Introduction to Controlled Drug Delivery

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www.engr.du.edu/clengsfel/drugdelivery.pdf

Classical drug delivery

For most of the pharmaceutical industries existence, drug delivery induced simple, fast-acting responses via oral or injection delivery routes

Problems associated with this approach
1. Reduced potencies because of partial degradation
2. Toxic levels of administration
3. Increase costs associated with excess dosing
4. Compliance issue due to administration pain

Why control drug delivery?

As the cost and complexity of individual drug molecules has risen the problems with the classical delivery strategies over took their benefits.

Goal of more sophisticated drug delivery techniques
1. Deploy to a target site to limit side effects
2. Shepard drugs through specific areas of the body without degradation
3. Maintain a therapeutic drug level for prolonged periods of time
4. Predictable controllable release rates
5. Reduce dosing frequent and increase patient compliance
History of Controlled Drug Delivery
- Wurster technique patented in 1949
- Coacervation (liquid encapsulation) in 1953
- Microencapsulation in the 1960’s
  - 65% of all current drugs use some form of micro-encapsulation
- Implants in the 1970’s
- Transdermal in the 1980’s
- Site directed systems in the 1990’s

Entrapment or Encapsulation
- During the 1970’s, scientists first began to encapsulate and entrap drugs within polymers
- Encapsulation involves surrounding drug molecules with a solid polymer shell
  ![Drug and Polymer](image)
- Entrapment involves the suspension of drug molecules within a polymer matrix.
  ![Drug and Polymer](image)

Drug release by diffusion
- Early encapsulation and entrapment systems released the drug from within the polymer via molecular diffusion
  - When the polymer absorbs water it swells in size
  - Swelling created voids throughout the interior polymer
  - Smaller molecule drugs can escape via the voids at a known rate controlled by molecular diffusion (a function of temperature and drug size)
  ![Drug and Polymer](image)
Drug release by erosion

- Modern delivery systems employ biodegradable polymers
  - When the polymer is exposed to water hydrolysis occurs
  - Hydrolysis degrades the large polymers into smaller biocompatible compounds

- Bulk erosion process
  - Water attacks bond

- Surface erosion process

Bulk erosion
(e.g. poly lactide, polyglycolic acid)
- When the polymer is exposed to water hydrolysis occurs
- Hydrolysis degrades the large polymers into smaller biocompatible compounds
- These small compound diffuse out of the matrix through the voids caused by swelling
- Loss of the small compounds accelerates the formation of voids thus the exit of drug molecules

Surface erosion
(e.g., polyanhydrides)
- When the polymer is exposed to water hydrolysis occurs
- Hydrolysis degrades the large polymers into smaller biocompatible compounds
- These small compound diffuse from the interface of the polymer
- Loss of the small compounds reveals drug trapped within
- Note these polymer do not swell.
How is entrapment or encapsulation obtained?

The physical entrapment and encapsulation of drugs within a polymer is complete via one of five techniques:

1. Wurster
2. Coacervation
3. Spray drying (or precipitation)
4. Coextrusion
5. Self-assembly methods

Wurster processing (1949)

- The Wurstur process is essentially a coating process applied after a drug core is formed.
- The polymer shell is applied via spraying while the drug cores (liquid or solid) is suspended and recirculated in a gas stream.

Coacervation Technique

- **STEP #1:**
  - Polymer dissolved in a solvent (or oil)
  - Drug dissolved in water
- **STEP #2:**
  - 2 liquids are rapidly mixed
  - Water droplets form within the solvent
- **STEP #3:**
  - Emulsion from step #2 is mixed rapidly with fresh water
  - Oil droplets within the fresh water phase
  - Oil droplets contain original dispersed water/drug phase
  - Oil diffuses into the fresh water phase precipitating the polymer & entrapping the drug
Supercritical fluid precipitation

Co-extrusion processing
- There are numerous co-extrusion processes but they all share one feature – the polymer shell is flowed concentrically around a pipe containing the drug formulation
- These concentric cylinders then breakup into individual packets either driven by air flow, electrostatic or mechanical vibration

Self-assembling delivery systems
The next advance was to construct materials/polymer that would self assemble with drugs to create controlled drug delivery vehicles
- Self assembly can is typically approach via one of two methods:
  1. Using a molecule that has a hydrophilic head and hydrophobic tail to form a shell, or
  2. Electrostatic interaction to entrap drug molecules
Micelles & Bilayers

- Entrapment by micelle or bilayer formation can be obtained using lipids, surfactants and block copolymers

Lipid entrapment or liposomes are the most common
- Small unilamellar (10 to 50 nm)
- Large unilamellar (50 nm to 1 μm)
- Large multilamellar (100 nm to 20 μm)

