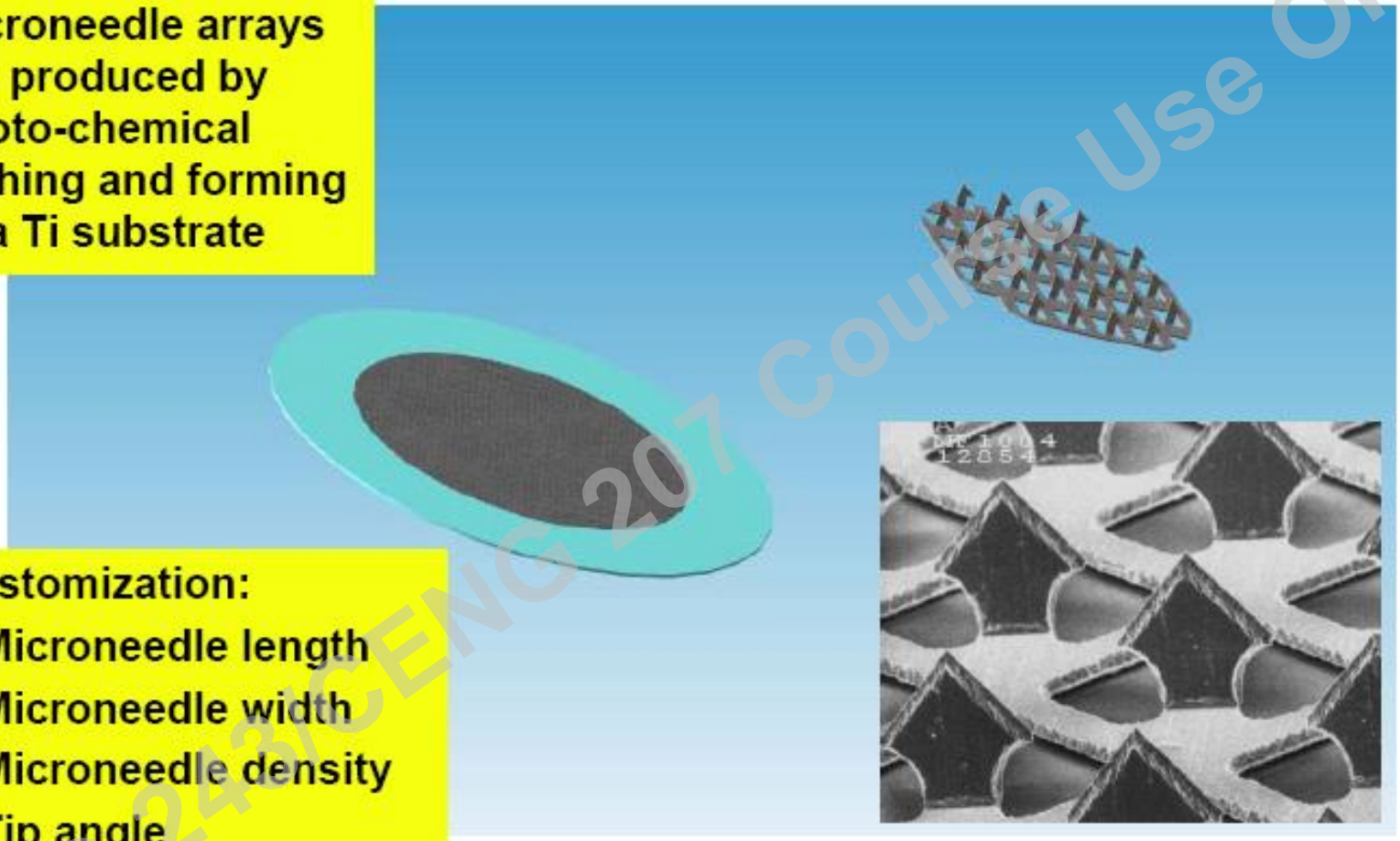
# Transdermal Iontophoretic Drug Delivery




**ALZA Corporation (Mountain View, CA), a division of Johnson and Johnson, has been developing an iontophoresis product, called E-TRANS®, for local or systemic administration of drug compounds. According to ALZA, design options include disposable systems for delivering drug over hours or days, and reusable systems with replaceable batteries and drug pads. The first product is designed to alleviate acute post-operative pain with patient-administered doses of fentanyl, a potent opioid analgesic.**

# Transdermal Microneedles

Microneedle arrays are produced by photo-chemical etching and forming of a Ti substrate

