Polymers – Controlled Drug Delivery systems

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Polymers – Controlled Drug Delivery systems

Objectives of this Session

The participant shall be able to:

Describe diffusion controlled devices, using polymers

Explain the chemically controlled devices and bioerodible polymer

Describe the release mechanisms in terms of hydrophilic and hydrophobic polymer
Polymers – Conventional Dosage Forms

Classification

Binding agents

   Acacia, gelatin, sodium alginate

Disintegrating agents

   Starch, crosscarmellose sodium

Plasticizers

   Polyethylene

Cosolvents

   PEG 300, PEG 400

Thickening agents

   Xanthin gum

Coating agents – nonenteric agents

   HPMC, povidone, PEG
Polymers – Conventional Dosage Forms

Classification

Coating agents – enteric agents

Cellulose acetate phthalate, HPMC phthalate

Bulking agents

Microcrystalline cellulose (MCC)
Polymers – Oral controlled delivery systems

Insoluble, inert polymers
These are release retardants
Examples - Polymers
Polyethylene, PVC, ethylcellulose
Examples – Dosage forms
Matrix tablets
These do not disintegrate
Direct compression is possible
Wet granulation is possible with ethyl alcohol
Mechanism of release
Liquid penetration, drug dissolution and diffusion
Channeling agents promote the permeation
Eg: Sorbitol
Polymers – Oral controlled delivery systems

Insoluble, inert polymers

Mechanism of release

Not sensitive to composition of GI fluids
Not useful for high mg formulation
Because high conc of polymer cannot be included

Not suitable for highly water insoluble drugs
Because release is dissolution rate limiting
Polymers – Biocompatibility

Characteristics
- Physiologically inert
- Compatible with biological tissue
- Degrade in the physiologic environment
- Toxicologically acceptable metabolites
  Eg: naturally occurring lactic acid

Bioerosion profile
Poly bis (o-carbophenoxy) propane (PCPP)
copolymered with sebacic acid
These have hydrolytic instability
Bioerosion is due to crystallinity changes
Polymers – Biocompatibility

Bioerosion profile

Polyanhydrides with sebacic acid are incorporated. It increases the bioerosion.
Polymers – Biocompatibility

Applications

Implant products

Peptide antitumor agents are delivered
These are more important in case of proteins
Peptides themselves can degrade in the biological environment
Then the polymers must protect these peptide drugs
Biodegradable polymers are also required for sc administration - implants
Poly (lactide-glycolide) for sc implantation
Polymers – Biocompatibility

Poly (lactide-glycolide) for \textit{sc} implantation

Degradability is 50\% in 50 days
Polymers – Biocompatibility

Applications

Intravenous/arterial products
  Cancer therapy needs these products

Examples - Polymers
  Poly (lactide-glycolide)
  Polypeptides, polysaccharides, orthoester
  Rate of release depends on the biodegradability of polymers
  Naltrexone (drug) pellets
Polymers – Diffusion Controlled Devices

A. Monolithic Devices
Dispersion of drug in the polymer
Slab type – polymer controls the release of drug due to diffusion
Drug may be:
   i) Solubilized
   ii) Dispersed

These do not release drug by zero order kinetics
These are simple and convenient
Polymers – Diffusion Controlled Devices

B. Reservoir Devices
Core is drug, coat is rate controlling membrane
Coat is micropororous, hydrophobic backbone membrane
Fick’s law is applicable
Liquid filled pores
Zero order kinetics can be achieved
Burst effect is also possible
Fabrication is complex, but zero order kinetics allowed its commercial applications
Polymers – Diffusion Controlled Devices

C. Solvent Controlled Devices
   Eg: Osmotically controlled devices
   
   Semipermeable membrane (polymer)
   Rigid impermeable flexible barrier (Polymer)
   Eg: Swelling controlled devices
Polymers – Chemically Controlled Devices

Release of drug from the polymer is controlled by a chemical reaction

Mechanism: Hydrolytic or enzymatic cleavage of liable bonds, ionization or protonation

Polymer erosion follows:
Conversion of water insoluble material to a water soluble materials

Bioerodible polymer are used as implantable devices

Device need not be removed from the site of application
Polymers – Chemically Controlled Devices

Type I Erosion
Water soluble macromolecules are cross-linked to form a network

Network is insoluble in aqueous environment
Polymer dissolve and swell to the extent that is allowed by cross-link density

These cross-links are cleaved (Type IA)