Polar Head Group (hydrophilic)
Fatty Tail (hydrophobic)

Liposome Formation

- Liposome are typically formed by:
  - Fissure homogenization
  - High pressure homogenization
  - Extrusion through polycarbonate membranes

- Large multimellar liposomes are prepared by hydration of a dry lipid film by an aqueous solution.
  - Thickness of the film, temperature, lipid composition effect lipid size
- Large multimellar liposomes are prepared by vigorous agitation (fissure or high pressure) during the hydration process
  - Mixing strength, lipid and surfactant control lipid size
- Small multimellar liposomes are typically prepared by taking LMV suspensions and passing them through fine matrix polycarbonate membrane.
  - Membrane pore size largely controls the resulting SML size

Electrostatic entrapment

- Ionic attraction between dissimilar charged molecules can be used to attach a molecule to the drug
- The resulting complex may provide protection by containing the drug molecule on the interior or simply inactivating the drug
More than protection and release: targeting a site

- The coating or matrix surrounding the therapeutic molecule can also be used to direct the particle to a targeted site.
- Such systems include:
  1. Liposomes
  2. Surfactant
  3. Nanoparticles
  4. Antibodies, enzymes and other proteins
  5. Viral vectors

Liposomal enhanced targeting

- Liposomes have demonstrated the tendency to collect in a specific tissue
  - There is some evidence that liposomes gather in the tissue of tumors
- Liposomes can take the form of positively charged, negatively charged and neutral – charge can help direct particles to specific oppositely charged locations
- Liposomes largely consist of Lecithin and cholesterol, naturally occurring substances in the body, therefore well tolerated and have some naturally occurring collection sites
Surfactants enhanced targeting

- Increase absorption into cell membrane
  - Acting as a wetting agent surfactants, increases the contact area between the drug and cell wall, facilitating the absorption of molecules into the cell membrane
- Increase solubility of drug into carrier
  - Introduction of a surfactant into a solvent lowers the surface tension thereby increasing solubility limits
- Increase stability of vehicle

Nanoparticles enhanced targeting

- Particle sizes ranging from 10nm to 1um
- Particle size alone can significantly affect biodistribution
  - Particles less than 10 nm are 400 time more likely to cross the intestinal wall than 1 micron particles
  - Particles between 1 and 10 micron deposit in the deep lung via impaction while other escape during breath or deposit in the mouth
  - Particles below 500 nm can escape the filtering of the liver and kidney for several cycles
- Nanoparticles are highly charged coupled high surface to volume ratio this property can effect cellular interaction

Antibody enhanced delivery

- The attachment of antibodies to delivery vehicles can be used to increase tissue sensitivity
- Attachment occurs by physical absorption or covalent bonding
- Monoclonal antibodies can be directed against a single determinant – similar to a lock and a key.

[Image of antibody targeting]
Viral vectors

- Viruses have evolved a way of encapsulating and delivering genes to human cells in a pathogenic manner.
- Scientists are attempting to take advantage of nature's delivery system.
- Viruses would be genetically altered to carry the desired normal gene and turn off the natural occurring disease within the virus.

[Video from www.biosciednet.org/portal]

Viral vectors

Candidate viruses

- Retroviruses [e.g., HIV]
  - RNA virus that infects humans
  - Ability to target genes
  - Dividing cells only
  - Risk of mutagenesis
  - 8kb
- Adenoviruses [e.g., virus that causes common cold]
  - Not highly pathogenic
  - Do not integrate into the genome
  - Can be aerosolized
  - Transient gene expression
  - 8-10kb
- Adeno-associated virus [inserts only at chromosome 19]
- Herpes simplex virus [e.g., virus that causes cold sores]

- Viral vectors will only be effective a few times before the body becomes resistant!

Other delivery vehicles

Up to this point I have concentration particle delivery vehicles, but several other have evolved in recent history
1. Hydrogels
2. Transdermal patches
3. Implantable pumps
Hydrogels (e.g. polyacrylic acids)

- Cross-linked, hydrophilic, 3-D polymer networks that are highly permeable
- Do not swell in the presence of water unless activated
- Swelling activate by pH, temperature, electric field
- Drug release happens via void generated & diffusion (diffusion rate is regulated by cross-linking ratio)

Add water + activator

Implantable pumps

The pumps usually use polymer swelling to drive drug formulations out of a reservoir

Transdermal patches

- Topical skin application
- 3 layer design
  - adhesive
  - polymer/drug matrix
  - water proof backing
- Drug is delivery to the skin up to saturation
- Blood via circulation removes drug locally and more escapes the matrix to return levels to saturation