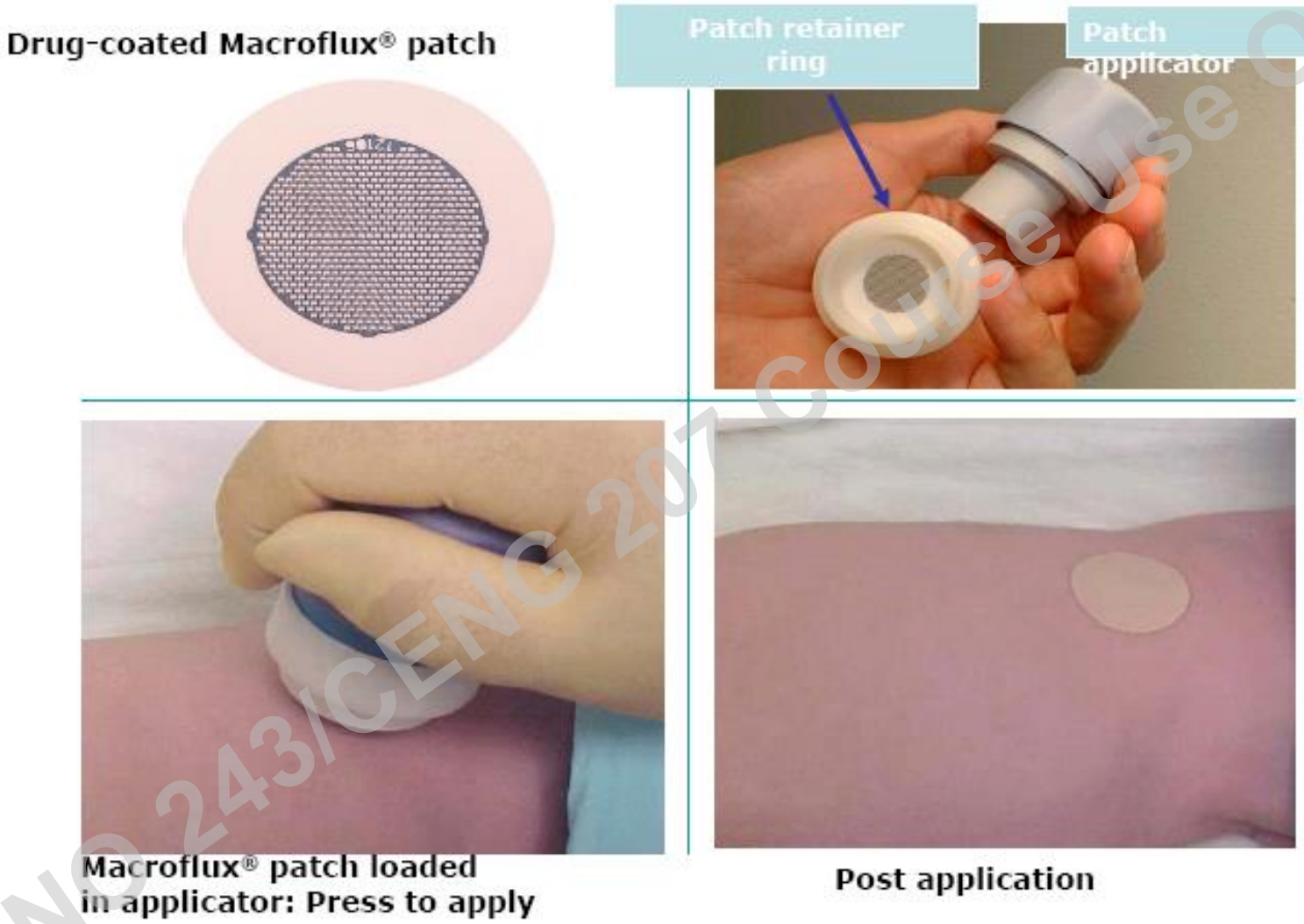


Customization:

- Microneedle length
- Microneedle width
- Microneedle density
- Tip angle

Macroflux® Patch (Alza)

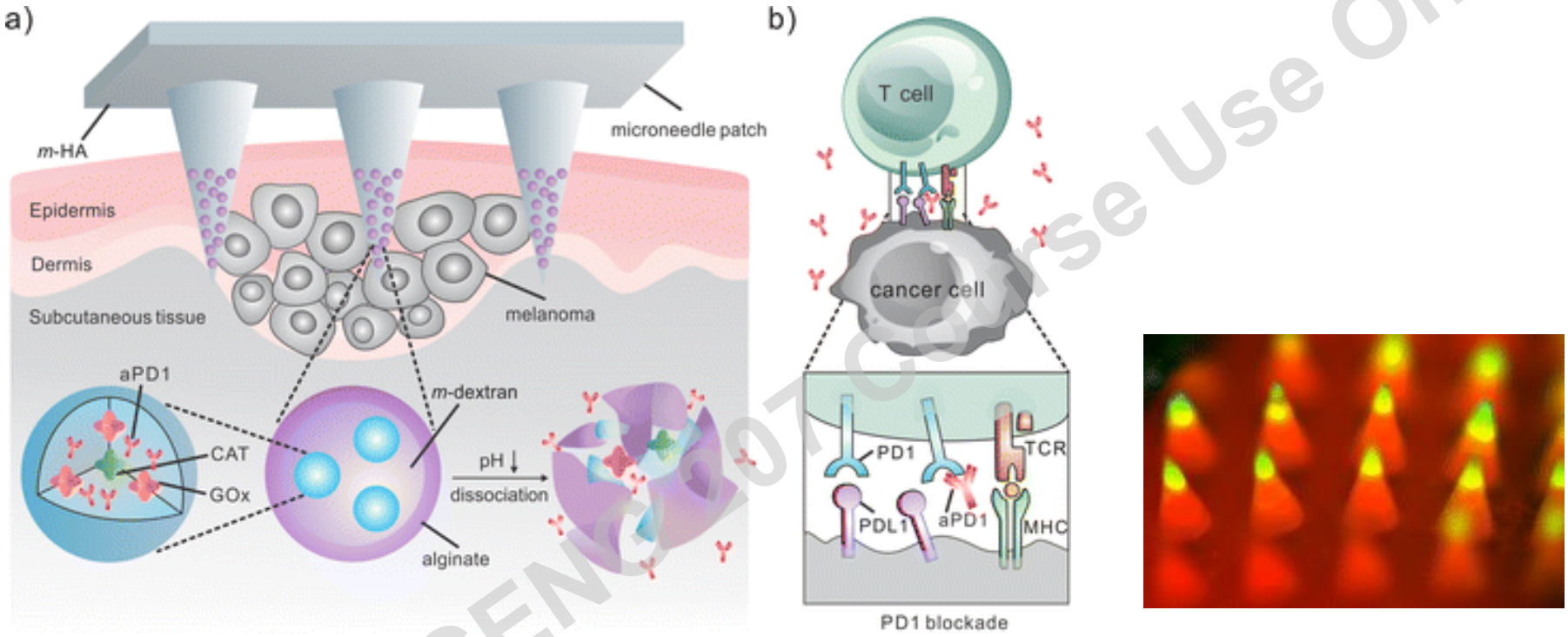
# Transdermal Microneedles






**Patch Application is Controlled by a Spring-Loaded Applicator System (Alza)**

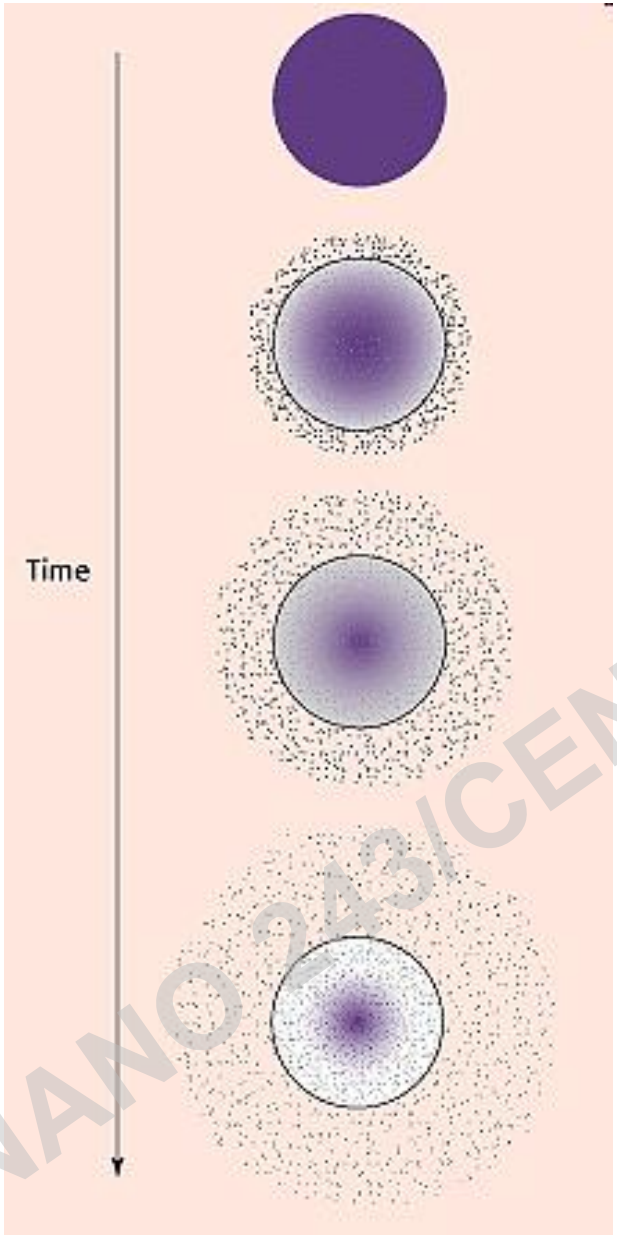
# Recent Development of Microneedles




Schematic of the MN patch-assisted delivery of aPD1 for the skin cancer treatment. (a) Schematic of the aPD1 delivered by an MN patch loaded with physiologically self-dissociated NPs. With GOx/CAT enzymatic system immobilized inside the NPs by double-emulsion method, the enzyme-mediated conversion of blood glucose to gluconic acid promotes the sustained dissociation of NPs, subsequently leading to the release of aPD1. (b) The blockade of PD-1 by aPD1 to activate the immune system to destroy skin cancer cells.