Cleaved parts are water soluble
Polymers – Chemically Controlled Devices

Type I Erosion

Cleavage of water soluble polymer backbone (Type IB)

Backbone is cleaved

As cleaving proceeds, the matrix begin to swell and eventually it will dissolve.
Polymers – Chemically Controlled Devices

Type I Erosion

Limitations

1) Matrix swell progressively, dissolution will limit its use

Three dimensional stability is of little importance

2) Cross linked water soluble polymer form hydrogels

Completely permeated by water

Then water solubility of drug is important

Therefore, low mol wt water soluble drug is leached rapidly

Then, it is independent of matrix erosion rate
Polymers – Chemically Controlled Devices

Type II Erosion
Mechanism: Hydrolysis, ionization, protonation of the pendant group
Backbone of the polymer is intact

1) Solubilization does not result, though mol wt of polymer changes

These type of polymers are used for topical applications, because backbone does not cleave

\[ \text{A} \rightarrow \text{B} \text{ represents hydrolysis, ionization or protonation} \]

High mol wt polymers get eliminated as water-soluble macromolecules
Polymers – Chemically Controlled Devices

Type III Erosion

Mechanism: Hydrolytic cleavage of labile bonds in the polymer backbone

Degradation products must be completely nontoxic

High mol wt (insoluble) polymer

These are used for systemic administration of therapeutic agents

Small water soluble molecules

Sc, im, ip implantation sites
Controlled Devices – Release Mechanisms

1) Drug is covalently attached to the polymer backbone

Hydrolysis of backbone releases the drug
Polymer fragments should not be attached to the drug
Reactivity of bond A should be significantly higher than reactivity of bond B
Polymer is a carrier or depot of drug
i.e., localised at a certain body site
Controlled Devices – Release Mechanisms

1) Drugs covalently attached to polymer backbone

Covalent bond gradually breaks (physical)

A chemical reaction is responsible for cleavage

Eg: Depot system or norethindrone coupled with water soluble poly (N$^5$-hydroxypropyl-L-glutamine) by reaction with phosgene
1) Drugs covalently attached to polymer backbone

After depletion of drug, the polymer should not remain at the site.

Polymer-OH group combine with steroids produce carbonate linkage.

Hydrolysis of carbonate linkage releases the steroids, release is effective for 144 days.

Carrier mode is the unique possibility of carrying the drug to specific body site.

Eg: p-Phenylene diamine mustard and immunoglobulin (homing group) are used against mouse lymphoma.

Immunoglobulin reaches the site and cleaves to release the drug.
2) Drug contained in a core surrounded by bioerodible rate controlling membrane. Subdermal delivery of contraceptive steroids and narcotic anagonist, eg, naltrexone. Eg: Poly (ε- caprolactone), poly (DL-lactic acid).

Drug is in the core (Reservoir type).
The polymer capsule remain in the tissue for varying lengths of time, after completion of therapy.

Surgical removal of drug depleted device is unnecessary, if polymer is bioerodible.
Controlled Devices – Release Mechanisms

2) Drug contained in a core surrounded by bioerodible rate controlling membrane

Degradation is bulk type
Hydrolysis of aliphatic poly esters with no enzymatic contribution
Devices erode only after the drug reservoir is depleted
Controlled Devices – Release Mechanisms

2) Drug contained in a core surrounded by bioerodible rate controlling membrane

Rapid fall of viscosity indicates that the degradation is bulk erosion
3) Drug is homogeneously dispersed in polymer matrix

Slab or monolithic system

Drug diffusion from this monolith is controlled by diffusion or erosion or a combination of both.

There are two categories – details follows
Polymers – Bioerodible Type

Hydrophilic Bioerodible Polymers
- Bulk erosion takes place – monolithic system
- Because completely permeated by water

Nature of drugs
- Low water soluble substances
- Macromolecules
- These physically entangle in good amounts and drug is immobilised

If drugs are hydrophilic, release is rapid
If polymers are non-digestable, these form a gel layer

Used as implants for topical, ocular rectal, utero applications
Toxicity of polymer is low
Polymers – Bioerodible Type

Hydrophilic Bioerodible Polymers – Type I A
Eg: Hydrogel prepared by copolymerizing vinylpyrrolidone or acrylamide with N,N’-methylene bis acrylamide

Acrylamide microspheres cross-linked with N, N’ methylene bis acrylamide
Microspheres cleave by hydrolysis at cross links

Hydrophilic Bioerodible Polymers – Type I B
Eg: Copolymerizing dextran with acrylic acid, glycidyl ester and N,N’-methylene bis acrylamide