*Nano Letters 2016, 16, 2334*

# II. Matrix Delivery Systems

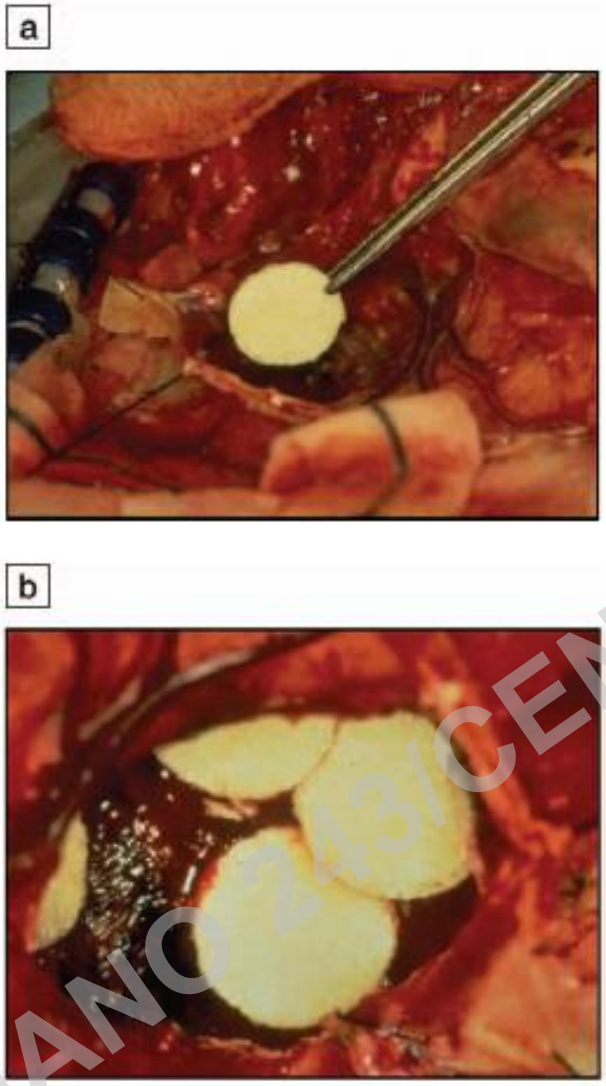



**For some therapeutic agents, it is not possible to find membrane materials that provide adequate permeability to permit release from a reservoir device.**

**In a matrix system, the drug molecules are dissolved or dispersed throughout a solid polymer phase.**

**The drug molecules will continuously diffuse out of the matrix**

# Biodegradable Polymer Matrix



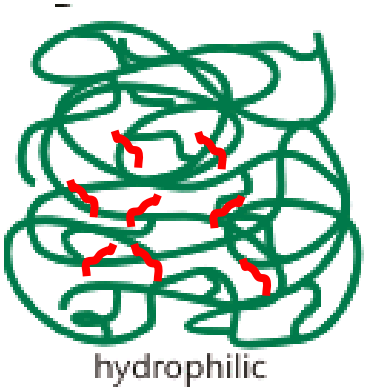

**Biodegradable polymers that dissolve slowly have been widely used in matrix drug delivery systems.**

**By careful design of the material and device, it is possible to design delivery systems in which the rate of polymer degradation and dissolution controls the rate of drug delivery, providing a new element for controlling the rate of release of dispersed drugs.**

***Polymer-based local chemotherapy. (a) Photograph of a polymer wafer containing chemotherapeutic drug BCNU being surgically inserted into a human brain. (b) Seven or eight wafers are inserted in the surgical site before the surgeon closes the brain.***

# III. Hydrogel Delivery Systems

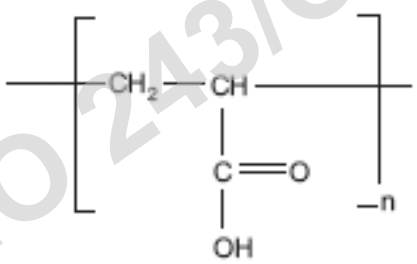
**Water-soluble polymers can be cross-linked to create materials, called hydrogel, that swell but do not dissolve in water.**



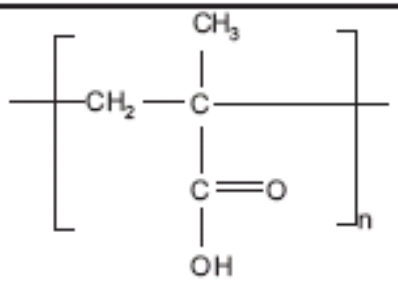

**Cross-links (covalent bonds or physical entanglements) convert the ensemble of individual polymer chains into a macromolecular network, to which drugs are encapsulated.**

**The rate of drug diffusion through the hydrogels depends on the extent of cross-linking (interchain separation).**

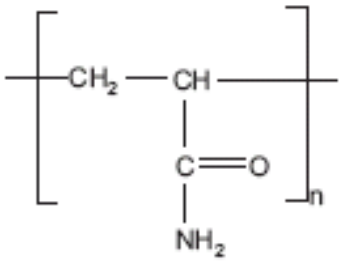
Ionic polymers




Poly(acrylic acid)
(PAA)

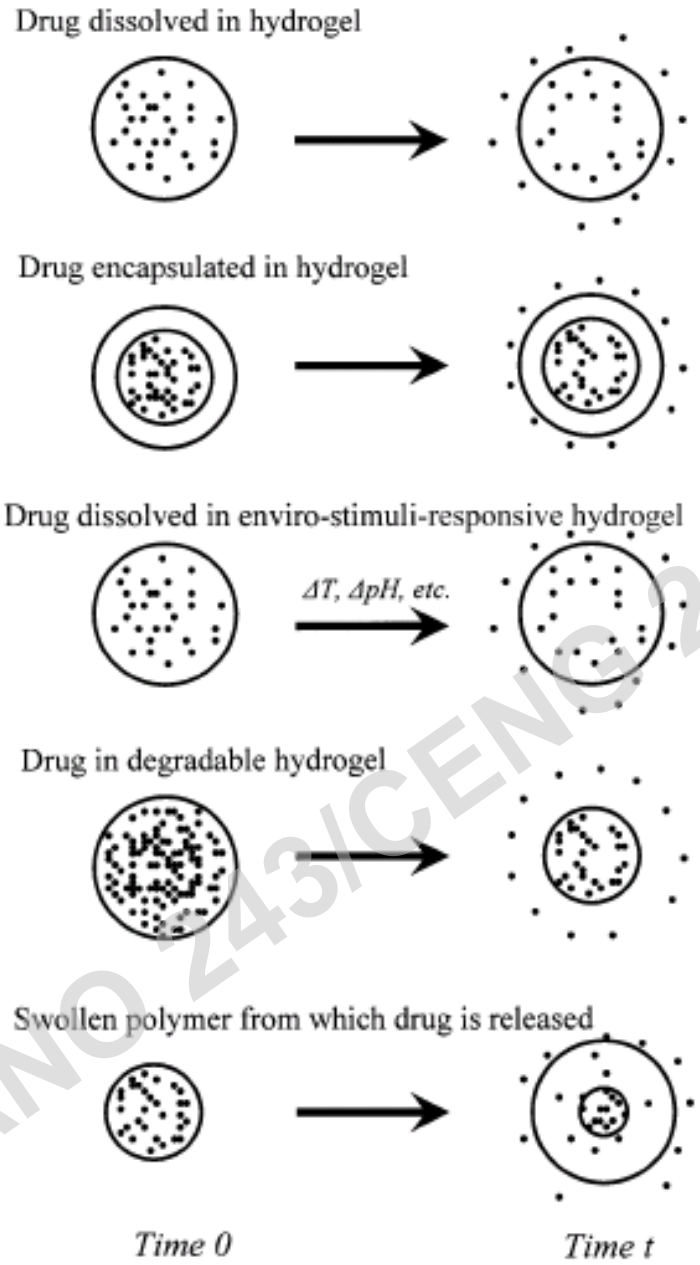



Poly(methacrylic acid)
(PMMA)




Polyacrylamide
(PAAm)

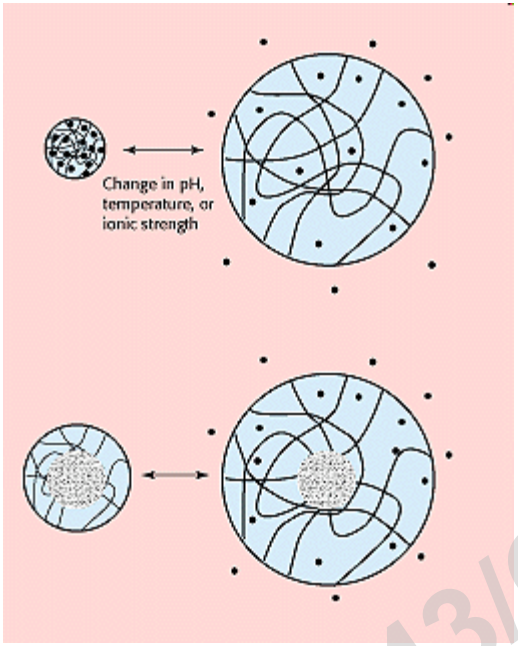
# Mechanisms of Hydrogel Drug Delivery

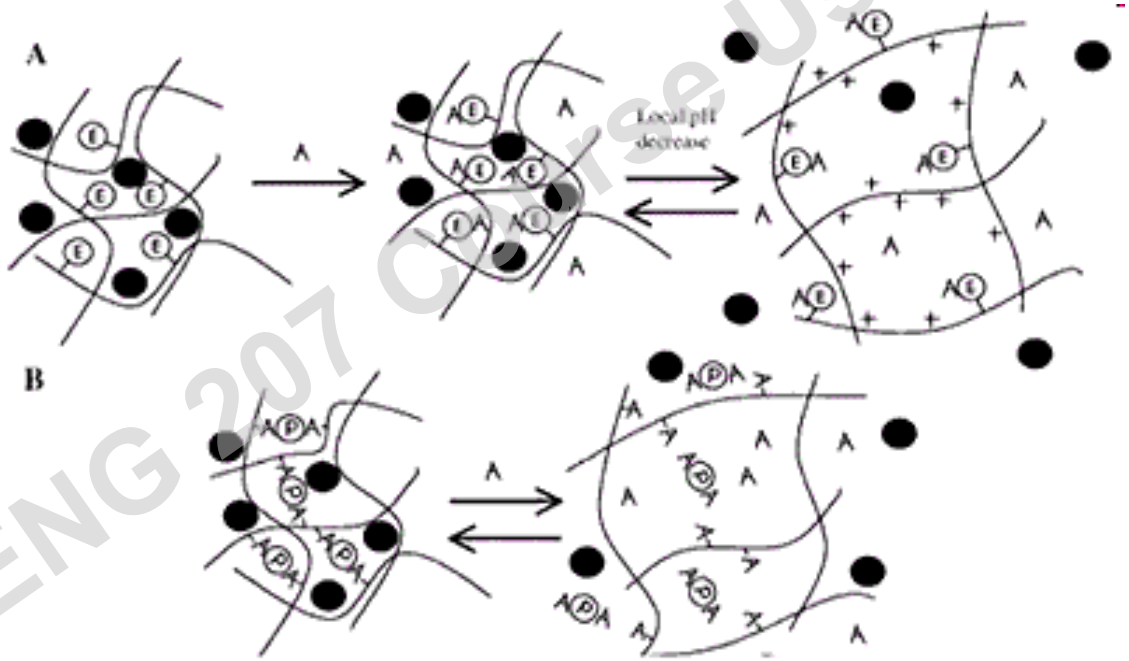



**Three primary mechanisms:**

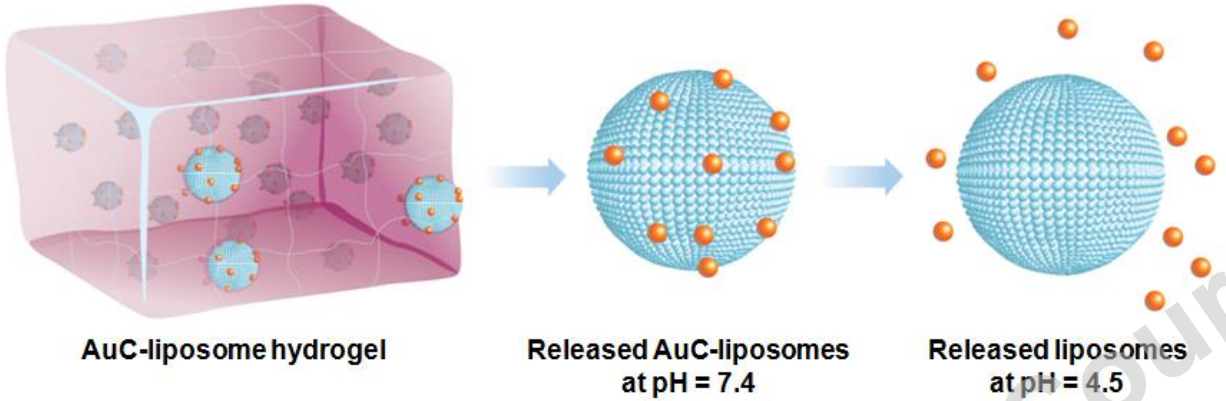
- **Diffusion**
- **Degradation**
- **Swelling followed by diffusion**