Stable at pH 2 to 7
As pH increases, hydrolysis increases
Degraded molecules are low mol wt
Polymers – Bioerodible Type

Hydrophilic Bioerodible Polymers – Type I B

BSA is entangled in the hydrogel (polyester) by performing the cross-linking reaction in an aqueous solution that contains dissolved macromolecules

Degradation occurs at amide linkage

Degradation depends on enzymatic activity

Eg: immunoglobulins, catalase etc.
Polymers – Bioerodible Type

Hydrophobic Bioerodible Polymers – Bulk Type

Hydrolysis occur throughout the bulk of polymer

Release is complex

Due to diffusion and erosion

Hence, permeability of drug from the polymer is not predictable

- Matrix can disintegrate before drug depletion
- Large burst in the rate of drug delivery also takes place

Examples - Polymers

Copolymers of glycolic and lactic acids

Historically these are used as bioerodible sutures

These polymers degrade to metabolic lactic acid and glycolic acids
Polymers – Bioerodible Type

Hydrophobic Bioerodible Polymers – Bulk Type

These are toxicologically innocuous

Examples - Drugs

Norethindrone, baboons from poly (lactic acid) microspheres

Kinetics of release is determined by diffusion, Highuchi’s equation
Polymers – Bioerodible Type

Hydrophobic Bioerodible Polymers – Bulk Type

Early stages: little erosion

Diffusion is predominant

Subsequent stages: rapidly bioerodible due to combined effect of diffusion and erosion
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Outer surface of polymer is effected by hydrolysis

Interior of the matrix remain unchanged

Release is direct consequence of surface erosion

Release is predictable

Drug release is constant, provided geometry

surface area is constant

Life time of device $\propto$ device thickness

Rate of release $\propto$ drug loading

Examples - Polymers

Copolymers of methyl vinyl ether and maleic anhydrate

Poly (ortho esters)

Polyanhydrids
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Mechanism of release

Pore diffusion and erosion

More sensitive to digestive fluid composition

Water permeation is promoted by the use of surfactants or wicking agents (hydrophilic)

These also promote erosion

The polymers promote the direct compression of ingredients

Eg: Sustained release theophylline tablets
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Eg: Hydrocortisone from n-butyl half ester of methyl vinyl ether-maleic anhydride copolymer

Degradation mechanism is Type II

Degraded product is high mol wt water soluble polymer

Further degradation is not possible

These are used for topical applications
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Dispersion of drug in the polymer

Dissolution of matrix is retarded at a define pH

Constant pH environment provide controlled release

Excellent linearity between drug release and polymer erosion
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Poly (ortho esters)

Degradation is spontaneous (exothermic)
Catalysed by traces of acid
Reaction completes instantaneously
Degradation products are dense and cross-linked

Hydrolyse at physiologic pH 7.4
As pH is lowered, more labile reaction is obtained
Side chain is manipulated to change, but backbone does not change
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Manipulation of erosion

Excipients in the matrix

Eg: Contraceptive steroids

Nature of excipients (polymer is hydrophobic)

- Slightly acidic salt, eg: Calcium lactate
- More hydrophilic polymer
- Stabilizer, eg: Magnesium hydroxide

As neutralization continues, levonorgestral release is observed due to erosion
Polymers – Bioerodible Type

Hydrophobic Polymers – Surface Erosion

Poly (ortho esters) - Levonorgestrel

Stable in base    Slow at pH 7.4
Cleave rapidly at acidic pH
Polymers – Bioerodible Type
Hydrophobic Polymers – Surface Erosion
Polyanhydrides
Aliphatic and aromatic diacids
These degrade rapidly in basic medium than in acidic media
Bioerosion – Regulated Drug Delivery Systems

Poly (vinyl methyl ether) half-ester (monolithic matrix)

Urease (immobilized)

Urea

\[
\text{urea} \quad \xrightarrow{\text{urease}} \quad \xrightarrow{\text{H}_{2}\text{O}} \quad 2\text{NH}_4^+ + \text{HCO}_3^- + \text{OH}^- 
\]

Polymer

\[
\text{polymer} \quad \xrightarrow{\text{alkaline pH}} \quad \text{erosion}
\]

Hydrocortisone

Near neutral pH, bioerodible

At higher pH, biodegradation of matrix
Bioerosion – Regulated Drug Delivery Systems

Presence of urea

Grcep
CVS
Thank you