# Swelling Followed by Diffusion

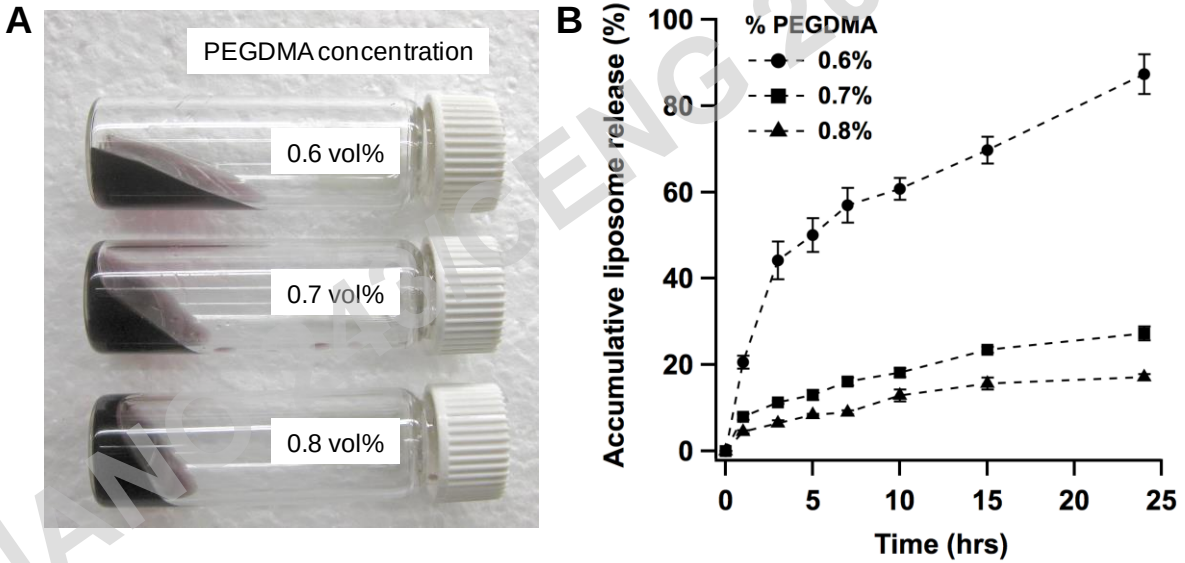


# Hydrogel for Topical Antimicroibal Delivery



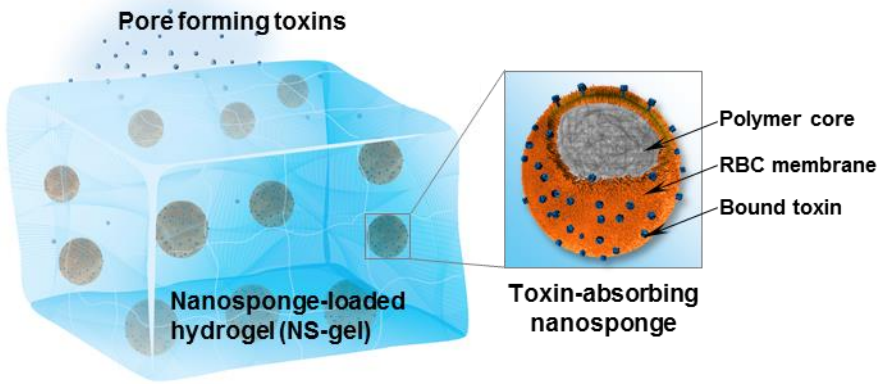

Schematic illustration of hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery



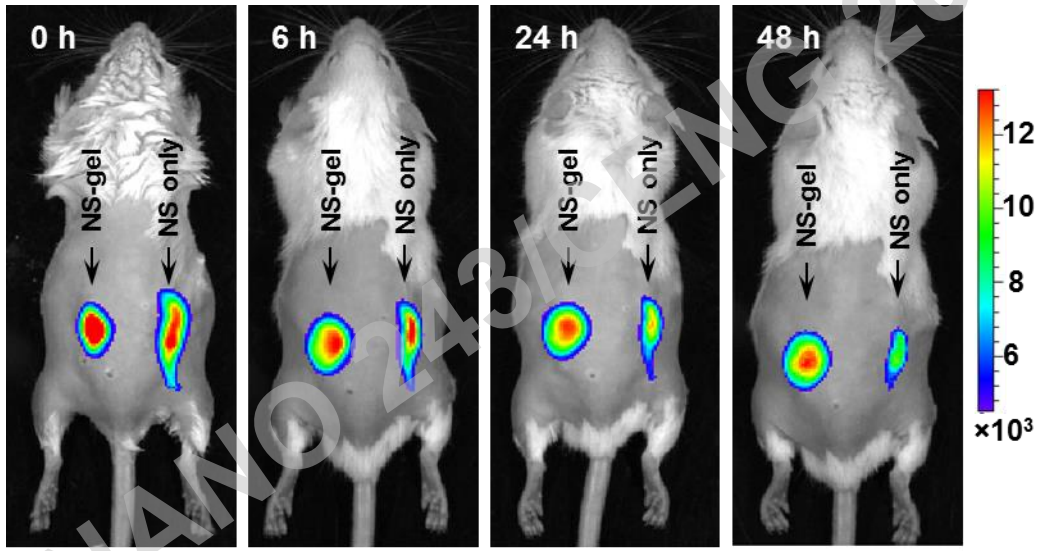

Formulation and drug release rate of AuC-liposome hydrogels.

*ACS Nano*, **2014**, *8*, 2900

# Hydrogel-Nanoparticle Hybrid System




Schematic illustration of a hydrogel retaining toxin-absorbing nanosponges for local treatment of methicillin-resistant Staphylococcus aureus (MRSA) infection. The toxin nanosponge was constructed with a polymeric core wrapped in natural red blood cell (RBC) bilayer membrane and was subsequently embedded into an acrylamide-based hydrogel.




In vivo nanosponge retention by hydrogel. Nanosponges labeled with DiD fluorescent dye was used to formulate NS-gel, which was then injected subcutaneously under the loose skin over the left flank of the mice. Free suspended nanosponges (without hydrogel) were injected as a control group at the right flank of the same mice. Fluorescence images taken at different time points show the retention of the nanosponges under mouse skin.



*Advanced Materials* **2015**, *27*, 3437

# IV. Degradable Delivery Systems

**Biodegradable polymers degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed.**

**Key requirements:**

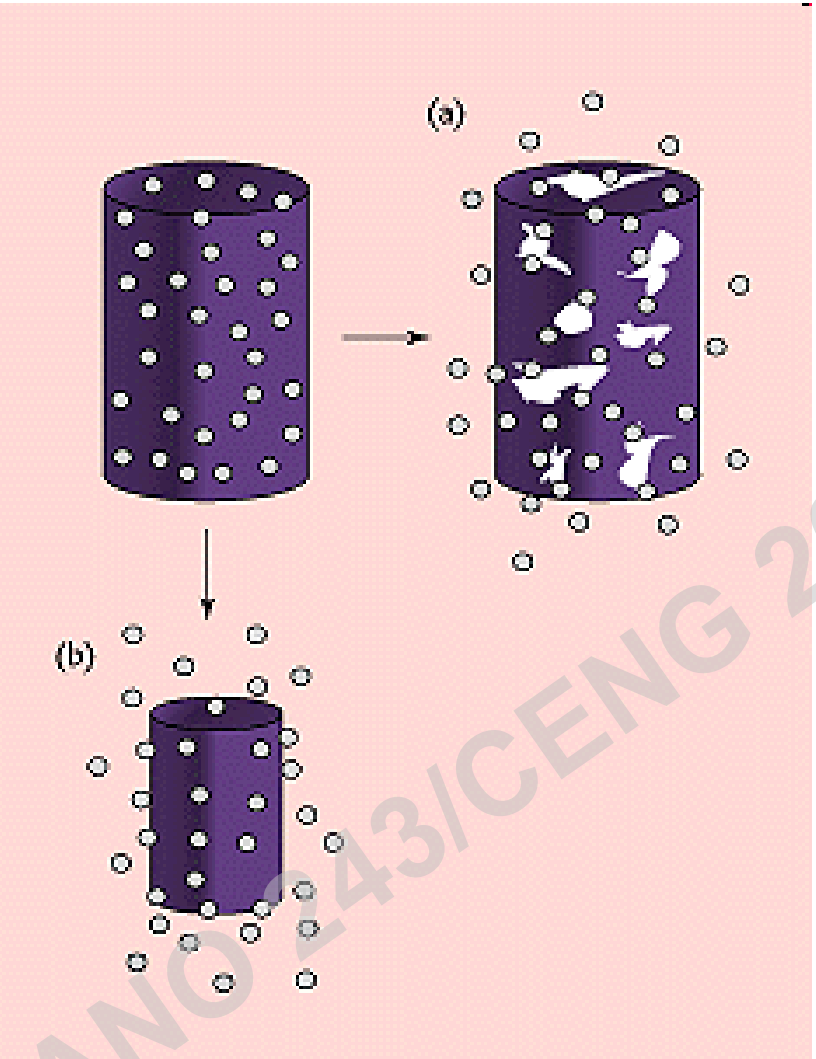
**(a) The biomaterials degrade into naturally occurring or inert chemicals, which are not harmful to the body.**

**(b) The biomaterials degrade in a controllable fashion.**

**Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable, and progressively smaller, compounds.**

**In some cases—as, for example, polylactides, polyglycolides, and their copolymers—the polymers will eventually break down to lactic acid and glycolic acid, enter the Kreb's cycle, and be further broken down into carbon dioxide and water and excreted through normal processes.**

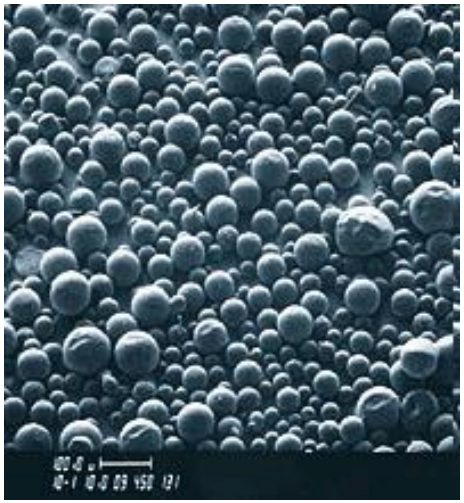
# Bulk Erosion vs. Surface Erosion



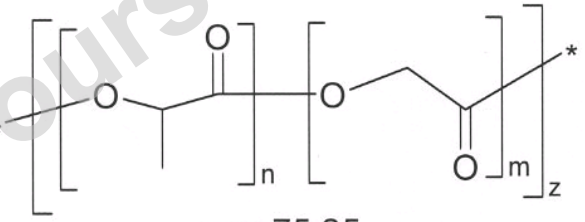

**Bulk erosion:** Degradation may take place through bulk hydrolysis, in which the polymer degrades in a fairly uniform manner throughout the matrix, as shown schematically in Figure a.

**Surface erosion:** For some degradable polymers, most notably the polyanhydrides and polyorthoesters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system , as shown schematically in Figure b.

# Bulk Erosion vs. Surface Erosion



*Bulk erosion: Biodegradable microparticle of 75:25 lactide:glycolide PLGA after 133 days of degradation in water*

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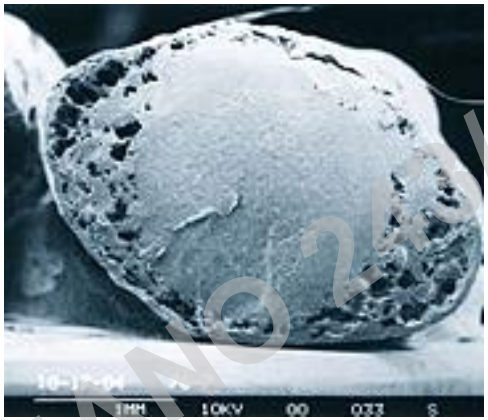
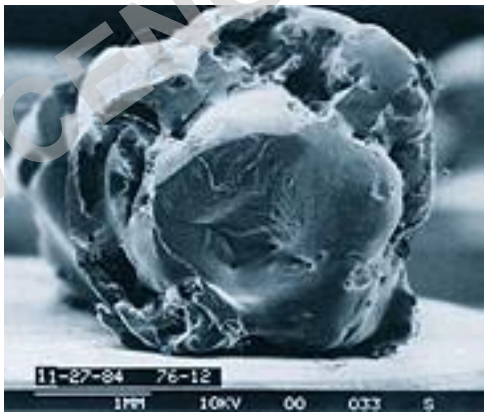
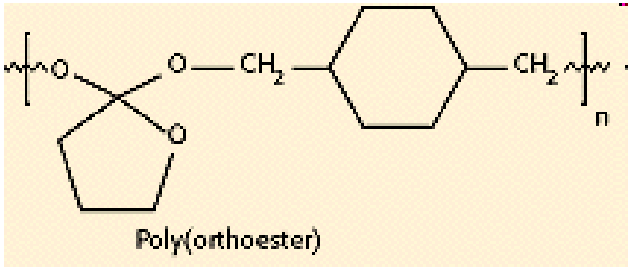




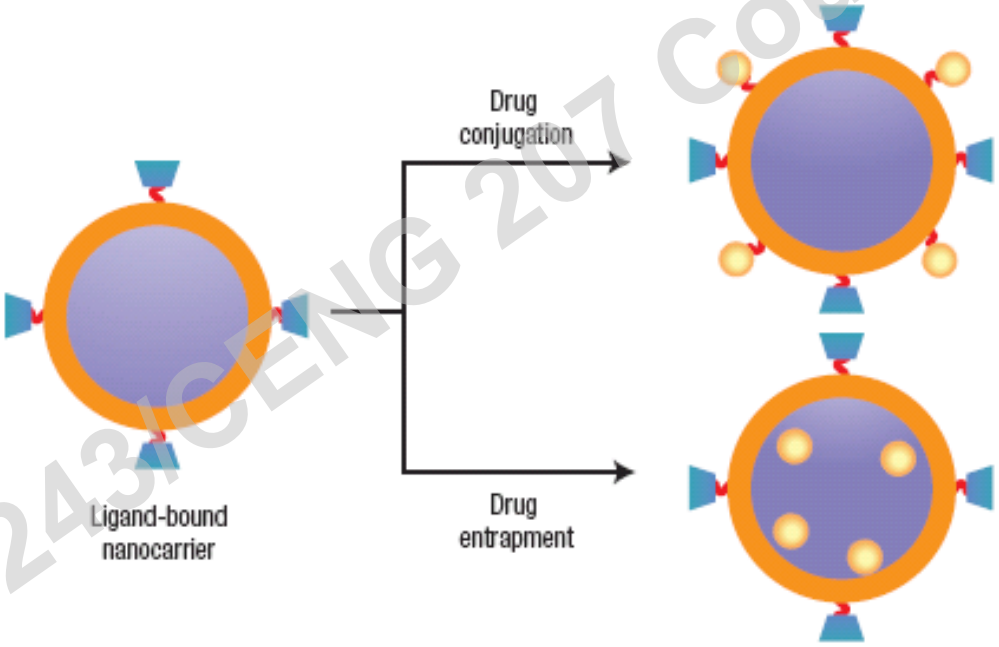
*Surface erosion: Biodegradable polyorthoester rods after (left) 9 and (right) 16 weeks of implantation in rabbits.*



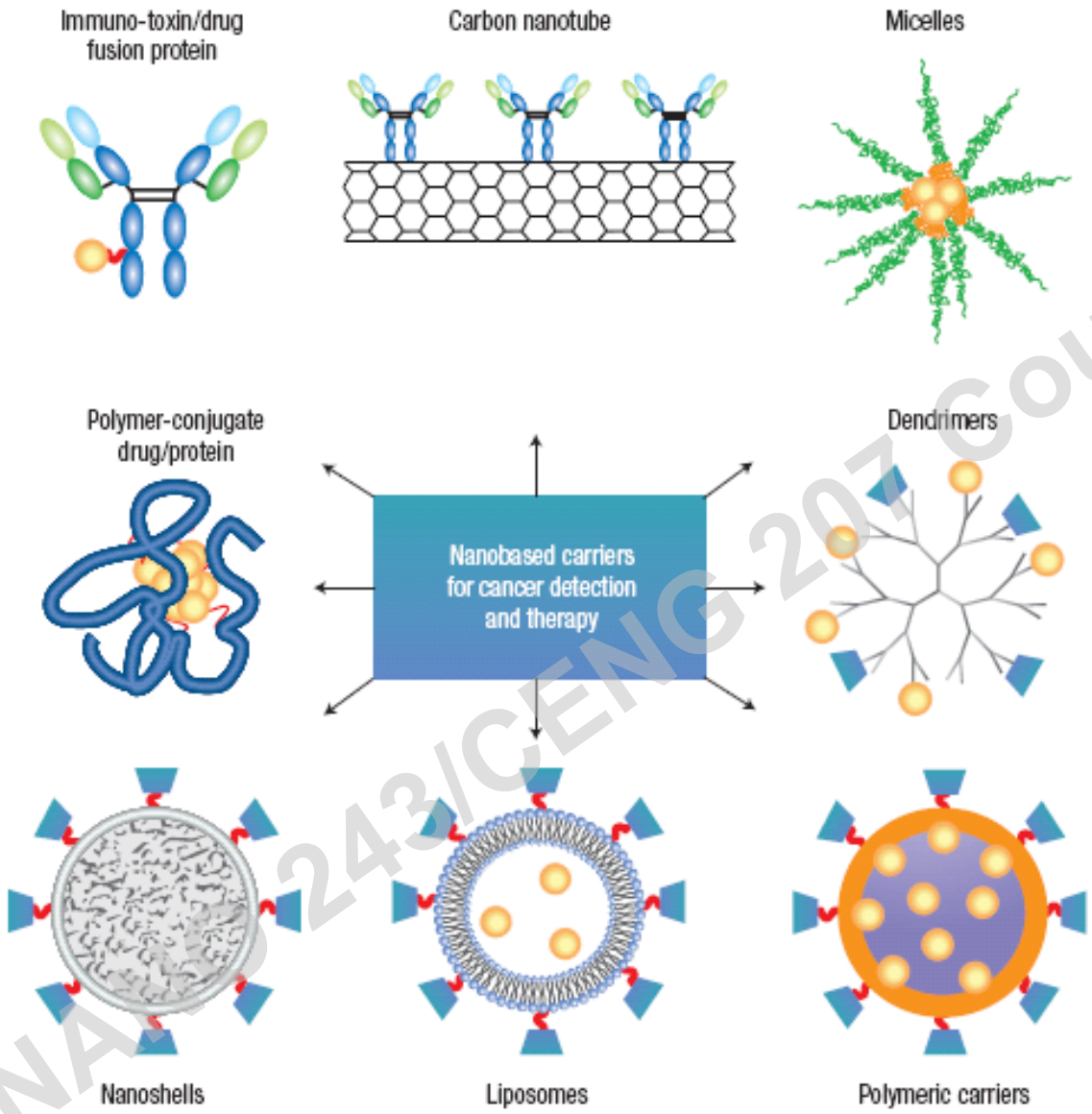

Poly(orthoester)

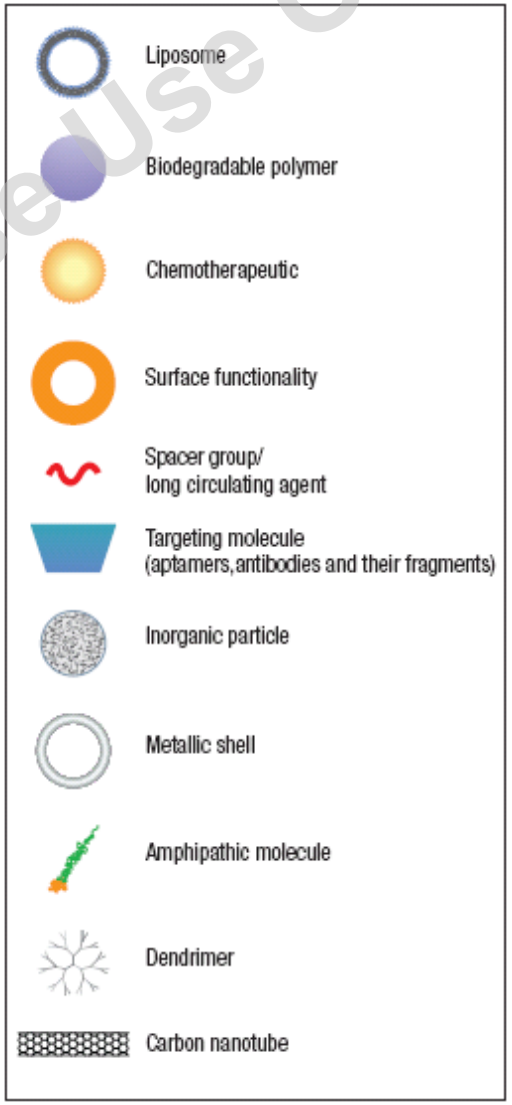
# V. Particulate Delivery Systems

**While implantable drug delivery systems are useful for certain applications, in many cases an injectable or ingestable delivery system is desired. For that reason, particulate delivery systems represent an important class of drug delivery systems.**



# Typical Particulate Delivery Systems

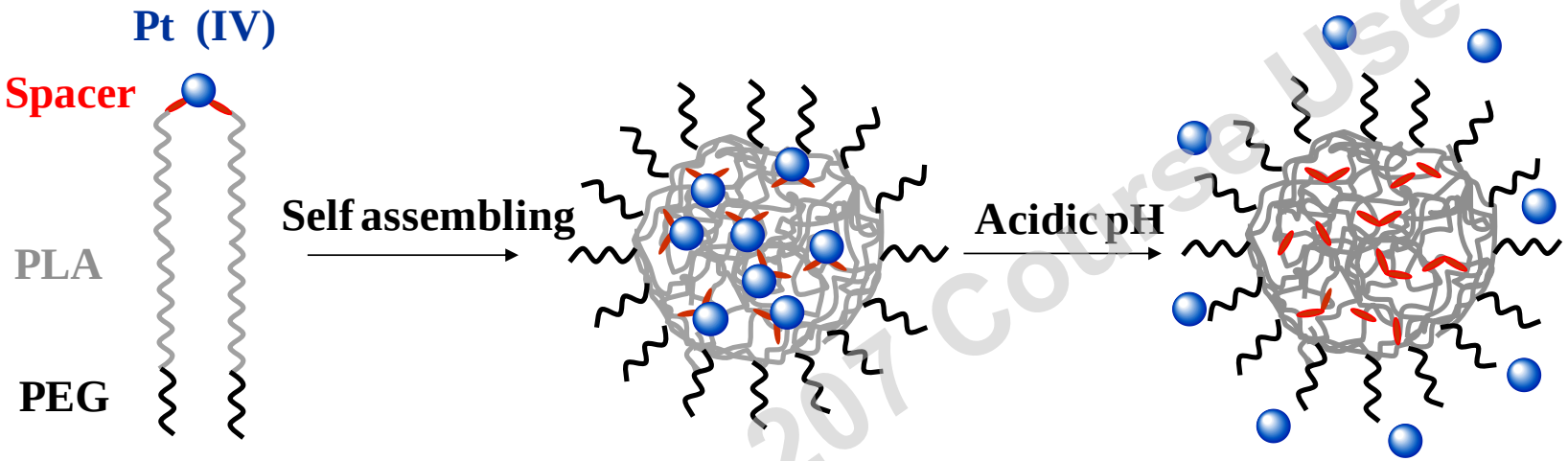


# VI. Responsive Delivery Systems

| Stimulus | Hydrogel | Mechanism |
|---|---|---|
| pH | Acidic or basic hydrogel | Change in pH — swelling — release of drug |
| Ionic strength | Ionic hydrogel | Change in ionic strength — change in concentration of ions inside gel — change in swelling — release of drug |
| Chemical species | Hydrogel containing electron-accepting groups | Electron-donating compounds — formation of charge/transfer complex — change in swelling — release of drug |
| Enzyme-substrate | Hydrogel containing immobilized enzymes | Substrate present — enzymatic conversion — product changes swelling of gel — release of drug |
| Magnetic | Magnetic particles dispersed in alginate microshperes | Applied magnetic field — change in pores in gel — change in swelling — release of drug |
| Thermal | Thermoresponsive hrydrogel poly(N-isopro-pylacrylamide) | Change in temperature — change in polymer-polymer and water-polymer interactions — change in swelling — release of drug |
| Electrical | Polyelectrolyte hydrogel | Applied electric field — membrane charging — electrophoresis of charged drug — change in swelling — release of drug |
| Ultrasound irradiation | Ethylene-vinyl alcohol hydrogel | Ultrasound irradiation — temperature increase — release of drug |

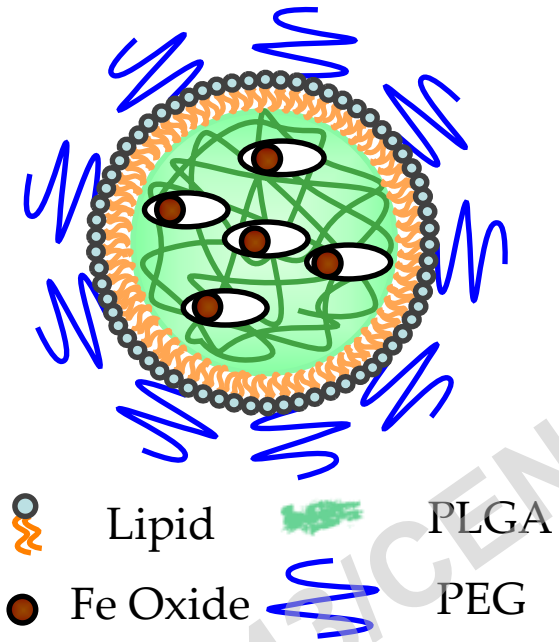
# pH-Triggered Drug Release

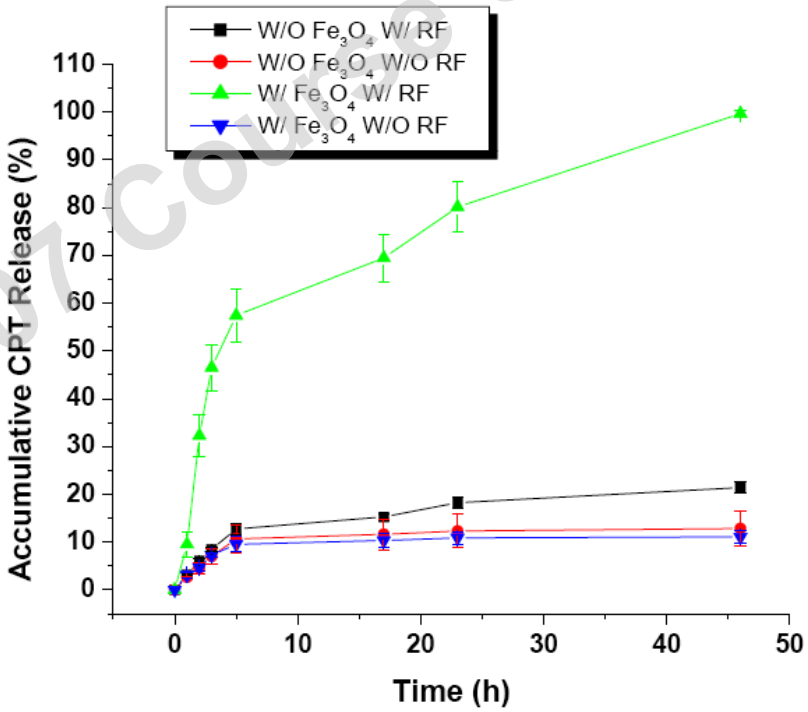



Schematic illustrations of the structure of polymer-cisplatin prodrug conjugate, the formation of Bi(PEG-PLA)-Pt(IV) NPs through self-assembling, and acid-responsive drug release from the NPs

*ACS Nano*, **2010**, *4*, 251.

# Magnetically Controlled Drug Release




*Acta Biomaterialia*, **2013**, *9*, 5447.